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SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Assessment report

Clopidogrel Winthrop

clopidogrel

Procedure No.: EMEA/H/C/000975/II/0017

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



1. Scientific discussion

1.1. Introduction

Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist. It is a potent and specific inhibitor of platelet aggregation. Its antiplatelet activity results from its selective and irreversible inhibition of adenosine diphosphate binding to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This mode of action on the ADP receptor is specific to thienopyridine compounds and differs from the mode of action of other antiplatelet agents such as acetylsalicylic acid (ASA).

In 1998, the EU commission issued a Marketing Authorisation for Plavix/Iscover (clopidogrel). It is currently registered in more than 120 countries worldwide and marketed in more than 110 countries. The available pharmaceutical form in Europe is a film-coated tablet of 75 mg and 300 mg.

The initially approved indication was for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease. This was based on the results of the CAPRIE study (Clopidogrel versus ASA in Patients at Risk of Ischaemic Events). An additional indication was approved for patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) in combination with ASA in 2003 based on the results of the CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events study).

In September 2006, an additional indication was approved for the extension of the acute coronary syndrome (ACS) indication to STEMI, so the current indication of Clopidogrel is in adults for the prevention of atherothrombotic events in:

- *Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.*
- *Patients suffering from acute coronary syndrome:*
 - *Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).*
 - *ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.*

The scope of this type II variation is to extend the indication of clopidogrel film-coated tablets in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation (AF) who have at least one risk factor for vascular events, who cannot take vitamin K antagonist (VKA) therapy and who have a low bleeding risk.

A randomized double-blind, placebo-controlled, superiority study of clopidogrel (75 mg once daily) in combination with acetylsalicylic acid (75-100 mg once daily recommended) versus acetylsalicylic acid alone has been conducted in patients with atrial fibrillation patients and at least one risk factor for vascular events who cannot take VKA (EFC4912/ACTIVE-A study).

Furthermore, the MAH has updated the information on pregnancy and lactation to reflect the EMA guideline "Risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (EMA/CHP/203927/2005; July 2008) and the QRD and CHMP comments received on the annexes for the ongoing application for the Fixed-dose combination of clopidogrel and acetylsalicylic acid.

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision P/122/2008 for the following condition:

- Prevention of thromboembolic events

On the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

1.2. Clinical aspects

3.2.1 Background

Atrial fibrillation is the most commonly sustained arrhythmia, and its prevalence increases from 1% in younger patients to 10% of patients over the age of 80 years. Both the prevalence and the incidence are increasing over time due to the aging population.

Pathophysiology of Stroke in AF

The pathogenesis of stroke in AF is complex and multifactorial, but mostly attributable to thrombus formation in the left atrium. Echocardiographic studies have consistently shown that there is tendency to thrombus formation in the fibrillating atrium. Coexisting complex aortic plaque in the aorta is also a factor favoring emboli. Hemostatic and platelet activation associated with inflammation and growth factor changes play key role in the pathophysiology. In patients with AF there is evidence for the presence of a prothrombotic or hypercoagulable state with platelet activation.

Prevention of stroke in AF

The updated 2006 ACC/AHA/ESC atrial fibrillation guidelines recommend either VKA or ASA, with the choice for each patient depending on his or her risk for stroke. VKA is recommended for stroke prevention in patients with moderate to high risk and ASA is recommended for patients with lower risk.

Rationale for the indication of interest

The increase in the risk of stroke in AF is directly related to formation of left atrial thrombus. Warfarin is the most effective therapy against this devastating complication, but it is a very difficult drug to use well over sustained periods. Failure to use warfarin effectively exposes a major unmet medical need, which is not necessarily 'bad practice' by physicians but is more linked to the fact that warfarin is a complex drug that is difficult to use well, so that in many patients it is not possible to achieve the stable levels of INR control needed to achieve the good results seen in clinical trials. Patients with suboptimal cognition, with poor social supports or other disadvantages are particularly vulnerable. The medical decision not to use warfarin in high risk patients needs to be made carefully. In many cases, patients also prefer not to use warfarin, either after trying it or based on the knowledge they have of it. For patients who are unsuitable for warfarin, the only available therapy at present is aspirin, which is only modestly effective. A better therapy to reduce stroke is urgently needed.

For AF patients with a moderate or high risk for stroke, VKAs are the recommended treatment. However, in those patients for whom warfarin cannot be prescribed, there is a clear unmet medical need for a more effective alternative therapy. Clopidogrel in combination with ASA could be an effective alternative, and this was the basis for the design of ACTIVE A.

