Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Clopidogrel/Aspirin

## Proprietary Product Name: CoPlavix/DuoCover

## Sponsors: Sanofi-Aventis Australia Pty Ltd and Bristol-Myers Squibb Australia Pty Ltd

**July 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | Extension of Indications |
| *Decision:* | Withdrawn with amendments to the Product Information (PI) |
| *Date of Decisions:* | Withdrawal: 11 March 2011, PI update: 7 April 2011 |
| *Active ingredient(s):* | Clopidogrel/aspirin |
| *Product Name(s):* | CoPlavix/DuoCover |
| *Sponsor's Name and Address:* | Sanofi-Aventis Australia Pty Ltd<br>12-24 Talavera Road<br>Macquarie Park NSW 2113<br><br>Bristol-Myers Squibb Australia Pty Ltd<br>556 Princes Highway<br>Noble Park Vic 3174 |
| *Dose form(s):* | Film coated tablets |
| *Strength(s):* | Clopidogrel 75 mg/aspirin 75 mg and clopidogrel 75 mg/aspirin 100 mg |
| *Container(s):* | Blister packs |
| *Pack size(s):* | Packs of 7 and 30 tablets |
| *Approved Therapeutic use:* | *Tradename* is a fixed-dose combination product intended as continuation of therapy in patients with acute coronary syndrome already initiated with separate clopidogrel and aspirin products:<br><br>Unstable angina or non-ST-elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischaemia). *Tradename* is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).<br><br>ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, *Tradename* has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke in medically treated patients eligible for thrombolytic therapy. |
| *Route(s) of administration:* | Oral |
| *Dosage:* | Treatment is initiated with or without a loading dose depending on the indication and then continued at a daily dose of one tablet. |
| *ARTG Number (s):* | 150443, 150448, 150469, 150470, 150473, 150474, 150477, 150478, 150479 |

## Product Background

Clopidogrel is an inhibitor of platelet aggregation: it selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP mediated activation of the glycoprotein (GP) IIb/IIIa complex. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Unlike acetylsalicylic acid (aspirin), clopidogrel has no activity on arachidonic acid metabolism in platelets. Hepatic biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation.

Clopidogrel is currently available as film coated tablets and is indicated in adults for the prevention of vascular ischaemia associated with atherothrombotic events (myocardial infarction, stroke and vascular death) in patients with a history of symptomatic atherosclerotic disease.

Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and the production of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

The currently approved indications and dosage recommendations for the combination of clopidogrel and aspirin are as follows:

*Tradename is a fixed-dose combination product intended as continuation of therapy in patients with acute coronary syndrome already initiated with separate clopidogrel and aspirin products:*

- *Unstable angina or non-ST-elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischaemia). Tradename is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).*
- *ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, Tradename has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke in medically treated patients eligible for thrombolytic therapy.*

This AusPAR describes the evaluation process for a submission by the sponsor of CoPlavix, Sanofi-Aventis Australia Pty Ltd (which also applies to DuoCover, sponsored by Bristol-Myers Squibb Australia Pty Ltd) for a proposed extended indication which is:

*CoPlavix/DuoCover is indicated 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. In adult patients with atrial fibrillation at increased risk of vascular events who can take VKA therapy, VKA has been shown to be associated with a better clinical benefit than aspirin alone or the combination of clopidogrel and aspirin for the reduction of stroke.*

The proposed dosage regimen for the atrial fibrillation (AF) indication is:

In patients with atrial fibrillation, CoPlavix/DuoCover is for initiation and maintenance therapy, given as a single tablet (75 mg/75 mg or 75 mg/100 mg) once a day taken with adequate water.

The dosage regimen for the acute coronary syndrome indication as stated in the product information (PI) is:

CoPlavix/DuoCover is used following an initial loading dose of 300 mg clopidogrel in combination with aspirin in patients with acute coronary syndrome:

- Unstable angina or non-ST elevation myocardial infarction:
  - Treatment should be initiated with a single 300 mg loading dose of clopidogrel plus aspirin (75 mg to 325 mg).
  - Long term daily treatment should be continued with one CoPlavix/DuoCover tablet (75 mg/75 mg or 75 mg/100 mg) once a day taken with adequate water.
- ST segment elevation acute myocardial infarction:
  - Treatment should be initiated with or without a 300 mg loading dose of clopidogrel in combination with aspirin and with or without thrombolytics as soon as possible after symptoms start. There are no data on the use of a 300 mg loading dose in elderly patients (aged 75 years or more) with ST segment acute myocardial infarction, as no patients over 75 years old were included in the CLARITY study and no loading dose was used in the COMMIT study.[1,2]
  - Daily treatment should continue with one CoPlavix/DuoCover tablet (75 mg/75 mg or 75 mg/100 mg) once a day with adequate water. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting.

In patients who have had percutaneous coronary intervention with stent insertion, clopidogrel and aspirin should be continued for as long as is currently recommended in evidence based guidelines for the type of stent and circumstances of implantation or for as long as otherwise indicated, taking into account the overall atherothrombotic risk profile of the patient.

Should doses of aspirin greater than 100 mg be required for daily maintenance therapy, clopidogrel and aspirin products should be administered separately.

In addition to CoPlavix and Duocover, the submission also relates to the identical products Clopidogrel Winthrop plus Aspirin, DuoPlavix, Plavasa and Plavix Combi. It will be referred to as CoPlavix for the remainder of this AusPAR

## Regulatory Status

In Australia, in July 2002, clopidogrel in combination with aspirin was initially indicated for acute coronary syndrome (ACS) to reduce atherothrombotic events. In September 2009, a fixed dose combination tablet of clopidogrel/aspirin was registered in Australia.

In Australia the application has been submitted for CoPlavix (clopidogrel and aspirin), as this was the only country where the fixed dose combination was approved at time of the indication extension submission.

The application to extend the indication for clopidogrel to include the prevention of atherothrombotic and thromboembolic events in atrial fibrillation has been submitted in the USA (December 2009), Canada, Switzerland (both February 2010) and the European Union (EU) under the Centralised Procedure.

In the EU, a positive Committee for Medicinal Products for Human Use (CHMP) Opinion was adopted on 18 November 2010 to extend indication as follows:

*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 in medically treated patients eligible for thrombolytic therapy.*

[1] CLARITY study: Clopidogrel as Adjunctive Reperfusion Therapy
[2] COMMIT study: Clopidogrel and Metoprolol in Myocardial Infarction Trial Cox Cyclooxygenase

### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

### Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

# III. Nonclinical Findings

### Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

# IV. Clinical Findings

### Introduction

The efficacy and safety data all derive from the same study, the ACTIVE study, which was a Phase III, multicentre study conducted in atrial fibrillation (AF) patients at risk of vascular events which comprised three separate but related trials:

ACTIVE W (a multicentre, prospective, randomized, non-inferiority trial of clopidogrel in combination with aspirin (ASA) compared with standard care oral anticoagulant) for patients who were candidates to receive VKAs;[3]

ACTIVE A (a multicentre, randomized, superiority trial of clopidogrel in combination with ASA versus ASA alone [with clopidogrel placebo]) for patients who could not receive VKA;

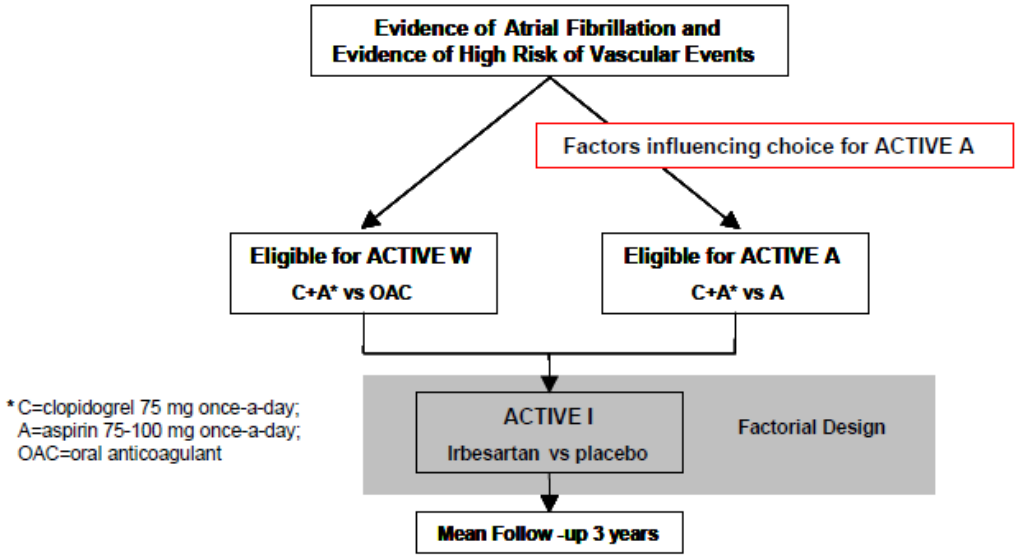
ACTIVE I (a multicentre, randomized, double blind, placebo controlled superiority trial of irbesartan) in a partial factorial design.

Data from the ACTIVE I trial were not included in the submission.

The ACTIVE Study is demonstrated diagrammatically in Figure 1.

[3] ACTIVE study: Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events

**Figure 1: Design of the ACTIVE study**




## Pharmacology

No new pharmacokinetic or pharmacodynamic data were included in the submission.

## Efficacy

### Efficacy Data for Clopidogrel/ASA Compared With ASA

#### *Study EFC4912A - ACTIVE A*

This was a multinational, multicentre, randomised, double blind, placebo controlled superiority trial of clopidogrel in combination with ASA compared with ASA alone; with factorial evaluation of irbesartan. The study was conducted at 580 sites in 33 countries, including Australia. Data from the factorial analysis of irbesartan was not included in the submission.

The inclusion criteria included:

AF, as evidenced by permanent, paroxysmal or persistent AF.

- AF demonstrated by baseline electrocardiogram (ECG) (unless cardiovascular surgery was performed in the previous month)
- AF documented by ECG on two separate occasions, at least 2 weeks apart in the 6 months prior to randomization (and not within 1 month of cardiovascular surgery), documented by routine ECG, rhythm strip, Holter ECG or pacemaker atrial lead telemetry electrogram.

High risk of vascular events as evidenced by at least one of the following risk criteria:

- age 75 years or greater
- on treatment for systemic hypertension
- prior stroke, transient ischaemic attack (TIA) or non-central nervous system (CNS) systemic embolus

- left ventricular dysfunction with left ventricular ejection fraction (EF) estimated by echocardiogram or angiogram (radionuclide or contrast) to be <45%
- peripheral vascular disease (previous peripheral artery revascularization, limb and foot amputation, or the combination of current intermittent claudication and ankle arm systolic blood pressure ratio <0.9)
- age 55 to 74 years and either diabetes mellitus requiring drug therapy or documented previous MI or documented coronary artery disease

Investigators assigned patients to ACTIVE A or ACTIVE W based on assessment of the absolute risks of stroke and bleeding according to the American College of Cardiology (ACC)/ American Heart Association (AHA)/ European Society of Cardiology (ESC) practice guidelines. Patients able and willing to receive oral anticoagulants with usual clinical care and willing to take Vitamin K antagonists (VKA) were enrolled in ACTIVE W; and those who were not eligible or unwilling to take VKA were enrolled into ACTIVE A.

Factors affecting eligibility to take VKA included:

- inability to comply with international normalized ratio (INR) monitoring
- predisposition to falling or to head trauma
- persistent blood pressure >160/100 mmHg despite treatment
- previous serious bleeding while receiving oral anticoagulant
- history of severe alcohol abuse within 2 years
- chronic renal insufficiency (serum creatinine >2.0 mg/dL)
- documented peptic ulcer disease within the last year (but not within the last 6 months)
- thrombocytopenia (platelet count <150 x $10^9$/L)
- requirement for chronic (>3 months) non-cyclooxygenase-2 (COX-2) inhibitor nonsteroidal antiinflammatory drug (NSAID) therapy
- patient's unwillingness to take oral anticoagulant
- primary care physician's assessment that oral anticoagulant was inappropriate for this patient

The exclusion criteria included:

- requirement for clopidogrel (such as recent coronary stent procedure)
- requirement for oral anticoagulant (such as prosthetic mechanical heart valve)
- prior intolerance to ASA or clopidogrel
- documented peptic ulcer disease within the previous 6 months
- prior intracerebral haemorrhage
- significant thrombocytopenia (platelet count <50 x $10^9$/L)
- ongoing alcohol abuse
- mitral stenosis

- pregnant or nursing women or women of child bearing potential and not on effective birth control for at least 1 month prior to start of study or not willing to continue on birth control for duration of study
- severe comorbid condition such that the patient was not expected to survive 6 months

The study treatments were:

1. Clopidogrel 75 mg and ASA (75 to 100 mg) once daily
2. Placebo and ASA (75 to 100 mg) once daily

The dose of ASA (75 or 100 mg) was at the discretion of the investigator. Treatment duration was up to 5 years. Randomization was by patient identification number and treatment identification number using an automated voice response system. There was block randomization by study centre. Oral anticoagulants, ticlopidine, open label clopidogrel and dipyridamole were not allowed as concomitant treatments.