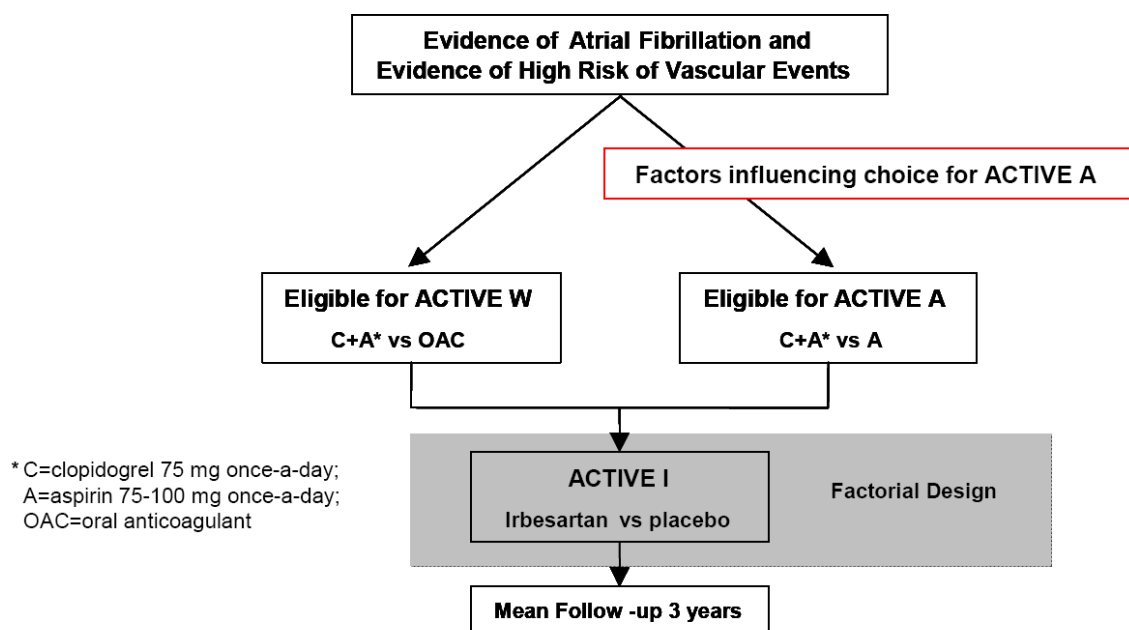
3.2.2 Clinical efficacy

The clinical data to support the extension of the indication is the efficacy data observed with the use of clopidogrel (75 mg QD), in combination with ASA, for reducing the risk of thrombotic events in patients with atrial fibrillation (AF) who have at least one risk factor for vascular events and who cannot take vitamin K antagonist (VKA) therapy. The efficacy data are based on the results of the ACTIVE A study, one of the three studies in the ACTIVE (EFC4912) program entitled "*A parallel randomized controlled evaluation of clopidogrel plus aspirin, with factorial evaluation of irbesartan, for the prevention of vascular events*". The ACTIVE program was a phase 3 study conducted in AF patients with at least one risk factor for vascular events and it comprised 3 separate but interrelated trials: ACTIVE A, ACTIVE W and ACTIVE I (in a partial factorial design).

ACTIVE A study demonstrated that clopidogrel 75 mg once daily in combination with ASA is superior to ASA alone in reducing the risk of vascular events (stroke, MI, non-central nervous system [CNS] embolism and vascular death), and also demonstrated a large reduction in the risk of stroke. ACTIVE W, another part of the ACTIVE program, showed that VKAs are superior to clopidogrel in combination with ASA in AF patients at risk for vascular events who are candidates for receiving VKAs. Taken

together, these two trials provide complete information on the use of clopidogrel in combination with ASA for the prevention of vascular events and stroke in AF patients.

Figure 1 Study design of ACTIVE



Objective of the studies

The EFC4912/ACTIVE program was a phase 3 study conducted in AF patients with at least one risk factor for vascular events, and it comprised 3 separate but interrelated trials: ACTIVE A, ACTIVE W, and ACTIVE I.

The objective of the **ACTIVE W** study was to assess whether clopidogrel in combination with ASA was noninferior to standard adjusted-dose oral anticoagulant (OAC) therapy in those AF patients at risk of vascular events who are candidates to receive VKA.

The objective of the **ACTIVE A** study was to assess whether clopidogrel in combination with ASA was superior to ASA alone (with clopidogrel placebo) in preventing vascular events in those AF patients at risk of vascular events who cannot take VKA (either due to well-accepted clinical factors associated with an increased risk of bleeding or the patient's unwillingness to take VKA). ACTIVE A is considered as the pivotal study to support the indication for this application.

ACTIVE I evaluated in a partial factorial design whether irbesartan 150 mg QD for 2 weeks and then up titrated to 300 mg QD, on top of standard therapy, was superior to placebo for reducing the risk of major vascular events, or major vascular events or hospitalization for cardiac failure. This study is not part of this dossier supporting the proposed indication.

Design of the studies

ACTIVE A was a multicenter, randomized, double-blind, placebo-controlled superiority trial of clopidogrel 75 mg QD in combination with ASA (75-100 mg QD recommended) versus ASA alone (with clopidogrel placebo), in a 1:1 ratio, in AF patients with at least one risk factor for vascular events who could not take VKA. A total of 7500 patients were to be enrolled; each enrolled patient was to be treated with the study drugs and followed up until a final follow-up visit date (planned to occur from 01 to 30 November 2008), targeting at least 1600 adjudicated primary outcome events (stroke, non-CNS systemic embolism, MI, vascular death) to occur in an event driven design. Stroke was the first secondary outcome.

ACTIVE W was a multicenter, prospective, randomized, open-label noninferiority trial of clopidogrel 75 mg QD in combination with ASA (75-100 mg QD highly recommended) versus standard adjusted-dose (target international normalized ratio [INR] 2.0 to 3.0) VKA (ie, oral anticoagulation) in

AF patients with at least one risk factor for vascular events who were candidates to receive VKA. The study was conducted with blinded evaluation of outcomes. A total of 6500 (1:1 ratio) patients were to be enrolled; each enrolled patient was to be treated with the study drugs and followed up until a common study end date (CSED), targeting at least 1450 adjudicated primary outcome events (stroke, non-CNS systemic embolism, MI, vascular death) in an event-driven design. In August 2005, the Data Safety Monitoring Board recommended to the Steering Committee that the ACTIVE W study be stopped due to clear evidence of the superiority of oral anticoagulants over clopidogrel in combination with ASA for the prevention of vascular events in these patients. In September 2005, the study was discontinued per the Steering Committee's decision.

Interim analyses

During the execution of the ACTIVE program, two formal interim analyses of the efficacy results were to be conducted by the DSMB-associated statistician after approximately 1/2 and 3/4 of the anticipated events had occurred in **ACTIVE A** and **ACTIVE W**. The primary efficacy outcome was monitored using a Haybittle-Peto boundary of 4 standard deviations (SDs) in the first half of the study and 3 SDs in the second half. This boundary refers to a treatment difference that is more than the prescribed number of SDs away from the relevant margin and in favor of the respective active therapy. This margin was 0 for ACTIVE A, and $0.171 = \ln(1.186)$ for ACTIVE W. The boundary had to be exceeded on at least two consecutive time points, 3 months apart, in order for a recommendation to be made to stop the study. Two interim analyses to assess futility were to be conducted at the same time as the interim analyses for efficacy (1/2 and 3/4 of expected events occurred). If the upper limit of the 95% confidence interval (CI) for the conditional power for the primary outcome of ACTIVE A fell below 15% then, all other things being equal, the Drug Safety Monitoring Board could recommend early termination. ACTIVE W was to be stopped for safety if, at the time of formal analysis of efficacy, it was demonstrated that clopidogrel plus ASA was significantly worse than oral anticoagulant based on the proposed noninferiority margin. The formal monitoring boundaries outlined for interim analyses would be applied. In other words, if the hazard ratio for clopidogrel plus ASA versus oral anticoagulant exceeded 1.186 by more than 4 SDs in the first half, or 3 SDs in the second half of the trial (must persist on two successive looks, at least 3 months apart), then the DSMB could recommend early termination. These boundaries were considered guidelines, not rules. Any decision for termination was to be based on the pattern of all outcomes (efficacy and safety) within each trial and the totality of evidence from each trial. ACTIVE W was not to be stopped unless, in addition to satisfying the stopping rule for the primary outcome, there was a clear ($p < 0.05$) result for the stroke outcome. Safety aspects, and more specifically severe bleeding, were monitored. No formal boundaries were proposed, but clear, consistent, and persistent evidence of net harm that overwhelmed any benefit had to be apparent. A recommendation to stop the trial was to be based on the pattern of treatment effect across all outcomes, as well as the benefit/risk ratio.

In August 2005, the DSMB recommended to the Steering Committee that the ACTIVE W study be stopped due to clear evidence of superiority of oral anticoagulants over clopidogrel in combination with ASA for the prevention of the vascular events in AF patients. On 05 September 2005, ACTIVE W was discontinued per the Steering Committee's decision. The ACTIVE A study continued to completion as planned.

Eligibility criteria

Patients were eligible for ACTIVE (either ACTIVE A or ACTIVE W) if they had evidence of permanent, paroxysmal or persistent AF (ie, atrial fibrillation at baseline or at least two episodes of intermittent atrial fibrillation in the previous 6 months) and had at least one factor indicating a high risk of vascular events (ie, ≥ 75 years or age 55 to 74 years and either diabetes requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for hypertension; prior stroke, TIA, or non-central nervous system systemic embolus; left ventricular dysfunction with left ventricular ejection fraction $< 45\%$; or documented peripheral vascular disease).

Patients eligible for and willing to take VKA were enrolled into ACTIVE W.

In order to assess the reasons for including a patient in ACTIVE A rather than in ACTIVE W, the following factors were recorded:

- a) inability to comply with INR monitoring
- b) predisposition to falling or head trauma

- c) persistent blood pressure >160/100 mmHg despite treatment
- d) previous serious bleeding while receiving oral anticoagulant
- e) history of severe alcohol abuse within 2 years
- f) chronic renal insufficiency (serum creatinine >2.0 mg/dL)
- g) documented peptic ulcer disease within the last year (but not within the last 6 months);
- h) thrombocytopenia (platelet count <150x10⁹/L)
- i) requirement for chronic (>3 months) non-cyclooxygenase-2 (COX-2) inhibitor non steroidal anti-inflammatory NSAID) therapy
- j) patient's unwillingness to take oral anticoagulant
- k) primary care physician's assessment that oral anticoagulant was inappropriate for this patient
- l) other reason

The above elements provide a description of the target population for the proposed indication.

Disposition of patients

All randomized patients were to be treated with study treatment from randomization to the final follow-up visit (ACTIVE A) or CSED (ACTIVE W) or death. The number and percentage of randomized patients actually receiving study medication, completing treatment, or permanently discontinuing study drug (subdivided by reason) was summarized, and the treatment groups were compared using Pearson's Chi-squared test.

Patients were to be followed up from randomization to the final follow-up visit (ACTIVE A) or CSED (ACTIVE W) or death, whenever possible, regardless of whether or not they discontinued study drug. The status of patients at the end of the study period (completed or lost to follow-up) was summarized. The duration of study participation (follow-up with or without study treatment drug administration) was summarized for each treatment group, along with the total patient-years of follow-up. All durations were calculated relative to the date of randomization.

Extent of exposure

The duration of study drug treatment (accounting for permanent discontinuation) was summarized for each treatment group and overall, including the incidence according to specific intervals of duration (<6, 6 to <12, 12 to <18, and >18 months for ACTIVE W, and additionally including 18 to <24, 24 to <30, 30 to <36, 36 to <42, 42 to ≤48, and >48 months for ACTIVE A). Treatment duration was additionally summarized by age group (<65, 65-74, ≥75) and gender.

Demographic and baseline characteristics

Demographic and baseline patient characteristics were summarized by randomized treatment group and overall using descriptive statistics (continuous variables) or frequencies and percentages (categorical variables). Data summarized included demographic and physical characteristics, heart rate and blood pressure, smoking status, CHADS2 score, select laboratory test results, vascular medical/surgical history, details of the main inclusion criteria, atrial fibrillation history, history of fainting, falling, or fractures, and electrocardiogram results. In addition, selected medications taken prior to randomization, including regular use of ASA or clopidogrel, were summarized. Basic demographic characteristics (age, weight, and height) were summarized by gender and by region.

Baseline/concomitant medications

The use of selected concomitant medications, preprinted on the case report form, was summarized in each treatment group. Specifically for ASA, the dose (mg daily) planned to be given with study drug at the randomization visit and the dose recorded at the final visit for the patient was also summarized by treatment group according to specified dosage intervals (0, <100 mg, ≥100 mg for ACTIVE W) and (no intake, <100, 100, ≥100 mg for ACTIVE A). No recording of the use of proton pump inhibitor (PPI) was done in ACTIVE.

Efficacy endpoints

The primary efficacy endpoint was the first occurrence of the composite cluster of stroke (fatal or nonfatal), MI (fatal or nonfatal), non-CNS systemic embolism, or vascular death. The first secondary endpoint was stroke.

Intended population description

ACTIVE A Patient disposition

A total of 7554 patients were randomly assigned to receive either clopidogrel in combination with ASA (3772 patients) or ASA alone (3782 patients). The mean duration of the study was 3.4 years, with a maximum of 5 years. Overall, the vast majority of randomized patients (99.3%) completed the study (ie, to death or the final follow-up visit). The percentage of patients who permanently discontinued study drug was slightly greater in the clopidogrel in combination with ASA group than in the ASA alone group (35.1% versus 33.0%), mainly linked to subject's request and other reasons (especially requirement for open-label OAC, or occurrence of nonserious AEs or thromboembolic/outcome events).

ACTIVE W Patient disposition

A total of 6706 patients (3335 clopidogrel in combination with ASA and 3371 VKA groups) were enrolled, mostly Caucasian (81%) and male (66%). The mean age was 70 years, and 35% of enrolled patients were older than 75 years. Most of these patients had permanent AF (69%), and 59% had a longstanding history of AF (>2 years). Previous stroke or TIA had occurred in 15% of patients. Most patients (77%) enrolled in ACTIVE W were receiving VKA at the time of randomization. The ACTIVE W population included patients at moderate to high risk for stroke, with a mean CHADS2 score of 1.9; patients receiving or not receiving VKA at the time of enrollment had almost the same mean CHADS2 score.