The primary efficacy outcome measure used a composite outcome measure comprising the first episode of: stroke (fatal or nonfatal), MI (fatal or nonfatal), non-CNS systemic embolism, or vascular death. The clinical definitions used for the purposes of the study included:

- The diagnosis of stroke required focal neurological symptoms with rapid onset, lasting at least 24 hours.
- Myocardial infarction (MI) was considered to have occurred if any of the three following criteria were met:
    - Typical rise and gradual fall of troponin or more rapid rise and fall of biochemical markers (creatinine kinase, myocardial bound [CK-MB]) of myocardial necrosis with at least one of the following: (a) ischaemic symptoms, (b) development of pathological Q-waves on the ECG, (c) ECG changes indicative of ischaemia, (d) coronary artery intervention
    - Pathological findings of an acute MI
    - New pathologic Q-wave on routine 12 lead ECG in patients suffering from diabetes mellitus
- Non-CNS systemic embolism was judged to have occurred where there was a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which was supported by evidence of embolism from surgical specimens, autopsy, angiography or other objective testing.
- Vascular death was considered to have occurred when there was no obvious nonvascular event to explain death, such as cancer, trauma or respiratory failure. Sudden or unwitnessed deaths were considered vascular.

The secondary efficacy endpoints were:

- First occurrence of stroke (nonfatal or fatal/ischaemic, haemorrhagic, or of uncertain type)
- Total death (cardiovascular and non-cardiovascular).
- First occurrence of MI (nonfatal or fatal)
- Non-CNS systemic embolism
- Vascular death

The safety outcome outcomes of special interest were:

- Major bleeding, defined as any bleeding requiring at least two units of red blood cells or equivalent whole blood or that met the criteria for severe bleeding. Severe bleeding was defined as bleeding associated with any of the following: death, drop in haemoglobin 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 haemorrhage (ICH) or requirement for a transfusion of at least 4 units of blood. Haemorrhagic stroke was part of the primary endpoint. Intracranial haemorrhage was defined as the cluster of any symptomatic intracranial haemorrhage, or any site or source of intracranial bleeding, that is, subdural bleeding, intracerebral bleeding and haemorrhagic stroke.
- Minor bleeding was defined as any other bleeding requiring modification of the study drug regimen.

Other safety outcome measures were: adverse effects (AEs); vital signs; ECGs; and episodes of fainting or loss of consciousness. There were follow up assessments at 1, 3, 6, 9, 12 months, and then every 6 months until the final follow up visit.

*Statistical Analysis for Study EFC4912A - ACTIVE A*

Hypothesis tests for efficacy were performed using Kaplan-Meier plots and Cox proportional hazards models. The rate of the primary safety outcome was compared between treatment groups using Pearson's Chi squared test. All hypothesis tests were performed using two sided tests at the 5% significance level.

The sample size calculation was performed using data from the Stroke Prevention in Atrial Fibrillation (SPAF) I, II and III trials, which included 2012 patients with AF who were treated with ASA. The primary outcome measure in the SPAF trials was ischaemic stroke, which differs from the composite primary efficacy outcome measure used in ACTIVE A. The rate of vascular events in the ACTIVE A ASA group was expected to be around 8% per year. To ensure at least 90% power to detect a 15% reduction, the study required a minimum of 1600 adjudicated events. This was estimated to require a sample size of 7500 subjects with an enrolment period of 3 years and subsequent follow up period of 2.5 years.

The currently approved indication for ASA in Australia does not specifically state prevention of thromboembolic events in adult patients with atrial fibrillation and at least one risk factor. The currently approved indication for ASA in Australia is:

*Prophylaxis and treatment of transient ischaemic attacks and other thromboembolic disorders.*

*Used in conjunction with anticoagulant therapy, to reduce the risk of systemic embolism and vascular death in post surgical patients who have undergone heart valve replacement.*

Hence, ASA is not an appropriate comparator treatment for the indication sought in the current application. ASA could therefore be viewed as a concomitant treatment in the placebo group. The study was not designed to demonstrate comparative efficacy for clopidogrel alone, but can be used to demonstrate efficacy compared with ASA.

Two formal interim analyses of the efficacy results were conducted after approximately 1/2 and 3/4 of the anticipated events had occurred. There was no adjustment for multiplicity.

*Results for Study EFC4912A - ACTIVE A*

A total of 7554 subjects were randomized to treatment: 3772 to clopidogrel/ASA and 3782 to placebo/ASA. There was a high completion rate: 99.3% in the clopidogrel/ASA group and 99.4% in the placebo/ASA. Only 25 (0.7%) subjects in the clopidogrel/ASA group and 24 (0.6%) in the placebo/ASA were lost to follow up. The rate of discontinuation of treatment was similar for the two treatment groups: 1323 (35.1%) subjects in the clopidogrel/ASA group and 1246 (33.0%) in the placebo/ASA. The treatment groups were similar in demographic and baseline characteristics. The age range was 25 to 102 years, 4397 (58.2%) subjects were male and 3157 (41.8%) were female. Some of the ranges of the demographic variables suggest data entry errors: for example, minimum body mass index (BMI) of 1.65 kg/m$^2$, minimum systolic blood pressure of 65 mmHg. The distribution of $CHADS_2$ scores was similar for the two treatment groups.[4] The characteristics of atrial fibrillation, past medical history, inclusion factors and concomitant medications at both the time of enrolment and those commenced during the study and ASA exposure during the study was similar for the two treatment groups.

For the primary efficacy outcome measure clopidogrel/ASA was superior to placebo/ASA: relative risk reduction (RRR) (95% confidence interval [CI]) 11.1% (2.4% to 19.1%) p=0.0133 (Table 1).

**Table 1: Summary of frequency of adjudicated primary outcome events**

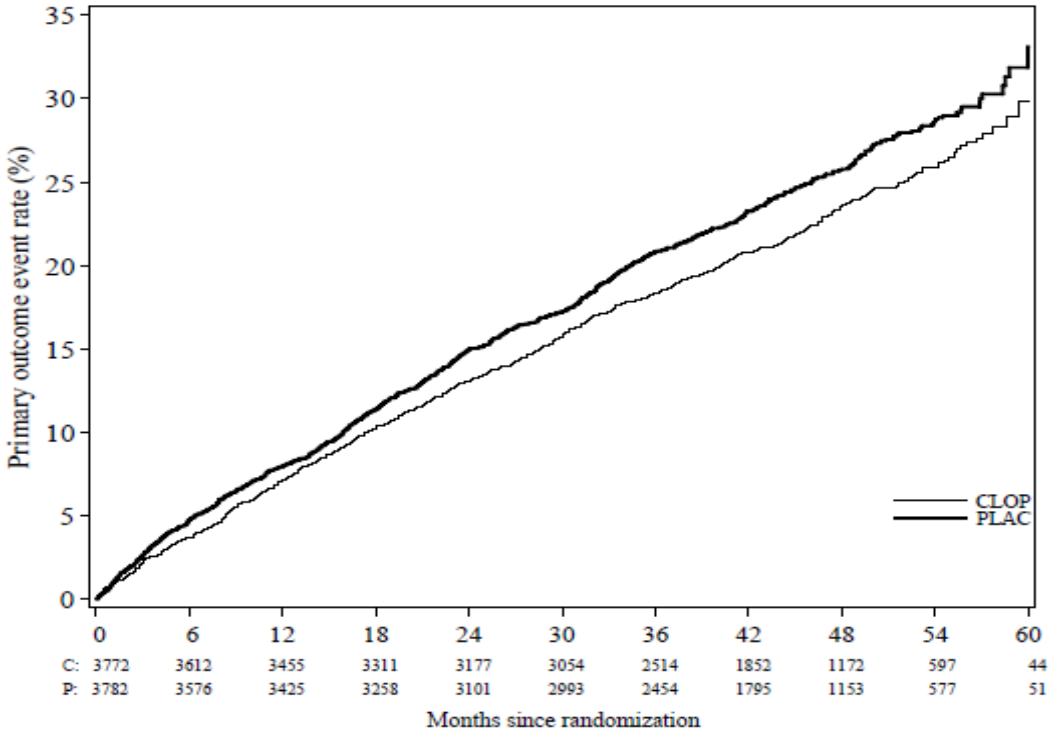
| | No. (%) of Events | | | |
|---|---|---|---|---|
| **Primary Outcome** | **Clopidogrel + ASA (N=3772)** | **Placebo + ASA (N=3782)** | **Relative Risk Reduction (%) (95% CI)** | **p-Value** |
| MI/Stroke/Non-CNS systemic embolism/Vascular death [a] | 832 (22.06) | 924 (24.43) | 11.1 (2.4 to 19.1) | 0.0133 |
| MI (fatal or not) | 84 (2.23) | 105 (2.78) | | |
| Stroke (fatal or not) | 285 (7.56) | 391 (10.34) | | |
| Non-CNS systemic embolism | 50 (1.33) | 48 (1.27) | | |
| Vascular death | 413 (10.95) | 380 (10.05) | | |

[a] Only the first event was counted.
CNS = central nervous system; MI = myocardial infarction.
Note: Two additional primary outcome events (1 MI in the clopidogrel + ASA group and 1 vascular death in the ASA alone group) were reported after database lock. These events are not included in the table.

The Kaplan-Meier analysis indicated that the treatment effect appears to increase over time, in proportion to time (Figure 2).

[4] **$CHADS_2$**: **C**ongestive heart failure, **H**igh blood pressure, **A**ge, **D**iabetes, **S**troke **2** (cerebrovascular accident/transient ischaemic attack)

**Figure 2: Event rate over time for adjudicated primary outcome events**




The absolute difference in event rate at 12 months was 0.78% (-0.41% to 1.98%), at 36 months was 2.45% (0.62% to 4.27%) and at 54 months was 2.82% (0.39% to 5.26%) (Table 2). Therefore, for the prevention of the primary outcome variable the number needed to treat (NNT) for 1 year was 128, for 3 years was 41 and for 4.5 years was 35. This translates to treating 35 subjects for 4.5 years in order to prevent one subject from having an event during that time. For investigator reported primary outcome events the result was similar: RRR (95% CI) 12.0% (3.4% to 19.9%) p=0.0073. Prior medical history and concomitant mediation did not influence efficacy.

**Table 2: Summary of cumulative event rates for primary outcome**

| | Cumulative Event Rate (%) | | Absolute |
|---|---|---|---|
| Time (Months) | Clopidogrel + ASA (N=3772) | Placebo + ASA (N=3782) | Difference (%) (95% C.I.) |
| Month 1 | 0.85 | 0.87 | 0.02 (-0.39 to 0.44) |
| Month 3 | 2.26 | 2.62 | 0.37 (-0.33 to 1.06) |
| Month 6 | 3.69 | 4.72 | 1.03 (0.12 to 1.93) |
| Month 9 | 5.49 | 6.43 | 0.94 (-0.13 to 2.01) |
| Month 12 | 7.15 | 7.93 | 0.78 (-0.41 to 1.98) |
| Month 18 | 10.31 | 11.36 | 1.06 (-0.35 to 2.47) |
| Month 24 | 13.06 | 14.97 | 1.91 (0.34 to 3.49) |
| Month 30 | 15.75 | 17.20 | 1.45 (-0.24 to 3.14) |
| Month 36 | 18.37 | 20.81 | 2.45 (0.62 to 4.27) |
| Month 42 | 20.75 | 23.22 | 2.46 (0.52 to 4.41) |
| Month 48 | 23.55 | 25.76 | 2.20 (0.06 to 4.35) |
| Month 54 | 25.90 | 28.72 | 2.82 (0.39 to 5.26) |

The results of the secondary efficacy outcome variables supported the primary efficacy outcome variable. For stroke overall there was a statistically significant reduction in risk: RRR (95% CI) 28.4% (16.8% to 38.3%) p=0.00001 (Table 3). Note that the numbers of events differ from Table 1 because the primary efficacy outcome was the occurrence of the first event of any of those listed in the composite primary efficacy outcome measure, while

Table 3 summarized the occurrence of the first event for each of the individual secondary efficacy outcome measures.