Statistical methods

Primary efficacy analyses

The primary efficacy outcome was the composite cluster of the first occurrence, over the duration of follow-up (including events occurring after permanent discontinuation of study drug), of the following events as validated by the Event Adjudication Committee: stroke (fatal or nonfatal), MI (fatal or nonfatal), non-CNS systemic embolism, or vascular death.

In **ACTIVE A**, the number and percentage of patients experiencing a primary outcome event were summarized in each treatment group. Event rates were estimated (1, 3, 6, 9, 12, 15, 18, 24, 30, 36, 42, 48, and 54 months) and plotted using the Kaplan-Meier method. The treatment effect of clopidogrel in combination with ASA versus ASA alone, as measured by relative risk reduction and the associated 95% CI, was estimated in the framework of the primary Cox model. The decision that clopidogrel in combination with ASA was superior to ASA alone was made if the computed p-value was ≤ 0.05 .

In **ACTIVE W**, event rates were estimated (months 1, 3, 6, 9, 12, 15, 18, and 21) and plotted using the Kaplan-Meier method. The treatment effect of clopidogrel in combination with ASA versus oral anticoagulant therapy, as measured by the hazard ratio and the associated 95% CI, was estimated using Cox's proportional hazards model. The decision that clopidogrel in combination with ASA was noninferior to oral anticoagulant therapy was to be made if the upper limit of the one-sided 97.5% CI around the hazard ratio excluded 1.186.

Testing of assumptions: The assumption of proportional hazards in the Cox model was tested by examining 2 different models with nonproportional hazards. First, the hazard was allowed to vary monotonically over time by adding a regression parameter β_2 to the standard Cox model, so that the hazard function, $h(t) = h_0(t) \exp(\beta_1 + \beta_2 \log(t))$ where $h_0(t)$ is the baseline hazard, and β_1 measures the treatment effect. In the second approach, the hazard ratio was assumed to be constant within each of four time periods: 0-6 months, 6-12 months, 12-24 months, and 24+ months, but allowed to vary between these periods. The four hazard ratios were compared using a Wald test. There was no statistically significant evidence of nonproportionality.

Interactions with demographic and baseline characteristics, and concomitant medications

The incidence of the primary outcome was summarized by a number of covariates, including age (<65, 65-74, ≥ 75 years), gender, and race, to test for potential interactions with treatment. Other variables of specific clinical interest were history of diabetes, hypertension, coronary artery disease (CAD), and peripheral arterial disease (PAD), prior MI, prior stroke, prior transient ischemic attack, prior stroke/ or transient ischemic attack, previous bleeding, heart failure, factors influencing decision to enroll patient

in ACTIVE A (bleeding, INR, physician request or patient preference) (ACTIVE A only), type of AF (permanent or persistent/paroxysmal), CHADS2 score (≥ 2 and < 2) and region, use of oral anticoagulant at time of randomization, angiotensin converting enzyme (ACE) inhibitors, statins, and beta-blockers, and dose of ASA prescribed at randomization (< 100 mg, ≥ 100 mg) to be taken daily with study drug (ACTIVE A only). The incidence of the primary outcome according to the concomitant use of ACE inhibitors, statins, beta-blockers, and dose of ASA at the final visit (no intake, < 100 mg, ≥ 100 mg).

(ACTIVE A only) was also summarized, although defined on the basis of post-randomization assessments. In this case, results could be confounded with treatment effects and must be interpreted with caution.

Each of these factors was analyzed statistically using a Cox's proportional hazards model with terms for treatment, the covariate and the treatment-by-covariate interaction. The number and percentage of patients experiencing a primary outcome were calculated, and the hazard ratios with 95% CIs were computed to assess the treatment effect within each of the subgroups generated by these analyses. The incidence of stroke was also summarized using the same covariates and analyzed by using the methods described for the analysis of the primary outcome.

Secondary efficacy analyses

Secondary efficacy outcomes were analyzed using the same statistical methodology as for the primary efficacy outcome. A post hoc analysis of ACTIVE W was also performed. All primary and secondary outcomes were analyzed for patients taking VKA at randomization, as well as patients who had not had received VKA at time of randomization.

Summary of results of individual studies

- **ACTIVE A**

The ACTIVE A study, which included 7554 AF patients with at least one risk factor for vascular events who could not receive VKA therapy, mostly enrolled patients receiving ASA (6246 [82.7%]) at the time of randomization. The mean duration of participation was 3.4 years.

ACTIVE A demonstrated that, in AF patients with at least one risk factor for stroke who could not take VKA, clopidogrel in combination with ASA reduced the risk of adjudicated stroke, myocardial infarction, non-CNS embolism and vascular death by 11.1% (95% CI: 2.4 to 19.1; $p = 0.013$). In this composite outcome, the main benefit of clopidogrel in combination with ASA was primarily seen in stroke, with 112 fewer strokes. The benefits of clopidogrel in association with ASA for the primary outcome and for stroke started early and were maintained throughout the duration of the study up to 5 years. The effectiveness of clopidogrel in combination with ASA was seen in all demographics groups and regardless of concomitant medication.

For the secondary outcome of stroke, there was a benefit of clopidogrel in combination with ASA compared to ASA alone, with a relative risk reduction of 28.4% (95% CI: 16.8 to 38.3, $p = 0.00001$). The rate of ischemic stroke was also lower in the clopidogrel in combination with ASA group than in the ASA alone group (1.9% per year versus 2.8% per year; RRR 32.4%, 95% CI: 20.2 to 42.7). There was no significant difference between groups for hemorrhagic stroke (0.8% in the clopidogrel in combination with ASA group versus 0.6% in the ASA alone group).

The benefit was seen for all severities of strokes, as measured by the modified Rankin score, with a greater benefit in disabling or fatal strokes. In addition, 46 fewer nondisabling strokes (modified Rankin Scale of 0 to 2, $p = 0.003$) and 69 fewer disabling or fatal strokes (modified Rankin Scale of 3 to 6) were reported with clopidogrel in combination with ASA compared to ASA alone. Consistently with the primary outcome, the effectiveness of clopidogrel in combination with ASA was seen in all subgroups analyzed. There was a trend for a benefit in reducing the risk of MI in the clopidogrel in combination with ASA group compared with the ASA alone group (RRR 21.9%, 95% CI: -3.0 to 40.7; $p = 0.0789$). Rates for non-CNS embolism and other vascular death were similar in both treatment groups.

In summary, ACTIVE A demonstrated that in AF patients with at least one risk factor for vascular events who could not take VKA, clopidogrel in combination with ASA reduced the risk of major vascular events and reduced the risk of stroke. The statistical significance was greater for disabling stroke.

- **ACTIVE W**

The ACTIVE W study, which included 6706 AF patients with at least one risk factor for vascular events who were eligible to receive oral anticoagulant therapy, enrolled mostly patients receiving VKA (77%) at time of randomization. The mean duration of participation was 14.9 months. In 6706 patients randomized, 234 (7.0%) patients in the clopidogrel in combination with ASA group compared with 166 (4.9%) patients in the VKA group experienced a primary outcome event (stroke, non-CNS systemic embolus, MI or vascular death) (hazard ratio 1.43, 95% CI: 1.17, 1.75). The main advantage of the oral anticoagulant was seen for non-disabling stroke and non- CNS embolism. Except for hemorrhagic stroke (more frequent with VKA) and for total death (similar rates in the VKA and the clopidogrel in combination with ASA groups), there was a greater benefit of VKA for all secondary outcomes. Overall, the observed efficacy in favour of VKA versus clopidogrel in combination with ASA was seen in all demographic subgroups examined and regardless of the usage of specific prior or concomitant medications. However, the significant benefit of VKA over clopidogrel in combination with ASA appeared amplified in patients who had received prior VKA (77% of the ACTIVE W population) and reduced in patients who had not.

In summary, ACTIVE W showed that, in these AF patients with at least one risk factor for vascular events who were candidates to receive VKA, oral anticoagulant therapy is more effective than clopidogrel in combination with ASA for the prevention of vascular events in this population. But this effect was of greater magnitude for those already receiving anticoagulation therapy at the time of randomization and for those remaining in the target INR range during the trial.

Comparison and analyses of results across studies study populations

Disposition of patients

- **ACTIVE A**

A total of 7554 patients were randomly assigned to receive either clopidogrel in combination with ASA (3772 patients) or ASA alone (3782 patients). Overall, the vast majority of randomized patients (99.3%) completed the study (ie, to death or the final follow-up visit). The mean duration of the study was 3.4 years. The percentage of patients who permanently discontinued study drug was slightly greater in the clopidogrel in combination with ASA group than in the ASA alone group (35.1% versus 33.0%), mainly linked to the subject's request and other reasons (especially requirement for open-label OAC, or occurrence of nonserious AEs, or thromboembolic/outcome events). The percentages of patients lost to follow-up (final follow-up visit did not occur and no information on their vital status was available) were similar in both treatment groups. Of this total of 50 patients, 7 had an outcome event before being lost to follow-up.

- **ACTIVE W**

A total of 6706 patients were randomly assigned to receive either clopidogrel in combination with ASA (3335 patients) or VKA (3371 patients). Overall, the vast majority of randomized patients (99.6%) completed the study (ie, to death or the CSED). The mean duration of the study was 14.94 months. The percentage of patients who permanently discontinued study drug was higher in the clopidogrel in combination with ASA group than in the VKA group (11.8% versus 6.8%), mainly due to subject's request and other reasons (especially Investigator/physician request, or nonserious AEs including minor bleeding). The percentages of patients lost to follow-up at the time of database lock (final follow-up visit did not occur and no information on the vital status was available) were higher with VKA (15) compared to clopidogrel and ASA (7). Follow-up information was later obtained for 3 patients in the VKA group, so only 12 patients were confirmed as lost to follow-up in the VKA group.

EFFICACY RESULTS

Primary efficacy outcome(s)

- **ACTIVE A**

ACTIVE A demonstrated that in AF patients with at least one risk factor for stroke who could not take VKA, clopidogrel in combination with ASA compared to ASA alone reduced the risk of stroke, myocardial infarction, non-CNS embolism and vascular death by 11.1% (95% CI: 2.4, 19.1; $p = 0.013$). The annual event rate decreased from 7.6% per year to 6.8% per year. In the composite outcome, the main effect of clopidogrel in combination with ASA was primarily seen in stroke; the benefit was seen for all severities of stroke (RRR of 28.4%, 95% CI: 16.8, 38.3), including disabling and fatal stroke. There was a trend for a benefit in reducing the risk of MI in the clopidogrel in combination with ASA group compared with the ASA alone group ($p = 0.0789$). Rates for non-CNS

embolism and other vascular death were similar in both treatment groups. The benefit of clopidogrel in association with ASA was noted early, increased up to 36 months and was maintained throughout the duration of the study up to 5 years.

- **ACTIVE W**

In 6706 AF patients with at least one risk factor for vascular events and able to receive VKA, 234 (7.0%) patients in the clopidogrel in combination with ASA group compared with 166 (4.9%) patients in the VKA group experienced a primary outcome event (adjudicated stroke, non-CNS systemic embolus, MI or vascular death) (hazard ratio 1.43, 95% CI: 1.17, 1.75; $p = 0.0004$). The main advantage of oral anticoagulation was seen in stroke and in non-CNS embolism. Vascular death rates were similar in both treatment groups. The benefit of oral anticoagulation was noted early and was maintained throughout the duration of the study.

Secondary efficacy outcomes

- **ACTIVE A**

The benefit of clopidogrel in combination with ASA was primarily seen in the reduction of stroke (RRR 28.4%, 95% CI: 16.8, 38.3; $p = 0.00001$), clinically the most devastating complication of AF, with 112 fewer strokes. The rate of ischemic stroke was significantly lower in the clopidogrel in combination with ASA group than in the ASA alone (1.9% per year versus 2.8% per year). There was no statistical difference between groups for hemorrhagic stroke (0.8% in the clopidogrel in combination with ASA group versus 0.6% in the ASA alone group). The effectiveness of clopidogrel in association with ASA for stroke was noted early, increased up to 36 months and was maintained throughout the duration of the study up to 5 years. There was a trend for a benefit in reducing the risk of MI in the clopidogrel in combination with ASA group compared with the ASA alone group (RRR 21.9%, 95% CI: -3.0, 40.7; $p = 0.0789$). There was no difference for non-CNS embolism and for vascular death between the treatment groups.