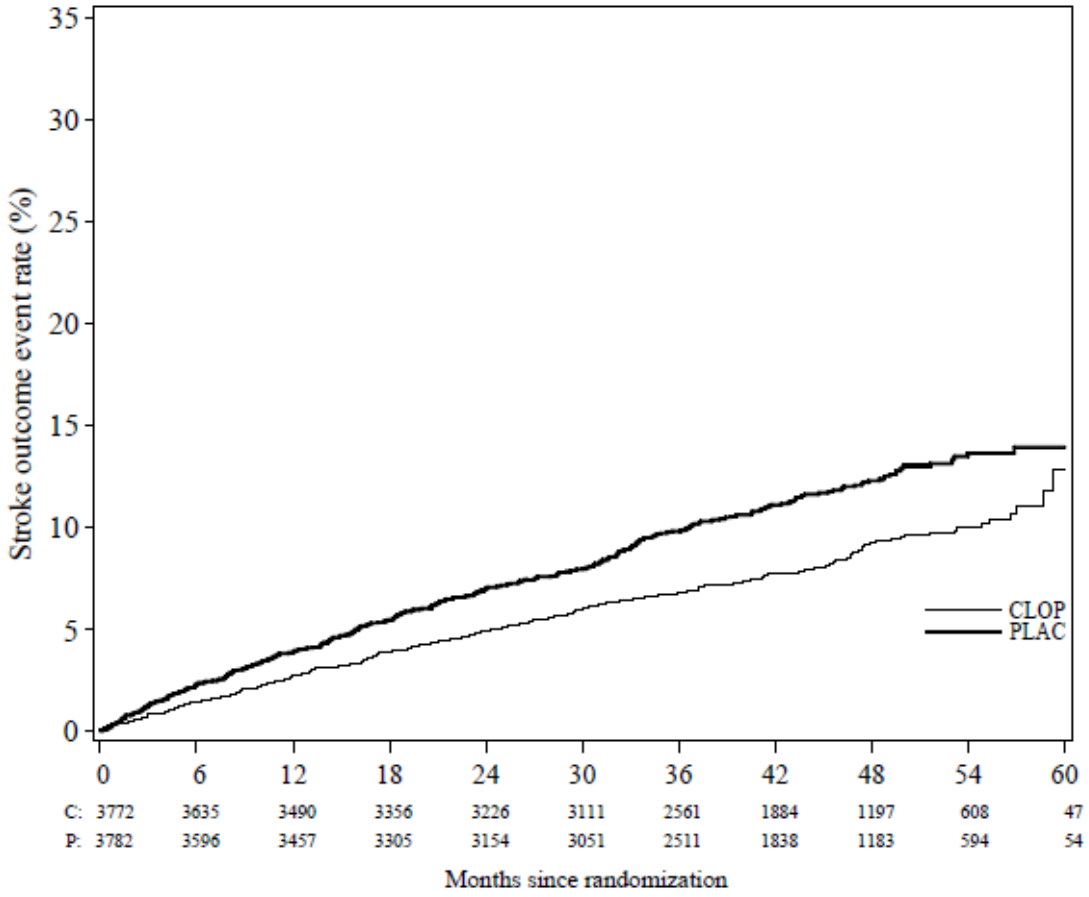
**Table 3: Summary of frequency of secondary and other outcomes (ITT - adjudicated outcome events)**

| Outcome | No. (%) of Events: Clopidogrel + ASA (N=3772) | No. (%) of Events: Placebo + ASA (N=3782) | Relative Risk Reduction (%) (95% CI) | p-Value |
|---|---|---|---|---|
| Stroke (fatal or not) | 296 (7.85) | 408 (10.79) | 28.4 (16.8 to 38.3) | 0.00001 |
| Ischemic Stroke | 235 (6.23) | 343 (9.07) | 32.4 (20.2 to 42.7) | |
| Hemorrhagic Stroke | 30 (0.80) | 22 (0.58) | -36.3 (-136 to 21.4) | |
| Uncertain Stroke | 41 (1.09) | 51 (1.35) | 19.6 (-21.4 to 46.7) | |
| Total Death | 825 (21.87) | 841 (22.24) | 1.9 (-8.0 to 10.9) | 0.6958 |
| MI (fatal or not) | 90 (2.39) | 115 (3.04) | 21.9 (-3.0 to 40.7) | 0.0789 |
| Vascular Death | 600 (15.91) | 599 (15.84) | -0.2 (-12.2 to 10.5) | 0.9759 |
| Non-CNS systemic embolism | 54 (1.43) | 56 (1.48) | 3.5 (-40.3 to 33.6) | 0.8521 |

CNS = central nervous system; MI = myocardial infarction.
Note: One additional MI in the clopidogrel + ASA group and two additional vascular deaths (ASA alone group) were reported after database lock. These events are not included in the table.

The treatment effect for stroke increased over time, in proportion to time (Figure 3).

**Figure 3: Event rate over time for stroke (adjudicated outcome events)**



However for haemorrhagic stroke there was an increase in risk, although this was not statistically significant: RRR (95% CI) -36.3% (-136% to 21.4%). There were reductions in risk that were not statistically significant for total death: RRR (95% CI) 1.9% (-8.0% to 10.9%); MI: 21.9% (-3.0% to 40.7%); and non-CNS systemic embolism: 3.5% (-40.3% to 33.6%). There was no apparent difference for vascular death: -0.2% (-12.2% to 10.5%). The decrease in risk for stroke overall was irrespective of stroke severity and was not influenced by prior $CHADS_2$ stroke risk assessment. The causes of death were predominantly vascular for both treatment groups, with no obvious differences between the treatment groups. The number of subjects experiencing a second primary outcome event was higher in the placebo/ASA group but this did not undergo hypothesis testing.

At 12 months stroke was reported by 2.69% of subjects in the clopidogrel/ASA group and 3.85% in the placebo/ASA (absolute reduction in incidence 1.16%); at 36 months 6.78% subjects in the clopidogrel/ASA group and 9.79% in the placebo/ASA (absolute reduction in incidence 3.1%); and at 54 months, 9.96% subjects in the clopidogrel/ASA group and 13.61% in the placebo/ASA (absolute reduction in incidence 3.65%). This translates to a NNT for 1 year of 86, for 3 years of 32 and for 4.5 years of 27. It would also indicate that most of the benefit for stroke prevention of clopidogrel/ASA is in the first three years of treatment.

**Efficacy In Comparison With Oral Anticoagulants (OAC)**

***Study EFC4912W – ACTIVE W***

This study was a multicentre, randomized, non-inferiority trial of clopidogrel/ASA compared with standard care oral anticoagulation. The study was an open trial with blinded outcome evaluation. The study was conducted at 520 sites in 31 countries. The study was terminated early due to inferiority for clopidogrel/ASA being demonstrated by an interim analysis.

The inclusion criteria for Study EFC4912W – ACTIVE W were identical to those for Study EFC4912A - ACTIVE A except that subjects able and willing to receive oral anticoagulants with usual clinical care and willing to take VKA were enrolled in EFC4912W – ACTIVE W; and those who were not eligible or unwilling to take VKA were enrolled into EFC4912A – ACTIVE A.

The exclusion criteria were also identical except for the addition for Study EFC4912W – ACTIVE W of:

- requirement for chronic (>3 months) non-COX-2 inhibitor NSAID therapy unless willing to be enrolled in ACTIVE A.

The study treatments were:

1. Clopidogrel 75 mg and ASA (75 to 100 mg) once daily. The dose of ASA (75 or 100 mg) was at the discretion of the Investigator

2. Oral anticoagulant.

Oral anticoagulant (OAC) was not supplied by the sponsor. The choice of the specific preparation was left to the investigator's usual practice and dosage was adjusted to a target INR of 2.0 to 3.0. INR interpretation and adjustments of OAC dosage were the responsibility of the investigator at the study site. Randomization was by patient identification number and treatment identification number using an automated voice response system. There was block randomization by study centre. Subjects and Investigators were not blinded to treatment. Oral anticoagulants, ticlopidine, open label clopidogrel and dipyridamole were not allowed concomitantly with clopidogrel study drug

administration. Duration of treatment was planned for up to 4 years but due to early termination was actually up to 2 years.

The outcome measures for Study EFC4912W – ACTIVE W were the same as those for Study EFC4912A - ACTIVE A. Evaluation of outcomes was blinded.

*Statistical Considerations for Study EFC4912W – ACTIVE W*

The margin for non-inferiority was that clopidogrel/ASA maintained at least 50% of the demonstrated benefit of warfarin. The sample size calculation used prior data from an unpublished meta-analysis of six placebo controlled trials of adjusted dose warfarin in AF which indicated a relative hazard reduction (95% CI) in favour of warfarin compared with either placebo or control of 42.1% (27.1% to 54.1%). From this, the excess risk due to placebo versus warfarin was then estimated as 1.73 and the lower limit of the 95% CI as 1.37. Thus, in order to show maintenance of at least 50% of the demonstrated benefit of warfarin, the upper limit of the one sided 97.5% CI of the comparison of clopidogrel/ASA to warfarin should not exceed 1.186. The sample size calculation used assumptions of a 2 year enrollment period, a 2 year follow up period, a 5% drop out rate over 3 years and a one sided type I error of 0.025. The expected event rate on warfarin was 7% per year. A trial of 6500 patients provided about 88% power.

Hypothesis tests for efficacy were performed using Kaplan-Meier plots and Cox proportional hazards models. The rate of the primary safety outcome was compared between treatment groups using Pearson's Chi squared test. Other than the non-inferiority test, all hypothesis tests were performed using two sided tests at the 5% significance level.

*Results for Study EFC4912W – ACTIVE W*

A total of 6706 subjects were randomised to treatment and 6685 received treatment. There were 3323 (99.6%) subjects that were randomized to clopidogrel/ASA and 3362 (99.7%) that were randomized to OAC that also received treatment. The completion rate was lower in the clopidogrel/ASA group: 2930 (88.2%) subjects compared with 3135 (93.2%) in the OAC group. There were 4430 (66.1%) males and 2276 (33.9%) females. There was a broad range of age (25 to 96 years) and of body size (BMI range 2.80 to 397.63) although the latter might reflect data entry errors. A high proportion of the study population was obese (37.5%). The treatment groups were similar in demographic and baseline characteristics, atrial fibrillation history, vascular medical/surgical history, inclusion criteria and inclusion risk factors. The treatment groups were similar in medications prior to randomization and, other than for ASA, in concomitant treatment after randomization. Of interest, 606 (18.0%) subjects in the OAC group were taking ASA at final visit and 92 (2.7%) were taking clopidogrel. In the clopidogrel/ASA group at final visit 1916 (58.6%) subjects were taking <100 mg ASA per day and 1352 (41.4%) were taking ≥100 mg/day.

For the primary efficacy outcome measure (adjudicated stroke, non-CNS systemic embolus, MI or vascular death) clopidogrel/ASA was inferior to OAC. The primary efficacy outcome occurred in 234 (7.0%) patients in the clopidogrel/ASA group and 166 (4.9%) patients in the OAC group: hazard ratio (HR) (95% CI) 1.43 (1.17 to 1.75). The incidence was higher in the clopidogrel/ASA group for all the components of the primary outcome measure (Table 4). The greater event rate in the clopidogrel/ASA group occurred throughout the follow up period. After 12 months treatment the increase in absolute risk (95% CI) with clopidogrel/ASA compared with OAC was 2.06% (3.10% to 1.02%), which translates to a number to harm (NNH) of 49.

**Table 4: Summary of frequency of primary outcome events (adjudicated outcome events)**

| Primary Outcome | Clopidogrel + ASA (N=3335) | Oral Anticoagulants (N=3371) | Hazard ratio (95% CI) |
|---|---|---|---|
| MI/Stroke/Non-CNS systemic embolism/Vascular death [a] | 234 (7.02) | 166 (4.92) | 1.43 (1.17, 1.75) |
| MI (fatal or not) | 34 (1.02) | 22 (0.65) | |
| Stroke (fatal or not) | 98 (2.94) | 58 (1.72) | |
| Non-CNS systemic embolism | 17 (0.51) | 4 (0.12) | |
| Vascular Death | 85 (2.55) | 82 (2.43) | |

[a] Only the first event was counted.
CNS = central nervous system; MI = myocardial infarction.

The results of the investigator reported primary outcome variable also demonstrated inferiority for clopidogrel/ASA compared with OAC: 235 (7.05%) subjects compared with 168 (4.98%), HR (95% CI) 1.42 (1.16 to 1.73). The per protocol analysis of the adjudicated primary outcome variable demonstrated inferiority for clopidogrel/ASA compared with OAC: 211 (6.35%) subjects compared with 154 (4.58%); HR (95% CI) 1.44 (1.17 to 1.78). There was no interaction with demographic characteristics or with medical history at the time of randomization. The benefit of OAC appeared to be more pronounced with concomitant statin medication.

There was a higher risk of stroke with clopidogrel/ASA: 100 (3.00%) subjects compared with 59 (1.75%); HR (95% CI) 1.72 (1.24 to 2.37) (Table 5). There was also a higher risk of non-CNS systemic embolism: 18 (0.54%) subjects compared with four (0.12%); HR (95% CI) 4.50 (1.52 to 13.29). There was no significant increase in the risk of death, MI or vascular death. The risk appeared to be increased for all severities of stroke except fatal stroke.

**Table 5: Summary of frequency of secondary and other outcomes (ITT – adjudicated outcome events)**

| Outcome | Clopidogrel + ASA (N=3335) | Oral Anticoagulants (N=3371) | Hazard ratio (95% CI) |
|---|---|---|---|
| Stroke (fatal or not) | 100 (3.00) | 59 (1.75) | 1.72 (1.24, 2.37) |
| Ischemic[a] | 90 (2.70) | 42 (1.25) | |
| Hemorrhagic | 5 (0.15) | 15 (0.44) | |
| Uncertain | 5 (0.15) | 2 (0.06) | |
| Total Death | 159 (4.77) | 159 (4.72) | 1.00 (0.81, 1.25) |
| MI (fatal or not) | 36 (1.08) | 23 (0.68) | 1.57 (0.93, 2.65) |
| Vascular Death | 120 (3.60) | 107 (3.17) | 1.13 (0.87, 1.46) |
| Non-CNS systemic embolism | 18 (0.54) | 4 (0.12) | 4.50 (1.52, 13.29) |

[a] 5 patients (3 in the clopidogrel group and 2 in the OAC group) were adjudicated to secondary hemorrhagic transformation.

**Evaluator's Overall Conclusions on Clinical Efficacy**

There was a statistically significant reduction in the risk of stroke (fatal or nonfatal), MI (fatal or nonfatal), non-CNS systemic embolism, or vascular death with clopidogrel/ASA in comparison with ASA: RRR (95% CI) 11.1% (2.4% to 19.1%). The treatment effect appeared to increase over time and in proportion to time. Prior medical history and concomitant mediation did not influence efficacy.

The greatest contribution to the overall decrease in event rates was the decrease in stroke. For stroke overall there was a statistically significant reduction in risk: RRR (95% CI) 28.4% (16.8% to 38.3%). The decrease in risk for stroke overall was irrespective of stroke severity and was not influenced by prior $CHADS_2$ stroke risk assessment. However for haemorrhagic stroke there was an increase in risk, although this was not statistically significant: RRR (95% CI) -36.3% (-136% to 21.4%).

The clinical significance of the treatment effect is less impressive. The absolute difference in event rate at 12 months was 0.78% (-0.41% to 1.98%), at 36 months was 2.45% (0.62% to 4.27%) and at 54 months was 2.82% (0.39% to 5.26%). Therefore, for the prevention of the primary outcome variable the NNT for 1 year was 128, for 3 years was 41 and for 4.5 years was 35. This translates to treating 35 subjects for 4.5 years in order to prevent one subject from having an event during that time.

Stroke was reported at 12 months in 2.69% subjects in the clopidogrel/ASA group and 3.85% in the placebo/ASA (absolute reduction in incidence 1.16%); at 36 months 6.78% subjects in the clopidogrel/ASA group and 9.79% in the placebo/ASA (absolute reduction in incidence 3.1%); and at 54 months, 9.96% subjects in the clopidogrel/ASA group and 13.61% in the placebo/ASA (absolute reduction in incidence 3.65%). This translates to a NNT for 1 year of 86, for 3 years of 32 and for 4.5 years of 27. It would also indicate that most of the benefit for stroke prevention of clopidogrel/ASA is in the first three years of treatment.

The ACTIVE-A study did not have a treatment arm for clopidogrel only. Hence it is not possible to compare the efficacy of clopidogrel/ASA with clopidogrel/placebo. A fixed dose combination product should have demonstrable efficacy that is superior to either of the component active entities (that is, either ASA or clopidogrel alone).

The sponsor did not provide data with regard to the effect of irbesartan upon efficacy. The sponsor did not provided data demonstrating no rebound effect upon ceasing clopidogrel/ASA. The sponsor did not calculate the incidence difference (95% CI) for stroke at any of the time points.

Clopidogrel/ASA was clinically and statistically significantly worse than OAC. In Study EFC4912W – ACTIVE W the margin of non-inferiority (50%) was generous and did not reflect a clinically significant difference in efficacy. However, despite this clopidogrel/ASA was demonstrated to be inferior to OAC and the study was terminated early, at 2 years. For the combined endpoint of stroke, non-CNS systemic embolus, MI or vascular death clopidogrel/ASA was inferior to OAC, with a 43% increase in risk. After 12 months treatment the increase in absolute risk (95% CI) with clopidogrel/ASA compared with OAC was 2.06% (3.10% to 1.02%), which translates to a NNH of 49. There was a 72% increase in the risk of stroke with clopidogrel/ASA compared to OAC and over four times the risk of non-CNS systemic embolism.

## Safety

### Introduction

Safety data from Study EFC4912A - ACTIVE A and Study EFC4912W – ACTIVE W were included in the submission. In addition, postmarketing data were provided in a *Summary Safety Update Report* that covered the time period 17 November 1997 to 28 February 2009.

### Patient Exposure

In Study EFC4912A - ACTIVE A, a total of 2989 subjects were treated with clopidogrel/ASA for 12 months or more, 2541 subjects were treated for 24 months or more, 1834 subjects were treated for 36 months or more and 814 subjects were treated for 48 months or more.

In Study EFC4912W – ACTIVE W, a total of 3323 subjects were exposed to clopidogrel/ASA and 2227 subjects were exposed for more than 12 months.

### Adverse Events

#### *More Common Adverse Events*

In Study EFC4912A - ACTIVE A, treatment emergent adverse events (TEAEs) were reported in 2678 (71.0%) subjects in the clopidogrel/ASA group and 2633 (69.6%) in the placebo/ASA group. The overall risk of TEAEs was similar for the two treatment groups. The most commonly reported TEAEs were infections followed by gastrointestinal events (Table 6). Injuries were more common in the clopidogrel/ASA group: 509 (13.5%) subjects compared with 441 (11.7%) in the placebo/ASA goup.

In Study EFC4912W – ACTIVE W, TEAEs were reported in 2469 (74.0%) subjects in the clopidogrel/ASA group and 2429 (72.1%) in the OAC. The most commonly reported TEAEs were infections followed by gastrointestinal events (Table 7). Injuries were more common in the clopidogrel/ASA group: 429 (12.9%) subjects compared with 354 (10.5%); and particularly contusions: 199 (6.0%) subjects compared with 54 (1.6%). Haematomas were more common in the clopidogrel/ASA group: 86 (2.6%) subjects compared with 30 (0.9%).

**Table 6: Number (%) of patients with treatment emergent adverse events by MedDRA System Organ Class regardless of incidence and preferred term in >=1% of patients in any treatment group**[5]

| Preferred Term by Primary System Organ Class | Clopidogrel + ASA (N=3772) | Placebo + ASA (N=3782) |
|---|---|---|
| Any AE | 2678 (71.0%) | 2633 (69.6%) |
| Infections and infestations | 1073 (28.4%) | 1043 (27.6%) |
| Pneumonia | 191 (5.1%) | 180 (4.8%) |
| Bronchitis | 189 (5.0%) | 165 (4.4%) |
| Urinary tract infection | 148 (3.9%) | 170 (4.5%) |
| Nasopharyngitis | 145 (3.8%) | 150 (4.0%) |
| Influenza | 108 (2.9%) | 149 (3.9%) |
| Upper respiratory tract infection | 60 (1.6%) | 70 (1.9%) |
| Cystitis | 38 (1.0%) | 15 (0.4%) |
| Herpes zoster | 37 (1.0%) | 39 (1.0%) |
| Lower respiratory tract infection | 32 (0.8%) | 47 (1.2%) |
| Sinusitis | 22 (0.6%) | 38 (1.0%) |
| Gastrointestinal disorders | 907 (24.0%) | 818 (21.6%) |
| Diarrhoea | 131 (3.5%) | 153 (4.0%) |
| Abdominal pain upper | 105 (2.8%) | 101 (2.7%) |
| Gastritis | 89 (2.4%) | 71 (1.9%) |
| Constipation | 79 (2.1%) | 87 (2.3%) |
| Nausea | 78 (2.1%) | 73 (1.9%) |
| Abdominal pain | 64 (1.7%) | 73 (1.9%) |
| Dyspepsia | 64 (1.7%) | 72 (1.9%) |
| Vomiting | 46 (1.2%) | 51 (1.3%) |
| Nervous system disorders | 709 (18.8%) | 719 (19.0%) |
| Dizziness | 301 (8.0%) | 314 (8.3%) |
| Headache | 136 (3.6%) | 153 (4.0%) |
| Syncope | 64 (1.7%) | 46 (1.2%) |
| General disorders and administration site conditions | 597 (15.8%) | 566 (15.0%) |
| Oedema peripheral | 180 (4.8%) | 156 (4.1%) |
| Chest pain | 126 (3.3%) | 143 (3.8%) |
| Fatigue | 110 (2.9%) | 96 (2.5%) |
| Asthenia | 87 (2.3%) | 80 (2.1%) |
| Oedema | 38 (1.0%) | 23 (0.6%) |
| Respiratory, thoracic and mediastinal disorders | 581 (15.4%) | 543 (14.4%) |
| Dyspnoea | 231 (6.1%) | 218 (5.8%) |
| Cough | 126 (3.3%) | 124 (3.3%) |
| Epistaxis | 72 (1.9%) | 54 (1.4%) |
| Chronic obstructive pulmonary disease | 49 (1.3%) | 44 (1.2%) |
| Musculoskeletal and connective tissue disorders | 546 (14.5%) | 639 (16.9%) |
| Back pain | 110 (2.9%) | 134 (3.5%) |
| Arthralgia | 96 (2.5%) | 118 (3.1%) |
| Osteoarthritis | 87 (2.3%) | 80 (2.1%) |
| Pain in extremity | 70 (1.9%) | 103 (2.7%) |
| Muscle spasms | 38 (1.0%) | 30 (0.8%) |
| Musculoskeletal pain | 33 (0.9%) | 49 (1.3%) |
| Myalgia | 23 (0.6%) | 41 (1.1%) |
| Injury, poisoning and procedural complications | 509 (13.5%) | 441 (11.7%) |
| Contusion | 116 (3.1%) | 54 (1.4%) |
| Fall | 104 (2.8%) | 94 (2.5%) |

[5] MedDRA = Medical Dictionary for Regulatory Activities

**Table 6 (cont)**

| Preferred Term by Primary System Organ Class | Clopidogrel + ASA (N=3772) | Placebo + ASA (N=3782) |
|---|---|---|
| Vascular disorders | 454 (12.0%) | 429 (11.3%) |
| Hypotension | 138 (3.7%) | 142 (3.8%) |
| Hypertension | 120 (3.2%) | 124 (3.3%) |
| Haematoma | 72 (1.9%) | 25 (0.7%) |
| Skin and subcutaneous tissue disorders | 343 (9.1%) | 290 (7.7%) |
| Rash | 55 (1.5%) | 49 (1.3%) |
| Pruritus | 49 (1.3%) | 45 (1.2%) |
| Cardiac disorders | 305 (8.1%) | 319 (8.4%) |
| Cardiac failure | 76 (2.0%) | 80 (2.1%) |
| Palpitations | 63 (1.7%) | 69 (1.8%) |
| Angina pectoris | 50 (1.3%) | 55 (1.5%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 290 (7.7%) | 265 (7.0%) |
| Metabolism and nutrition disorders | 259 (6.9%) | 275 (7.3%) |
| Gout | 56 (1.5%) | 62 (1.6%) |
| Renal and urinary disorders | 224 (5.9%) | 224 (5.9%) |
| Eye disorders | 202 (5.4%) | 210 (5.6%) |
| Cataract | 105 (2.8%) | 114 (3.0%) |
| Psychiatric disorders | 188 (5.0%) | 193 (5.1%) |
| Depression | 57 (1.5%) | 60 (1.6%) |
| Insomnia | 36 (1.0%) | 50 (1.3%) |
| Investigations | 187 (5.0%) | 203 (5.4%) |
| Weight decreased | 42 (1.1%) | 34 (0.9%) |
| Blood pressure increased | 37 (1.0%) | 45 (1.2%) |
| Reproductive system and breast disorders | 116 (3.1%) | 127 (3.4%) |
| Benign prostatic hyperplasia | 35 (0.9%) | 48 (1.3%) |
| Blood and lymphatic system disorders | 111 (2.9%) | 115 (3.0%) |
| Anaemia | 75 (2.0%) | 71 (1.9%) |
| Ear and labyrinth disorders | 110 (2.9%) | 122 (3.2%) |
| Vertigo | 73 (1.9%) | 79 (2.1%) |
| Hepatobiliary disorders | 109 (2.9%) | 113 (3.0%) |
| Cholelithiasis | 37 (1.0%) | 44 (1.2%) |
| Surgical and medical procedures | 68 (1.8%) | 68 (1.8%) |
| Endocrine disorders | 61 (1.6%) | 67 (1.8%) |
| Immune system disorders | 24 (0.6%) | 26 (0.7%) |
| Congenital, familial and genetic disorders | 14 (0.4%) | 13 (0.3%) |
| Social circumstances | 12 (0.3%) | 13 (0.3%) |