Stroke severity

The comparative benefit of clopidogrel in combination with ASA was seen for all severities of strokes, as measured by the modified Rankin score, with a greater benefit in disabling or fatal strokes. In addition, 46 fewer nondisabling strokes (modified Rankin Scale of 0 to 2, $p = 0.003$) and 69 fewer disabling or fatal strokes (modified Rankin Scale of 3 to 6, $p = 0.001$) were reported with clopidogrel in combination with ASA compared to ASA alone.

In **ACTIVE A**, 91 patients receiving clopidogrel in combination with ASA compared to 114 patients receiving ASA alone died from stroke. Of these, 16 and 15, respectively, were hemorrhagic strokes in patients receiving clopidogrel in combination with ASA and ASA alone. When considering the outcome of disabling or fatal strokes, there were fewer deaths observed when receiving clopidogrel in combination with ASA compared to ASA alone.

- **ACTIVE W**

Except for hemorrhagic stroke (more frequent with VKA) and total death (similar rates in the VKA and in the clopidogrel + ASA groups), there was a greater benefit of VKA versus clopidogrel in combination with ASA for all secondary outcomes, in particular for stroke (hazard ratio 1.72, 95% CI: 1.24-2.37; $p = 0.0009$).

Discussion on Efficacy

In atrial fibrillation, vitamin-K antagonists have been shown to reduce the risk for stroke by 38% over aspirin therapy and so are recommended for stroke prevention by all guidelines.

In the (ACTIVE) trial program, patients with atrial fibrillation and one or more additional risk factors for stroke were enrolled in one of two trials. If they were considered suitable candidates for warfarin therapy, they were enrolled in **ACTIVE-W**, a comparison of warfarin with the combination of clopidogrel and aspirin. The results of ACTIVE-W showed that use of a vitamin-K antagonist reduced the risk for stroke by 42% over clopidogrel and aspirin. Those considered unsuitable for warfarin therapy were enrolled in ACTIVE-A and randomized to receive clopidogrel (75 mg/day) or placebo on a background of aspirin therapy. The reasons patients were not considered suitable for vitamin-K-antagonist therapy and enrollment in ACTIVE-W included the presence of a specific risk factor for bleeding in 23%, a physician assessment that the patient was inappropriate in 50%, and in 26%, "the only reason given for enrollment in ACTIVE-A was a patient preference not to receive a vitamin-K antagonist."

The primary outcome was a composite of major vascular events, including stroke, MI, non-central-nervous-system (CNS) systemic embolism, or death from vascular causes. A total of 7554 patients were enrolled from 580 centers in 33 countries. Median follow-up was 3.6 years.

The primary outcome was reduced by 11% with the combination of clopidogrel and aspirin, a statistically significant reduction. This reduction was in large part due to a substantial reduction in the outcome of stroke, which was reduced by 28%, a result that is statistically significant. There was a trend to a reduction in MI, but this was not statistically significant. There was no reduction in vascular death and no reduction in non-CNS systemic embolism. During this procedure the CHMP adopted 3 RSI in order to clarify the outstanding issues that the CHMP had regarding efficacy and safety (1st RSI 18 March 2010, 2nd RSI 23 September 2010 and 3rd RSI 21 October 2010).

3.2.3 Clinical safety

No integration of safety data was performed across the 2 studies (ACTIVE A and ACTIVE W) supporting the current application due to differences in study designs (ie, control groups) and in the study duration. Data are generally presented by study in this document. However, cross-study presentations are given for patient baseline characteristics.

Safety parameters

ACTIVE A and ACTIVE W

The primary safety outcome was the rate of major bleeding, over the duration of study follow-up (ie, major bleeding, including that occurring after permanent discontinuation of study drug). Major bleeding events were validated by the EAC.

Secondary safety measures included severe bleeding (as validated by the EAC), minor bleeding, other bleeding, any bleeding, any adverse events, any serious adverse events, death, and other specific events/groups of events occurring in 1% or more of patients or of particular clinical interest including rash or urticaria, allergic reaction, abnormal hepatic function, abnormal renal function, neutropenia, and thrombocytopenia.

Bleeding events

The following definitions for bleeding events were used:

Major bleeding: Major bleeding was defined as any bleeding requiring at least 2 units of red blood cells or whole blood or that met the criteria for severe bleeding.

Severe bleeding: Severe bleeding was defined as bleeding associated with any of the following: death, drop in hemoglobin of at least 5 g/dL, significant hypotension with the need for inotropic agents, intraocular bleeding leading to significant loss of vision, bleeding requiring surgical intervention (other than vascular site repair), symptomatic intracranial hemorrhage or requirement for a transfusion of at least 4 units of blood.

Hemorrhagic stroke was included in both the primary efficacy and safety outcomes. In this safety summary, for both ACTIVE A and ACTIVE W, intracranial hemorrhage (ICH) was defined as any of the following: subdural bleeding, intracerebral bleeding, or hemorrhagic stroke.

TIMI major bleeding: TIMI major bleeding was defined as any fatal bleeding, symptomatic ICH, or bleeding with a drop in hemoglobin of at least 5 g/dL or where the site/source was intracranial.

Minor bleeding: Minor bleeding was defined as any other bleeding requiring modification of the study drug regimen.

All bleeding events were recorded, but only major/severe bleeding events were validated by the EAC. Major bleeding, including ICH, was considered as treatment emergent (on-treatment analysis) if the onset was any time on or after randomization through 28 days after the end of study drug treatment (but not beyond the final follow-up visit for ACTIVE A or the CSED for ACTIVE W).

Bleeding event analyses

The primary safety outcome was the rate of major bleeding validated by the EAC, over the duration of follow-up (including after permanent discontinuation of study drug). The rate of the primary safety outcome was compared between treatment groups using Pearson's Chi-squared test. Furthermore, an analysis of the time to validated major bleeding (Kaplan-Meier plots) was performed using the same statistical time-to-event methodology as for the primary efficacy outcome. The rates of the secondary safety criteria were compared between treatment groups using Pearson's Chi-squared test.

ICH bleeding, including subdural hematomas, hemorrhagic strokes, and other ICH bleeding was summarized. An additional analysis was also performed including events on treatment (+28 days after discontinuation).