Only rows with frequency of at least 1% in at least one column are shown
All primary system organ class rows are shown and includes all preferred terms, as does the Any AE row
AE = adverse event

**Table 7: Number (%) of patients with treatment emergent adverse events by MedDRA system organ class and preferred term in ≥1% of patients in any treatment group**

| Preferred Term by Primary System Organ Class | Clopidogrel + ASA (N=3335) | Oral Anticoagulants (N=3371) |
|---|---|---|
| Any AE | 2378 (71.3%) | 2360 (70.0%) |
| Infections and infestations | 786 (23.6%) | 831 (24.7%) |
| Nasopharyngitis | 112 (3.4%) | 139 (4.1%) |
| Bronchitis | 99 (3.0%) | 99 (2.9%) |
| Influenza | 92 (2.8%) | 92 (2.7%) |
| Urinary tract infection | 91 (2.7%) | 92 (2.7%) |
| Pneumonia | 83 (2.5%) | 75 (2.2%) |
| Upper respiratory tract infection | 63 (1.9%) | 69 (2.0%) |
| Herpes zoster | 34 (1.0%) | 18 (0.5%) |
| Lower respiratory tract infection | 34 (1.0%) | 35 (1.0%) |
| Sinusitis | 33 (1.0%) | 34 (1.0%) |
| Gastrointestinal disorders | 641 (19.2%) | 563 (16.7%) |
| Diarrhoea | 105 (3.1%) | 122 (3.6%) |
| Nausea | 89 (2.7%) | 65 (1.9%) |
| Constipation | 68 (2.0%) | 40 (1.2%) |
| Abdominal pain upper | 67 (2.0%) | 40 (1.2%) |
| Abdominal pain | 53 (1.6%) | 46 (1.4%) |
| Dyspepsia | 48 (1.4%) | 30 (0.9%) |
| Gastritis | 35 (1.0%) | 19 (0.6%) |
| Nervous system disorders | 590 (17.7%) | 603 (17.9%) |
| Dizziness | 275 (8.2%) | 293 (8.7%) |
| Headache | 112 (3.4%) | 97 (2.9%) |
| Syncope | 38 (1.1%) | 44 (1.3%) |
| Hypoaesthesia | 36 (1.1%) | 27 (0.8%) |
| General disorders and administration site conditions | 581 (17.4%) | 569 (16.9%) |
| Fatigue | 163 (4.9%) | 152 (4.5%) |
| Oedema peripheral | 150 (4.5%) | 175 (5.2%) |
| Chest pain | 111 (3.3%) | 121 (3.6%) |
| Asthenia | 67 (2.0%) | 54 (1.6%) |
| Respiratory, thoracic and mediastinal disorders | 519 (15.6%) | 511 (15.2%) |
| Dyspnoea | 199 (6.0%) | 173 (5.1%) |
| Epistaxis | 98 (2.9%) | 65 (1.9%) |
| Cough | 85 (2.5%) | 94 (2.8%) |
| Dyspnoea exacerbated | 34 (1.0%) | 36 (1.1%) |
| Chronic obstructive pulmonary disease | 27 (0.8%) | 37 (1.1%) |
| Musculoskeletal and connective tissue disorders | 508 (15.2%) | 512 (15.2%) |
| Back pain | 108 (3.2%) | 98 (2.9%) |
| Arthralgia | 90 (2.7%) | 100 (3.0%) |
| Pain in extremity | 81 (2.4%) | 68 (2.0%) |
| Joint swelling | 36 (1.1%) | 34 (1.0%) |
| Muscle spasms | 36 (1.1%) | 29 (0.9%) |
| Shoulder pain | 36 (1.1%) | 27 (0.8%) |
| Osteoarthritis | 32 (1.0%) | 38 (1.1%) |

**Table 7 (cont)**

| Preferred Term by Primary System Organ Class | Clopidogrel + ASA (N=3335) | Oral Anticoagulants (N=3371) |
|---|---|---|
| Injury, poisoning and procedural complications | 429 (12.9%) | 354 (10.5%) |
| Contusion | 199 (6.0%) | 54 (1.6%) |
| Fall | 56 (1.7%) | 61 (1.8%) |
| Vascular disorders | 397 (11.9%) | 290 (8.6%) |
| Hypertension | 120 (3.6%) | 102 (3.0%) |
| Hypotension | 119 (3.6%) | 106 (3.1%) |
| Haematoma | 86 (2.6%) | 30 (0.9%) |
| Skin and subcutaneous tissue disorders | 339 (10.2%) | 292 (8.7%) |
| Rash | 60 (1.8%) | 72 (2.1%) |
| Pruritus | 46 (1.4%) | 30 (0.9%) |
| Ecchymosis | 42 (1.3%) | 12 (0.4%) |
| Cardiac disorders | 241 (7.2%) | 223 (6.6%) |
| Palpitations | 45 (1.3%) | 52 (1.5%) |
| Cardiac failure | 42 (1.3%) | 35 (1.0%) |
| Angina pectoris | 40 (1.2%) | 39 (1.2%) |
| Investigations | 183 (5.5%) | 189 (5.6%) |
| Metabolism and nutrition disorders | 176 (5.3%) | 198 (5.9%) |
| Gout | 53 (1.6%) | 70 (2.1%) |
| Eye disorders | 159 (4.8%) | 159 (4.7%) |
| Cataract | 61 (1.8%) | 64 (1.9%) |
| Psychiatric disorders | 146 (4.4%) | 135 (4.0%) |
| Depression | 41 (1.2%) | 47 (1.4%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 140 (4.2%) | 165 (4.9%) |
| Renal and urinary disorders | 127 (3.8%) | 127 (3.8%) |
| Surgical and medical procedures | 100 (3.0%) | 104 (3.1%) |
| Ear and labyrinth disorders | 86 (2.6%) | 100 (3.0%) |
| Vertigo | 57 (1.7%) | 62 (1.8%) |
| Reproductive system and breast disorders | 74 (2.2%) | 78 (2.3%) |
| Blood and lymphatic system disorders | 63 (1.9%) | 63 (1.9%) |
| Anaemia | 37 (1.1%) | 47 (1.4%) |
| Hepatobiliary disorders | 45 (1.3%) | 30 (0.9%) |
| Endocrine disorders | 25 (0.7%) | 29 (0.9%) |
| Immune system disorders | 22 (0.7%) | 15 (0.4%) |
| Congenital, familial and genetic disorders | 14 (0.4%) | 5 (0.1%) |
| Social circumstances | 2 (<0.1%) | 1 (<0.1%) |
| Pregnancy, puerperium and perinatal conditions | 0 | 1 (<0.1%) |

Only preferred term rows with a frequency of at least 1% in at least one column are shown
All primary system organ class rows are shown and includes all preferred terms, as does the Any AE row
AE = adverse event.

### *AEs of special interest*

*AEs of special interest in Study EFC4912A - ACTIVE A*

In Study EFC4912A - ACTIVE A the incidence of adjudicated major bleeding (primary safety endpoint) was greater with clopidogrel/ASA group than with placebo/ASA: 251 (6.65%) subjects compared to 162 (4.28%), absolute risk increase (95% CI) 2.37% (1.35% to 3.40%) p<0.001 (Table 8). Hence the number needed to harm (NNH) for major bleeding was 42 subjects. Severe bleeding was reported in190 (5.04%) subjects in the clopidogrel/ASA group compared with 122 (3.23%) in the placebo/ASA group, absolute risk increase (95% CI) 1.81% (0.91% to 2.71%) p<0.001. The NNH for severe bleeding was 55 subjects. The incidence of intracranial haemorrhage (ICH) was also higher in the clopidogrel/ASA group: 54 (1.43%) subjects compared to 29 (0.77%), absolute risk increase 0.66% (0.19% to 1.13%) p=0.0056. The NNH for ICH was 168 subjects. The

incidence of fatal bleeds was higher in the clopidogrel/ASA group: 42 (1.11%) subjects compared with 27 (0.71%), absolute risk increase 0.40% (-0.03% to 0.83%) p=0.0680, NNH 250 subjects. The incidence of haemorrhagic stroke was higher in the clopidogrel/ASA group: 30 (0.80%) subjects compared with 22 (0.58%); absolute risk increase 0.21% (-0.16% to 0.59%) p=0.2615; NNH 476 subjects.

**Table 8: Number (%) of patients with bleeding events Study EFC4912A - ACTIVE A**

| | No. (%) with Event | | | |
|---|---|---|---|---|
| Bleeding | Clopidogrel + ASA (N=3772) | Placebo + ASA (N=3782) | Difference Clopidogrel - Placebo (%) (95% CI) | p-Value |
| Major[ab] | 251 (6.65) | 162 (4.28) | 2.37 (1.35 to 3.40) | <0.001 |
| Severe[ab] | 190 (5.04) | 122 (3.23) | 1.81 (0.91 to 2.71) | <0.001 |
| Fatal | 42 (1.11) | 27 (0.71) | 0.40 (-0.03 to 0.83) | 0.0680 |
| ICH[ab] | 54 (1.43) | 29 (0.77) | 0.66 (0.19 to 1.13) | 0.0056 |
| Major, but not Severe[a] | 76 (2.01) | 46 (1.22) | 0.80 (0.23 to 1.37) | 0.0059 |
| Minor | 408 (10.82) | 175 (4.63) | 6.19 (4.99 to 7.39) | <0.001 |
| Minor/Other[c] | 859 (22.77) | 539 (14.25) | 8.52 (6.78 to 10.26) | <0.001 |
| Other[c] | 560 (14.85) | 412 (10.89) | 3.95 (2.44 to 5.46) | <0.001 |
| Any[b] | 1014 (26.88) | 651 (17.21) | 9.67 (7.81 to 11.53) | <0.001 |

[a] As adjudicated.
[b] Includes 1 patient in the clopidogrel + ASA group with an ischemic stroke adjudicated to hemorrhagic, but no bleed reported in the database.
[c] Includes 1 patient in the ASA alone group with a bleed reported as major, but adjudicated to minor.
ICH = intracranial hemorrhage.
Note: Two additional major bleeding events (ASA alone group) were reported after database lock. These events are not included in the table.

The most common sites for bleeding were gastrointestinal and intracranial. The risk of bleeding increased with age but there did not appear to be an interaction between clopidogrel and age. There were no statistically significant interactions for disease state or concomitant medications.

The incidence of episodes of fainting or loss of consciousness was 3.3% in the clopidogrel/ASA group and 2.9% in the placebo/ASA group at the final visit.

*AEs of special interest in Study EFC4912W - ACTIVE W*

In Study EFC4912W – ACTIVE W the rate of bleeding episodes was greater in the clopidogrel/ASA group compared with OAC: 644 (19.31%) subjects compared with 556 (16.49%), increase in absolute risk 2.82% (0.98 to 4.65), p=0.003 (Table 9). This translates to a NNH for bleeding episodes of 35 subjects. The rate of major bleeding episodes was higher in the clopidogrel/ASA group than in the OAC group: 101 (3.03%) subjects compared with 93 (2.76%), increase in absolute risk 0.27% (-0.53 to 1.07), p=0.510. This translates to a NNH for major bleeding episodes of 370 subjects. Fatality due to bleeding occurred for seven (0.21%) subjects in the clopidogrel/ASA group and eleven (0.33%) in the OAC. The most common site for bleeding was the upper gastrointestinal tract: 38 (1.1%) subjects in the clopidogrel/ASA group and 27 (0.8%) in the OAC. There appeared to be an interaction between clopidogrel/ASA and statins with an increased risk of bleeding in comedicated subjects: 57 (3.65%) subjects compared with 44 (2.48%) subjects treated with clopidogrel/ASA but not with statins, p=0.011. There was no influence of demographic subgroup upon rate of bleeding episodes.