Subgroup analyses

The incidence of validated major bleeding was summarized by a number of covariates, including age (<65, 65-74, ≥75), gender, and race to examine their potential effects. Other variables of specific clinical interest were history of diabetes, hypertension, coronary artery disease, and peripheral arterial disease; prior MI, prior stroke, heart failure, prior TIA, prior stroke/ or TIA, previous bleeding, factors influencing decision to enroll patient in ACTIVE A (bleeding, INR, physician request or patient preference) (ACTIVE A only), type of AF (permanent or persistent/paroxysmal), CHADS2 score (≥2 and <2) and region; use of oral anticoagulant (OAC) at randomization, angiotensin converting enzyme (ACE) inhibitors, statins, and beta-blockers, and dose of ASA prescribed at randomization (<100 mg, ≥100 mg) to be taken daily with study drug (ACTIVE A only). The incidence of these bleeding events according to the concomitant use of ACE inhibitors, statins, beta-blockers, and dose of ASA at the final visit (no intake, <100 mg, ≥100 mg) (ACTIVE A only) was also of clinical interest, although defined on the basis of postrandomization assessments. In these cases, the results could be confounded with treatment effects and must be interpreted with caution. Analysis based on renal insufficiency at baseline was not performed due to the low number of patients with creatinemia ≥150 micromole/L. Each of these factors was analyzed using a logistic regression model incorporating terms for treatment, the covariate, and the treatment-by-covariate interaction.

The incidence of severe and ICH bleeding was also summarized using the same covariates and analyzed by using the methods described for the analysis of major bleeding. A post hoc analysis of ACTIVE W was also performed. All major bleeding outcomes were analyzed for patients taking VKA at randomization, as well as patients who had not had received any VKA at the time of randomization.

Adverse event analyses

The frequency of patients experiencing any adverse event, events by organ class, and specific events were summarized in each treatment group using counts and percentages. Summaries according to maximal intensity and relationship to study drug were also produced. For events of particular clinical interest, summary statistics were calculated for the time from randomization to onset and the duration of events.

A summary of all treatment-emergent adverse events by organ class and preferred term, identifying each patient having the event by treatment, intensity, and relationship to study drug, was created. Serious adverse events (including fatal events), serious adverse events leading to death, and adverse events leading to permanent discontinuation of study drug were summarized overall and by organ class and preferred term.

Analysis of adverse events

Bleeding events

Bleeding events which are the most expected with antiplatelet drugs are presented first, followed by other type of AEs.

- **ACTIVE A**

The rate of adjudicated major bleeding (primary safety endpoint), was greater in the clopidogrel in combination with ASA group than in the ASA alone group (251 [6.65%] versus 162 [4.28%]), and this relationship was also seen for severe bleeding (190 [5.04%] versus 122 [3.23%]). When considering the rate of emergent major bleeding that occurred during the treatment period (+ 28 days after discontinuation), the rate was 205 (5.4%) with clopidogrel in combination with ASA versus 111 (2.9%) with ASA alone.

The annual event rate of major bleeding was 2.0% in the clopidogrel in combination with ASA group versus 1.3% in the ASA alone group. For severe bleeding, the annual event rates were 1.5% and 1.0%,

respectively. There was no excess of fatal bleeding, which was rare in both groups. The excess of major or severe bleeding started early and continued to increase during the study up to 5 years. [There was an excess of all types of bleeding with clopidogrel in combination with ASA, consistent with results with dual antiplatelet therapy in previous clinical studies conducted in other clinical settings and also consistent with the known safety profile of clopidogrel.

Major bleeding was mostly of extracranial origin in both groups (200 in the clopidogrel + ASA group; 134 in the ASA alone group), mainly from the gastrointestinal tract). There were 5 fatal bleeds of gastrointestinal origin in both groups. There was an excess of intracranial bleeding (54 [1.43%] versus 29 [0.77%], respectively; hazard ratio 1.86; 95% CI: 1.19-2.93) in the clopidogrel + ASA treatment group. When considering emergent ICH that occurred during the treatment period (+ 28 days after discontinuation), the rate of ICH was 46 (1.2%) with clopidogrel in combination with ASA versus 18 (0.5%) with ASA alone (hazard ratio 2.50; 95% CI: 1.45-4.32).

The rate of hemorrhagic stroke did not differ between groups, and the main cause of the imbalance between groups for ICH was related to subdural hematoma (ITT analysis and on-treatment analysis). In addition, analysis of the subdural hematoma outcome showed that, among those that were not fatal, 15 recovered spontaneously (10 on clopidogrel in combination with ASA versus 5 on ASA alone).

- **ACTIVE W**

The rate of major bleeding, as well as severe bleeding, did not differ between groups. Fatal bleeding was rare in both groups.

Intracranial bleeding rates (including subdural hemorrhage) were 0.7% with VKA versus 0.4 % with clopidogrel in combination with ASA. This imbalance was mainly due to a difference in the rate of hemorrhagic stroke, which was more frequent with VKA compared to clopidogrel in combination with ASA. When considering ICH that occurred during the treatment period (+28 days after discontinuation), the rate of ICH was 0.4% with clopidogrel in combination with ASA versus 0.7 % with VKA (hazard ratio 0.52; 95% CI: 0.26-1.05).

Other common adverse events

- **ACTIVE A**

Overview of adverse events

The overall incidence of TEAEs, and SAEs with an outcome of death was similar between the 2 treatment groups. The rate of SAEs and AEs leading to discontinuation of study drug was slightly higher in the clopidogrel in combination with ASA group than in the ASA alone group

Display of adverse events

The overall incidence of TEAEs by primary system organ class was similar between the 2 treatment groups except for "gastrointestinal disorders SOC," which were more frequently reported in the clopidogrel in combination with ASA group than in the ASA alone group, and "injury, poisoning and procedural complications SOC". Individual adverse events (preferred terms) were generally infrequently reported.

For non-hemorrhagic AEs occurring in at least 1% of patients in either treatment group, contusion (mainly reported as bruises) was more frequently reported in the clopidogrel in combination with ASA group compared to the ASA alone group.

- **ACTIVE W**

Overview of adverse events

The overall incidence of treatment-emergent AEs, SAEs, and SAEs with an outcome of death was similar between the 2 treatment groups. The rate of AEs leading to discontinuation was higher in the clopidogrel in combination with ASA group than in the VKA group, due to gastrointestinal disorder.