The incidence of episodes of fainting or loss of consciousness was 0.9% in the clopidogrel/ASA group and 1.0% in the OAC group at the final visit.

**Table 9: Number (%) of patients with bleeding events - Study EFC4912W – ACTIVE W**

| Bleeding | Clopidogrel + ASA (N=3335) | Oral Anticoagulants (N=3371) | Difference Clopidogrel-OAC (%) (95% CI) | p-Value |
|---|---|---|---|---|
| Major | 101 (3.03) | 93 (2.76) | 0.27 (-0.53,1.07) | 0.510 |
| Fatal | 7 (0.21) | 11 (0.33) | -0.12 (-0.36,0.13) | |
| Non-fatal | 94 (2.82) | 82 (2.43) | 0.39 (-0.38,1.15) | |
| Any | 644 (19.31) | 556 (16.49) | 2.82 (0.98,4.65) | 0.003 |
| Severe | 69 (2.07) | 63 (1.87) | 0.20 (-0.47,0.87) | 0.555 |
| Major, but not severe | 35 (1.05) | 34 (1.01) | 0.04 (-0.44,0.52) | 0.868 |
| Minor/other | 568 (17.03) | 482 (14.30) | 2.73 (0.99,4.47) | 0.002 |
| Minor | 208 (6.24) | 238 (7.06) | -0.82 (-2.02,0.37) | 0.176 |
| Other | 410 (12.29) | 286 (8.48) | 3.81 (2.35,5.27) | <0.001 |

NOTE: Major and severe bleeds are adjudicated.

## Serious Adverse Events (SAEs) and Deaths

### *SAEs and Deaths in Study EFC4912A - ACTIVE A*

In Study EFC4912A - ACTIVE A, SAEs were reported in 1154 (30.6%) subjects in the clopidogrel/ASA group and 1069 (28.3%) in the placebo/ASA group. More subjects in the clopidogrel/ASA group were reported with gastrointestinal disorders 287 (7.6%) compared with 191 (5.1%) in the placebo/ASA group. More subjects in the clopidogrel group died as a result of injuries: 12 (0.3%) subjects compared with three (<0.1%). Haemorrhagic SAEs were reported in 257 (6.8%) subjects in the clopidogrel/ASA group and 129 (3.4%) in the placebo/ASA group. Mortality was similar for the two treatment groups: 825 (21.9%) subjects in the clopidogrel/ASA group and 841 (22.2%) in the placebo/ASA group.

### *SAEs and Deaths in Study EFC4912W - ACTIVE W*

In Study EFC4912W – ACTIVE W, SAEs were reported in 608 (18.2%) subjects in the clopidogrel group and 607 (18.0%) in the OAC group. The only SAE to occur at a rate of >1% in either treatment group was pneumonia: 56 (1.7%) subjects in the clopidogrel/ASA group and 42 (1.2%) in the OAC group. Mortality was similar for the two treatment groups: 159 (4.8%) subjects in the clopidogrel/ASA group and 159 (4.7%) in the OAC group. There were no clear differences between the treatment groups in the SAEs leading to death.

## Laboratory Findings

In both studies, blood dyscrasias and thrombocytopenia were reported to the same extent in both treatment groups.

Laboratory tests as safety outcome measures were not conducted as part of the study protocol for either study.

## Immunological Events

Immunological adverse events were not reported separately and there was no excess of immunological adverse events in the clopidogrel/ASA group in Study EFC4912A - ACTIVE A. In Study EFC4912W - ACTIVE W there were more immune system AEs in the clopidogrel/ASA group: 22 (0.7%) subjects compared with 15 (0.4%). This might be attributable to the ASA component.

## Safety Related to Drug-Drug Interactions and Other Interactions

In Study EFC4912W – ACTIVE W there appeared to be an interaction between statins and the risk of haemorrhage, with a decreased risk in those subjects treated with OAC and statins.

**Discontinuation Due To Adverse Events**

***AEs leading to discontinuation in Study EFC4912A - ACTIVE A***

In Study EFC4912A - ACTIVE A, a total of 388 (10.3%) subjects in the clopidogrel/ASA group and 281 (7.4%) in the placebo/ASA discontinued because of AEs. There was no clear difference in the pattern of AEs leading to discontinuation except for an increased incidence of haemorrhage and gastrointestinal haemorrhage in the clopidogrel/ASA group. In 173 (4.6%) subjects in the clopidogrel/ASA group, and 67 (1.8%) in the placebo/ASA group there was discontinuation because of haemorrhagic AEs.

***AEs leading to discontinuation in Study EFC4912W - ACTIVE W***

In Study EFC4912W – ACTIVE W, discontinuation due to AEs was reported in 660 (19.8%) subjects in the clopidogrel group and 502 (14.9%) in the OAC group. Discontinuation due to minor bleeds was more common in the clopidogrel/ASA group: 205 (6.1%) subjects compared to 149 (4.4%). Discontinuation due to gastrointestinal disorders was also more common in the clopidogrel/ASA group: 149 (4.5%) subjects compared with 88 (2.6%).

**Post Marketing Experience**

A *Summary Safety Update Report* was provided that covered the time period 17 November 1997 (the International Product Birthdate) to 28 February 2009. The sponsor estimated that during this time period 89 million patients had been treated worldwide. This includes an estimated 451,942,000 tablets sold in Australia, which were estimated to have treated 1,575,000 patients. During the same time period there were reports to Sanofi-Aventis or Bristol-Myers Squibb of a total of 33,030 cases worldwide, of which 19,911 were medically confirmed. These were recorded in the Sanofi-Aventis global pharmacovigilance database. In the 19,911 medically confirmed cases, there were 36,373 reactions coded of which 22,114 were serious.

There were 8,600 adverse reactions in 7,205 patients that were related to bleeding. Gastrointestinal haemorrhage was the most common site: 2,678 adverse reactions in 2220 patients. There were 418 reports of cerebral haemorrhage/infarction, 138 of intracranial haemorrhage/haematoma and 86 of haemorrhagic stroke or haemorrhagic cerebral infarction. There were 990 reports of thrombocytopenia, 131 of thrombocytopenic purpura and 145 of thrombotic thrombocytopenic purpura. In addition there were 395 reports of decreased haemoglobin concentrations.

Hepatobiliary disorders were reported in 551 patients: including 144 hepatocellular injury, 130 abnormal hepatic function, 36 hepatic failure, 29 hepatic necrosis and eleven hepatitis fulminant. Possibly related to these cases, there were 188 reports of raised alanine transaminase, 152 of raised aspartate transaminase and 172 of raised gamma glutamyl transaminase. There were 361 adverse reactions categorised as immune system disorders in 355 patients, including hypersensitivity in 229 and anaphylaxis in 72. There were 48 reports of rhabdomyolysis but in most of these cases there was concomitant statin treatment. There were 1034 reports of rash but 871 (84%) were non-serious. There were 31 reports of Stevens Johnson syndrome.

There were 1178 medically confirmed cases with a fatal outcome. Fatality was attributed to haemorrhage in >52% of these cases and lack of efficacy in <11%.

Drug-drug interactions resulting in bleeding were attributed to thrombolytic and/or a glycoprotein IIb/IIIa inhibitor and/or an injectable or oral anticoagulant and/or acetylsalicylic acid and/or another nonsteroidal antiinflammatory drug. At the time of the preparation of the report, the sponsor had received requests from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and various other country

health authorities to update the clopidogrel labeling to include information on the question of interaction between clopidogrel and CYP2C19 inhibitors, such as proton pump inhibitors (PPIs).

**Evaluator's Overall Conclusions on Clinical Safety**

For the requested indication, 2989 subjects have been treated with clopidogrel/ASA for 12 months or more, 2541 for 24 months or more, 1834 for 36 months or more, and 814 for 48 months or more.

Injuries are more common with clopidogrel/ASA than with ASA alone or OAC. The excess in injuries appears to be due to contusions and haematomas. Major bleeding episodes, including severe bleeding, occur more frequently with clopidogrel/ASA than with ASA alone (absolute risk increase [95% CI] 2.37% [1.35% to 3.40%]) or with OAC (absolute risk increase [95% CI] 0.27% (-0.53 to 1.07). Other than fatal bleeding, all types of bleeding episodes occurred more frequently with clopidogrel/ASA than with ASA. In Study EFC4912A - ACTIVE A the most common sites for bleeding were gastrointestinal and intracranial. The risk of haemorrhagic stroke was higher with clopidogrel/ASA than ASA alone.

Laboratory tests were not performed as safety outcome measures in either Study EFC4912A - ACTIVE A or Study EFC4912W - ACTIVE W. There was no excess of abnormal test results for clopidogrel/ASA reported in either study.

Discontinuation due to gastrointestinal AEs and haemorrhage was more common with clopidogrel/ASA than with ASA alone or OAC.

The postmarketing data indicate signals for hepatic AEs, thrombocytopenia, immunological AEs and Stevens Johnson syndrome that are not present in the clinical trial data. This may be because of the poor quality of the postmarketing data and concomitant medication with other drugs. However, these events should also be added to the safety specification.

## List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

**Pharmacokinetics**

Could the sponsor provide a brief summary of the findings from the studies conducted to investigate:

- Potential reduction in clinical efficacy of clopidogrel in presence of PPIs
- Diminished antiplatelet response of clopidogrel in patients with genetically reduced CYP2C19 function

**Efficacy**

Does the Sponsor have efficacy data for clopidogrel alone in comparison with clopidogrel/ASA in fixed dose combination for the indication sought in the present application?

What are the 95% CIs for the absolute risk reduction for stroke at 1 year, 3 years and 4.5 years?

Could the sponsor please provide a brief summary of the major findings with regard to any treatment interaction with irbesartan from the ACTIVE studies? Did irbesartan have any effect upon the efficacy of either clopidogrel/ASA or ASA? Did either clopidogrel/ASA or ASA have any effect on the efficacy of irbesartan?

What happens if clopidogrel/ASA is stopped? Are there any rebound effects?

In the reporting of the demographic variables in the ACTIVE A and ACTIVE W trials suggest data entry errors: for example, minimum BMI of 1.65 kg/$m^2$, minimum systolic blood pressure of 65 mmHg. Was there double entry of data onto the study database? Were internal audits performed of data entry? Do these values represent data entry errors or are they true values? If these values represent data entry errors, could similar errors have occurred with other data entry (such as efficacy and safety outcome measurements)?

**Safety**

Could the Sponsor please provide a brief summary of the major findings with regard to any safety interaction with irbesartan from the ACTIVE studies? Did irbesartan have any effect upon the adverse effect profile of either clopidogrel/ASA or ASA? Did either clopidogrel/ASA or ASA have any effect on the adverse effect profile of irbesartan?

## Clinical Summary and Conclusions

### Clinical Aspects

The fixed dose combination of clopidogrel 75 mg and low dose ASA has been developed as an alternative treatment to prevent stroke (fatal or nonfatal), MI (fatal or nonfatal), non-CNS systemic embolism or vascular death in subjects who cannot take OAC. However it should be noted that some patients object to taking OAC because of the perceived risks of AEs. Therefore it is important that patents are advised that not only is the efficacy of clopidogrel/ASA inferior to OAC but also that the risks of AEs are greater.

### Benefit Risk Assessment

#### *Benefits*

There was a statistically significant reduction in the risk of stroke (fatal or nonfatal), MI (fatal or nonfatal), non-CNS systemic embolism, or vascular death with clopidogrel/ASA in comparison with ASA: RRR (95% CI) 11.1% (2.4% to 19.1%). The treatment effect appeared to increase over time and in proportion to time. Prior medical history and concomitant mediation did not influence efficacy.

The greatest contribution to the overall decrease in event rates was the decrease in stroke. For stroke overall there was a statistically significant reduction in risk: RRR (95% CI) 28.4% (16.8% to 38.3%). The decrease in risk for stroke overall was irrespective of stroke severity and was not influenced by prior $CHADS_2$ stroke risk assessment.

The clinical significance of the treatment effect is less impressive. The absolute difference in event rate at 12 months was 0.78% (-0.41% to 1.98%), at 36 months was 2.45% (0.62% to 4.27%) and at 54 months was 2.82% (0.39% to 5.26%). Therefore, for the prevention of the primary outcome variable the NNT for 1 year was 128, for 3 years was 41 and for 4.5 years was 35. This translates to treating 35 subjects for 4.5 years in order to prevent one subject from having an event during that time.

Stroke was reported at 12 months in 2.69% subjects in the clopidogrel/ASA group and 3.85% in the placebo/ASA group (absolute reduction in incidence 1.16%); at 36 months 6.78% subjects in the clopidogrel/ASA group and 9.79% in the placebo/ASA (absolute reduction in incidence 3.1%); and at 54 months, 9.96% subjects in the clopidogrel/ASA group and 13.61% in the placebo/ASA (absolute reduction in incidence 3.65%). This translates to a NNT for 1 year of 86, for 3 years of 32 and for 4.5 years of 27. It would also indicate that most of the benefit for stroke prevention of clopidogrel/ASA is in the first three years of treatment.

### *Risks*

For the requested indication, 2989 subjects have been treated with clopidogrel/ASA for 12 months or more, 2541 for 24 months or more, 1834 for 36 months or more, and 814 for 48 months or more.

Injuries are more common with clopidogrel/ASA than with ASA alone or OAC. The excess in injuries appears to be due to contusions and haematomas. Major bleeding episodes, including severe bleeding, occur more frequently with clopidogrel/ASA than with ASA alone (absolute risk increase [95% CI] 2.37% [1.35% to 3.40%]) or with OAC (absolute risk increase [95% CI] 0.27% (-0.53 to 1.07). Other than fatal bleeding, all types of bleeding episodes occurred more frequently with clopidogrel/ASA than ASA. In Study EFC4912A - ACTIVE A the most common sites for bleeding were gastrointestinal and intracranial. The risk of haemorrhagic stroke was higher with clopidogrel/ASA than ASA alone.

Laboratory tests were not performed as safety outcome measures in either Study EFC4912A - ACTIVE A or Study EFC4912W - ACTIVE W. There was no excess of abnormal test results for clopidogrel/ASA reported in either study.

Discontinuation due to gastrointestinal AEs and haemorrhage was more common with clopidogrel/ASA than ASA alone or OAC.

Clopidogrel/ASA was clinically and statistically significantly worse than OAC. In Study EFC4912W – ACTIVE W the margin of non-inferiority (50%) was generous and did not reflect a clinically significant difference in efficacy. However, despite this clopidogrel/ASA was demonstrated to be inferior to OAC and the study was terminated early, at 2 years. For the combined endpoint of stroke, non-CNS systemic embolus, MI or vascular death clopidogrel/ASA was inferior to OAC, with a 43% increase in risk. After 12 months treatment the increase in absolute risk (95% CI) with clopidogrel/ASA compared with OAC was 2.06% (3.10% to 1.02%), which translates to a NNH of 49. There was a 72% increase in the risk of stroke with clopidogrel/ASA compared to OAC and over four times the risk of non-CNS systemic embolism.

### *Balance*

The risk benefit balance is in favour of clopidogrel/ASA for the requested indication but only if prescribers and patients are fully informed of the risks and benefits. The clinical significance of the clopidogrel/ASA benefit is marginal for the requested indication. Unless the inferior efficacy and greater AE rate for clopidogrel/ASA in comparison to OAC is explained fully then there is a risk that patients who would be more appropriately treated with OAC will be diverted to clopidogrel/ASA. The proposed Product Information document fails to provide adequate information to enable rational decision making on the part of prescribers and patients.

### *Conclusions*

The data presented in the submission support the requested extension of indications to include:

*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. In adult patients with atrial fibrillation at increased risk of vascular events who can take VKA therapy, VKA has been shown to be associated with a better clinical benefit than aspirin alone or the combination of clopidogrel and aspirin for the reduction of stroke.*

The requested extension of indications should be approved provided the Product Information document is amended in order to provide sufficient information to enable rational decision making by prescribers and patients in the presence of a risk benefit assessment that is only marginally favourable. This is because clopidogrel/ASA could result in net harm if used for the wrong patient group.

# V. Pharmacovigilance Findings

## Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

### Safety Specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 10.

**Table 10: Ongoing Safety Concerns**

| | |
|---|---|
| **Important identified risks** | Major bleeding<br>Thrombotic Thrombocytopenic Purpura<br>Increased risk of bleeding, including occult GI blood loss in case of combination with other antiplatelet agents or other medicinal products acting on haemostasis |
| **Important potential risks** | Potential reduction in clinical efficacy of clopidogrel in presence of PPIs<br>Diminished antiplatelet response of clopidogrel in patients with genetically reduced CYP2C19 function |
| **Important missing information** | Use in pregnant and lactating women<br>Use in paediatric population<br>Use in renal impaired patients<br>Use in hepatic impaired patients |

### *Clinical comments on the RMP Safety Specification*

Clinical aspects were reviewed by the clinical evaluator. The evaluator noted that in addition to the above safety concerns there are concerns with regard to reduced effect with:

- Co-medication with proton pump inhibitors (specifically omeprazole, esomeprazole, pantoprazole and lansoprazole).
- Presence of poor metaboliser CYP2C19 genotype.

It was noted that the sponsor was conducting additional clinical studies to investigate these risks.

The postmarketing data indicate signals for hepatic AEs, thrombocytopenia , immunological AEs and Stevens Johnson syndrome that are not present in the clinical trial data. This may be because of the poor quality of the postmarketing data and concomitant medication with other drugs. However, these events should also be added to the safety specification.

The data presented in the current submission confirm bleeding as the major issue in the safety specification. However, the data contained in the submission also indicate an increased risk of injuries. This might be because haematomas and bruising could have been categorised as injuries. However, injuries should also be added to the safety specification.

**Pharmacovigilance Activities**

The OPR evaluator noted that the sponsor stated that routine pharmacovigilance activities were sufficient to monitor the specified ongoing safety concerns with a special emphasis in the Periodic Safety Update Report (PSUR) on the important identified risks: 'Major bleeding' and 'Thrombotic Thrombocytopenic Purpura'.[6] In addition to routine pharmacovigilance activities, additional pharmacovigilance activities were proposed for the important potential risks: 'Potential reduction in clinical efficacy of clopidogrel in presence of PPIs' and 'Diminished antiplatelet response of clopidogrel in patients with genetically reduced CYP2C19 function' and the important missing information: 'Use in paediatric population'.

The additional pharmacovigilance activities proposed for these safety concerns include:

- 4 drug-drug interaction studies to investigate the interaction with PPIs (clopidogrel versus clopidogrel with omeprazole 80 mg or pantoprazole 80 mg);
    - INT11146: a randomised, placebo controlled, two period, two treatment, two sequence, crossover pharmacodynamic and pharmacokinetic interaction study after 5 days repeated oral doses of clopidogrel (300 mg loading dose followed by 75 mg/day) alone or given concomitantly with omeprazole 80 mg/day in young healthy male and female subjects. The planned date for the study report completion was late 2009.
    - INT11166: a randomised, placebo controlled, two period, two treatment, two sequence, crossover pharmacodynamic and pharmacokinetic interaction study after 5 days repeated oral doses of clopidogrel (300 mg loading dose followed by 75 mg/day) alone or given concomitantly with omeprazole 80 mg/day (12 hours apart on the same days) in young healthy male and female subjects. The planned date for the study report completion was late 2009.
    - INT11208: a randomised, placebo controlled, two period, two treatment, two sequence, crossover pharmacodynamic and pharmacokinetic interaction study after 5 days repeated oral doses of clopidogrel (600 mg loading dose followed by 150 mg/day) alone or given concomitantly with omeprazole 80 mg/day in young healthy male and female subjects. The planned date for the study report completion was early 2010.
    - INT11374: a randomised, placebo controlled, two period, two treatment, two sequence, crossover pharmacodynamic and pharmacokinetic interaction study after 5 days repeated oral doses of clopidogrel (300 mg loading dose followed by 75 mg/day) alone or given concomitantly with pantoprazole 80 mg/day in healthy male subjects. The planned date for the study report completion was mid 2010.

[6] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- a pharmacokinetic/pharmacodynamic genomic study in 4 groups with selected CYP2C19 genotype status; and
    - PKD11147 study: a randomised, double blind, double dummy, two period, two treatment crossover pharmacodynamic and pharmacokinetic study of clopidogrel given as 5 day repeated oral doses (300 mg loading dose followed by 75 mg/day and 600 mg loading dose followed by 150 mg/day) in 4 different groups of CYP2C19 genotyped healthy male and female subjects. The planned date for the study report completion was early 2010.
- a Phase III clinical trial conducted in the paediatric population in line with the Paediatric Investigational Plan agreed with EMA on 5 December 5 2008.

In principle, the OPR evaluator had no objection to the sponsor implementing the proposed application of routine and additional pharmacovigilance activities for the ongoing safety concerns as detailed above. However, the specified studies were not considered to be a part of the planned clinical studies in the pharmacovigilance plan and therefore the related study protocols have not been reviewed. According to the sponsor's *Overview*, all of the studies discussed should have been completed by mid 2010. The sponsor included the study reports from study numbers INT11146 and INT11166, however these were not been assessed as a part of this RMP. The outstanding study reports should also be provided to the TGA.

In the summary of safety concerns and planned pharmacovigilance actions the sponsor has stated it will undertake a Phase III clinical trial in a paediatric population as an additional pharmacovigilance activity. The sponsor has not provided any further details of this study, nor has it been included in the overview of the study protocols for the pharmacovigilance plan; this study should be included in the overview of study protocols. The results of this study should be made available to the TGA for review.

**Risk Minimisation Activities**

The OPR reviewer noted that the sponsor stated that since the approval of this drug in 1997, the safety profile of clopidogrel, either given alone or in combination with aspirin, has been well characterised both by completion of the clinical studies that led to the extensions of indications in the acute coronary syndrome field and by extensive post marketing experience.

A safety profile consistent with existing data in the approved indications has been observed in the ACTIVE A trial supporting the new target indication for prevention of atherothrombotic and thromboembolic events in patients with AF who cannot take VKA therapy.

The sponsor further stated that the proposed PI for clopidogrel/aspirin describes its safety profile and the recommendations for its safe use in real life, and underlines that VKA remains the primary choice for AF patients who are candidates for antithrombotic therapy: "clopidogrel/aspirin is a fixed dose combination product 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 VKA therapy. In adult patients with atrial fibrillation at increased risk of vascular events who can take VKA therapy, VKA has been shown to be associated with a better clinical benefit than aspirin alone or the combination of clopidogrel and aspirin for the reduction of stroke."

As a result, the sponsor feels that no additional risk minimisation activities are necessary beyond these appropriate labelling statements.[7] This was acceptable to the OPR reviewer.

The OPR reviewer made a number of recommendations about the draft PI and Consumer Medicines Information but these are beyond the scope of this AusPAR.

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

There was no requirement for a quality evaluation in a submission of this type.

## Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

## Clinical

As noted by the clinical evaluator, the efficacy and safety data all derive from the same study, the ACTIVE study, which was a Phase III, multicentre study conducted in patient with AF at risk of vascular events. The ACTIVE study in turn comprised three separate but related clinical trials:

- ACTIVE W, a multicentre, prospective, randomized, non-inferiority trial of clopidogrel in combination with ASA compared with standard care oral anticoagulant, given to patients who were candidates to receive VKAs,
- ACTIVE A, a multicentre, randomized, superiority trial of clopidogrel in combination with ASA versus ASA alone (with clopidogrel placebo), given to patients who could not receive VKAs, and
- ACTIVE I, a multicentre, randomized, double blind, placebo controlled superiority trial of irbesartan versus placebo, a factorial design trial done in tandem with both ACTIVE A and ACTIVE W (using the participants of these two trials).

Data from the ACTIVE I trial were not included in this submission. Therefore included in this submission were the efficacy and safety data from ACTIVE A and ACTIVE W.

The clinical evaluator recommended approval in the evaluation report. The concerns noted by the evaluator in this submission included:

- The marginal clinical significance of the clopidogrel/ASA treatment benefit for the requested indication
- The need for a full explanation in the proposed PI of the inferior efficacy and greater AE rate for clopidogrel/ASA in comparison to oral anticoagulant therapy

### Efficacy

#### *Efficacy Data for the fixed dose combination clopidogrel/ASA compared with ASA – Study EFC4912A, ACTIVE A*

This was a multinational, multicentre, randomized, double blind, placebo controlled superiority trial of clopidogrel in combination with ASA compared with ASA alone and also involving a factorial evaluation of irbesartan vs placebo. Patients who were not eligible or

[7] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

who were unwilling to take vitamin K antagonist therapy were enrolled into ACTIVE A whereas those able and willing to take such oral anticoagulant therapy with usual clinical care were enrolled into ACTIVE W.