Display of adverse events

The overall incidence of TEAEs by system organ class was similar between the 2 treatment Groups. Overall, the incidence of TEAEs was similar between the 2 treatment groups. Consistent with findings from ACTIVE A, for non-hemorrhagic AEs occurring in at least 1% of patients

in either treatment group, contusion (mostly described by the Investigator as bruises) was more frequently reported in the clopidogrel in combination with ASA group compared to the VKA group.

Deaths

Of note, cardiovascular deaths were included in the primary efficacy outcome and as such were not reported as serious adverse events. Non-cardiovascular deaths (including major bleeding) were reported as serious adverse events.

- **ACTIVE A**

There was no difference in the overall mortality rate between the 2 treatment groups.

Overall, the incidence of treatment-emergent SAEs leading to death was similar between the 2 treatment groups, and no specific SAE leading to death was identified. Of note, cardiovascular deaths were included in the primary efficacy outcome and as such were not reported as serious adverse events. Non-cardiovascular deaths (including major bleeding) were reported as serious adverse events.

- **ACTIVE W**

There was no difference in the total death rate between the 2 treatment groups.

Overall, the incidence of treatment-emergent SAEs leading to death was similar between the 2 treatment groups. Non-hemorrhagic-emergent SAEs leading to death were infrequently reported. Of note, cardiovascular deaths were included in the primary efficacy outcome and as such were not reported as serious adverse events. Non-cardiovascular deaths (including major bleeding) were reported as serious adverse events. Descriptions of CV death rate (an efficacy outcome) are presented in the clinical study report.

Other serious adverse events

- **ACTIVE A**

The overall incidence of treatment-emergent SAEs by system organ class was slightly higher in the clopidogrel in combination with ASA group than in the ASA alone group, mainly due to gastrointestinal serious disorders (mainly gastrointestinal bleeding). The most common SAE reported was pneumonia, no other individual SAEs were infrequently reported.

- **ACTIVE W**

The overall incidence of treatment-emergent SAEs by system organ class was similar between the treatment groups, with a slightly greater rate of serious gastrointestinal bleeding disorders in the clopidogrel in combination with ASA group than in the VKA group. The overall incidence of treatment emergent SAEs was similar between the treatment

Discussion on Safety

The safety profile of clopidogrel is well established and no new safety concerns were discovered during the analysis of ACTIVE A and W trials. What must be analysed is the rates on known risks namely bleeding in the context of the benefits.

When stroke severity was evaluated by treatment, there was a similar effect on both disabling and fatal vs non disabling strokes with clopidogrel; disabling strokes accounted for about 65% of all strokes in ACTIVE-A. Overall, there were 26 fewer fatal ischemic strokes and three more fatal hemorrhagic strokes with clopidogrel, for a net reduction of fatal strokes of 23.

However, the rate of major bleeding was significantly increased, from 1.3% to 2.0% per year, with treatment, and there was a trend to increased fatal bleeding that did not reach statistical significance. There were also significant increases in intracranial and extracranial bleeding.

1.3. SPC Changes

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of atherothrombotic events

Clopidogrel is indicated in ~~adults for the prevention of atherothrombotic events in:~~

- Adult pPatients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- Adult pPatients suffering from acute coronary syndrome:
 - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
 - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

For further information please refer to section 5.1.

4.2 Posology and method of administration

[...]

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Breastfeeding

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breastfeeding should not be continued during treatment with Plavix.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.8 Undesirable effects

Clopidogrel has been evaluated for safety in more than ~~42,000~~44,000 patients who have participated in clinical studies, including over ~~9,000-12,000~~ patients treated for 1 year or more. ~~The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below.~~ Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY, COMMIT and ACTIVE-A studies are discussed below. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

[...]

In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo +ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

5.1 Pharmacodynamic properties

[...]

The safety and efficacy of clopidogrel have been evaluated in ~~45~~ double-blind studies involving over ~~80,000~~88,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, ~~and~~ COMMIT and ACTIVE-A studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

[...]

Atrial fibrillation

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.

The ACTIVE-A study (N=7,554) was a multicenter, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA (N=3,772) to placebo + ASA (N=3,782). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age ≥ 75 years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction $< 45\%$; or documented peripheral vascular disease. The mean CHADS₂ score was 2.0 (range 0-6).

The major exclusion criteria for patients were documented peptic ulcer disease within the previous 6 months; prior intracerebral hemorrhage; significant thrombocytopenia (platelet count $< 50 \times 10^9/l$); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

Seventy-three percent (73%) of patients enrolled into the ACTIVE-A study were unable to take VKA due to physician assessment, inability to comply with INR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk of bleeding; for 26% of the patients, the physician's decision was based on the patient's unwillingness to take VKA.

The patient population included 41.8 % women. The mean age was 71 years. 41.6% of patients were ≥ 75 years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group (relative risk reduction of 11.1%; 95% CI of 2.4% to 19.1%; $p=0.013$), primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA (relative risk reduction, 28.4%; 95% CI, 16.8% to 38.3%; $p=0.00001$).

2. Conclusion

On 18 November 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

3. EPAR changes

The EPAR will be updated following the granting of a Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

EPAR scope:

The MAH is applying for an extension of indication of clopidogrel film-coated tablets for the prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation who have at least one risk factor for vascular events and who cannot take vitamin K antagonist (VKA) therapy.

Summary / scientific discussion:

A randomized double-blind, placebo-controlled, superiority study of clopidogrel (75 mg once daily) in combination with acetylsalicylic acid (75-100 mg once daily recommended) versus acetylsalicylic acid alone has been conducted in patients with atrial fibrillation patients and at least one risk factor for vascular events who cannot take VKA (EFC4912/ACTIVE-A study). In the (ACTIVE) trial program, patients with atrial fibrillation and one or more additional risk factors for stroke were enrolled in one of two trials. If they were considered suitable candidates for warfarin therapy, they were enrolled in ACTIVE-W, a comparison of warfarin with the combination of clopidogrel and aspirin. The results of ACTIVE-W showed that use of a vitamin-K antagonist reduced the risk for stroke by 42% over clopidogrel and aspirin. Those considered unsuitable for warfarin therapy were enrolled in ACTIVE-A and randomized to receive clopidogrel (75 mg/day) or placebo on a background of aspirin therapy. The safety profile of clopidogrel is well established and no new safety concerns were discovered during the analysis of ACTIVE A and W trials what must be analysed is the rates on known risks namely bleeding in the context of the benefits.