*The sponsor was requested to give more detail on how patients were determined to be "not eligible" to take VKA. In particular, what proportion of patients deemed "not eligible" were patients deemed to be at an unacceptably high risk of haemorrhage on VKA? The sponsor was also requested to give more detail on the unwillingness of patients to take VKA. What precise degree of "unwillingness" was accepted as an eligibility criterion for ACTIVE A? Was anything at all done to counter any inaccurate perceptions or perceptions based solely on anecdotal evidence held by prospective subjects? Was a patient's "unwillingness" simply accepted on face value without any discussion being entered into?*

The primary efficacy outcome measure used a composite comprising the first episode of: stroke (fatal or non-fatal), MI (fatal or non-fatal), non-CNS systemic embolism or vascular death. There were also a number of secondary efficacy endpoints and two safety outcome measures of special interest; major bleeding and minor bleeding. It was not clear to the Delegate over what period of time were the assessments for the primary efficacy outcome measure carried out. *The sponsor was asked to clarify this issue in its pre-Advisory Committee on Prescription Medicines (ACPM) response.*

The sample size calculation was performed using data from the Stroke Prevention in Atrial Fibrillation (SPAF) I, II and III trials, which included 2,012 patients with AF who were treated with ASA.

*The sponsor was requested to clarify the exact dose of ASA used in the SPAF trials since the Delegate understood that a higher dose (325 mg) of ASA was used in these trials. Was the sponsor able to demonstrate that doses of aspirin of 75 to 100 mg have been proven in randomised, prospective, double blind clinical trials to have had a positive treatment benefit in patients with atrial fibrillation? If the latter cannot be convincingly demonstrated, then the sponsor was asked to justify why aspirin at doses of 75-100 mg can be an appropriate comparator in any clinical trial of patients with atrial fibrillation. Furthermore, if the sample size calculations were performed using data from the SPAF trials which in turn used doses of aspirin much higher than those used in ACTIVE A, then what impact does the latter have on the validity of those same calculations.*

As noted by the clinical evaluator, the currently approved indication for ASA in Australia does not specifically include prevention of thromboembolic events in adult patients with atrial fibrillation and at least one risk factor. This was another reason why ASA may not be an appropriate comparator treatment for the indication sought in the current application. Furthermore, the study was not designed to test the comparative efficacy of clopidogrel alone. That clopidogrel is part of the fixed dose combination being tested means that there is an assumption at least that it will have efficacy in the prevention of atherothrombotic and thromboembolic events in patients with AF. Furthermore, it is currently approved in Australia for the prevention of vascular ischaemia associated with atherothrombotic events in a patient population which must overlap to some degree with the proposed population of patients with AF. However, by its design, ACTIVE A was not able to provide any elucidation of the degree of efficacy and safety which clopidogrel alone may have as a preventer of atherothrombotic and thromboembolic events in patients with AF. *The sponsor was requested to comment on these deficiencies in its pre-ACPM response.*

The rates of discontinuation of treatment were similar for the two treatment groups: 1,323 (35.1%) subjects from the clopidogrel/ASA group and 1,246 (33.0%) in the placebo/ASA group. The treatment groups were similar with respect to demographic and other baseline characteristics, although the clinical evaluator has noted some unrealistic

values for some of the ranges of values of these variables. *The sponsor was requested to make a comment on these inconsistencies in its pre-ACPM response.*

For the primary efficacy outcome measure, clopidogrel/ASA was shown to be superior to placebo/ASA with a relative risk reduction of 11.1%, 95% CI [2.4%, 19.1%], p = 0.0133. The corresponding absolute risk reduction is much more modest, 2.37% (24.43% - 22.06%). Details of the primary outcome are shown in Table 1. The Kaplan-Meier analysis indicated that the treatment effect appears to increase over time (Figure 2). For the prevention of the primary outcome variable, the NNT for 3 years was 41.

The results of the secondary efficacy variables supported the primary outcome. For stroke overall, there was a statistically significant reduction in relative risk of 28.4%, 95% CI [16.8%, 38.3%], p = 0.00001, with an absolute risk reduction of 2.94% (10.79%-7.85%). For haemorrhagic stroke there was an increase in the relative risk of 36.3% but this was not statistically significant as the numbers of such events were low in comparison with the numbers of ischaemic stroke. The haemorrhagic stroke event rate for the clopidogrel + ASA group was 30/3772 or 0.80% while that for the placebo + ASA group was 22/3782 or 0.58%. The absolute risk difference is a very small 0.22% (0.80%-0.58%).

### *Efficacy Data for the fixed dose combination clopidogrel/ASA compared with oral anticoagulant therapy (VKA) – Study EFC4912W, ACTIVE W*

This was a multicentre, randomized, non-inferiority trial of clopidogrel/ASA compared with standard care oral anticoagulation. The study was terminated early because the inferiority of clopidogrel/ASA, that is, the superiority of vitamin K antagonist therapy was demonstrated by an interim analysis. Participants in this study were able and willing to take VKA therapy.

The outcome measures were the same as those for Study EFC4912A – ACTIVE A. There were 4430 (66.1%) males and 2276 (33.9%) females, with a broad range of ages from 25 to 96 years and of BMI from 2.80 to 397.63. The latter nonsensical upper limit prompted the clinical evaluator to question whether this was the result of data entry errors. *If such was the case, then the sponsor must clearly indicate the extent of data entry errors in the submission.*

For the primary efficacy measure (adjudicated stroke, non-CNS systemic embolus, MI or vascular death), clopidogrel/ASA was shown to be inferior to oral anticoagulant therapy. The primary efficacy outcome occurred in 234 (7.0%) patients in the clopidogrel/ASA group and 166 (4.9%) patients in the oral anticoagulant group, the hazard ratio (HR) being equal to 1.43, 95% CI [1.17, 1.75]. The incidence of each of the components of the primary outcome measure was higher in the clopidogrel/ASA group. All these results are shown in Table 4.

## Safety

### *Safety Data for the fixed dose combination clopidogrel/ASA compared with ASA – Study EFC4912A, ACTIVE A*

A total of 3765 subjects were exposed to clopidogrel ASA for a mean of 32 months (median 35.5 months) vs 3774 patients in the placebo/ASA group for a mean of 32.7 months (median 36.6). A total of 2,989 subjects were treated with clopidogrel/ASA for at least 12 months, 2,541 subjects for at least 24 months, 1834 subjects for at least 36 months and 814 for at least 48 months. TEAEs were reported in 2,678 (71.0%) subjects in the clopidogrel/ASA group and 2,633 (69.6%) in the placebo/ASA. The most commonly reported TEAEs were infections followed by gastrointestinal events. Injuries were more common in the clopidogrel/ASA group, 509 (13.5%) subjects vs 441 (11.7%) in the placebo/ASA group.

The incidence of adjudicated major bleeding (primary safety endpoint) was greater in the clopidogrel/ASA group than in the placebo/ASA group with 251 (6.65%) subjects vs 162 (4.28%), representing an absolute risk increase of 2.37%, 95% CI [1.35%, 3.40%], p < 0.001. The NNH for major bleeding was 42 subjects. The incidence rates for severe bleeding, intracranial haemorrhage, fatal bleeds and haemorrhagic stroke were all higher in the clopidogrel/ASA group than in the placebo/ASA. These results are all shown in Table 8. The most common sites for bleeding were gastrointestinal and intracranial.

SAEs were reported in 1154 (30.6%) subjects in the clopidogrel/ASA group vs 1069 (28.3%) in the placebo/ASA group, with haemorrhagic SAEs more common in the former, 257 (6.8%) vs 129 (3.4%). Overall mortality, however, was similar: 825 (21.9%) for subjects in the clopidogrel/ASA group vs 841 (22.2%) in the placebo/ASA. Blood dyscrasias and thrombocytopenia were reported to the same extent in each treatment group. There was no excess of immunological AEs. A total of 388 (10.3%) subjects in the clopidogrel/ASA group and 281 (7.4%) in the placebo/ASA group discontinued because of AEs, including 173 (4.6%) subjects in the clopidogrel/ASA group vs 67 (1.8%) in the placebo/ASA group who discontinued because of haemorrhagic AEs. The excess of about 3% of discontinuations in the clopidogrel/ASA group would appear to be the result of the latter.

***Safety Data for the fixed dose combination clopidogrel/ASA compared with oral anticoagulant therapy (VKA) – Study EFC4912W, ACTIVE W***

A total of 3323 subjects were exposed to clopidogrel/ASA for a mean of 14 months (median 14.9 months) vs 3361 subjects exposed to oral anticoagulants for a mean of 14.95 months (median 15.6 months). TEAEs were reported in 2469 (74.0%) subjects in the clopidogrel/ASA group and 2429 (72.1%) in the oral anticoagulant group. As with ACTIVE A, the most commonly reported TEAEs were infections followed by gastrointestinal events. Injuries were more common in the clopidogrel/ASA group: 429 (12.9%) vs 354 (10.5%), as were contusions: 199 (6.0%) vs 54 (1.6%) and haematomas: 86 (2.6%) vs 30 (0.9%).

The rate of bleeding episodes was greater in the clopidogrel/ASA group vs the oral anticoagulant group: 644 (19.31%) vs 556 (16.49%) with an increase in absolute risk of 2.82%, 95% CI [0.98%, 4.65%], p = 0.003. Similarly, the rate of major bleeding episodes was higher in the clopidogrel/ASA group than in the oral anticoagulant group. However, the situation was reversed for fatality due to bleeding with 7 (0.21%) subjects in the clopidogrel/ASA group vs 11 (0.33%) in the oral anticoagulant group. The most common site for bleeding was the upper gastrointestinal tract. There appeared to be an interaction between clopidogrel/ASA and statins with an increased risk of bleeding in co-medicated subjects: 57 (3.65%) subjects vs 44 (2.48%) subjects treated with clopidogrel/ASA but not with statins, p = 0.011.

SAEs were reported in 608 (18.2%) subjects in the clopidogrel/ASA group vs 607 (18.0%) in the oral anticoagulant group. Mortality was similar for the two groups: 159 (4.8%) vs 159 (4.7%), respectively. Blood dyscrasias and thrombocytopenia were reported to the same extent in both treatment groups. There were more immune system AEs in the clopidogrel/ASA group: 22 (0.7%) vs 15 (0.4%) in the other. As noted by the clinical evaluator, this may be attributable to the ASA component. Discontinuation due to AEs was reported in 660 (19.8%) subjects in the clopidogrel/ASA group vs 502 (14.9%) in the oral anticoagulant group. Discontinuations due to minor bleeds and gastrointestinal disorders were each more common in the clopidogrel/ASA group.

### *Postmarketing experience*

A *Summary Safety Update Report* covering the period 17 November 1997 to 28 February 2009 was included in the submission. The Delegate was uncertain, given the commencement date, whether all the data in this report refers to the fixed dose combination of clopidogrel and ASA. *The sponsor was asked to comment on this issue.* The report appeared to confirm what is known about the safety profile of the medicine, except that the clinical evaluator stated that the postmarketing data indicate signals for hepatic AEs, thrombocytopenia, immunological AEs and Stevens Johnson syndrome which were not present in the clinical trial data. *The sponsor was requested to comment on this issue.* Notably, out of a total of 19,911 medically confirmed cases, 1178 were fatal and in approximately 52% of the latter, the fatality was attributed to haemorrhage.

**Comments on the Evaluator's Overall Conclusions on Clinical Safety**

The clinical evaluator stated that other than fatal bleeding, all types of bleeding episodes occurred more frequently with clopidogrel/ASA than ASA. However, this was inconsistent with what the evaluator says elsewhere in the report where it is clear that the rates of adjudicated major bleeding, severe bleeding, intracranial haemorrhage, fatal bleeds and haemorrhagic stroke were all higher in the clopidogrel/ASA group vs the placebo/ASA group. It was for the comparison with the oral anticoagulant group that the rate of fatality due to bleeding was lower in the clopidogrel/ASA group, although for both bleeding episodes and major bleeding episodes, the rates were higher in the clopidogrel/ASA group than in the oral anticoagulant group. *Would the sponsor please confirm this to be the case. Also would the sponsor please confirm whether or not the terms, "fatal bleed" and "fatality due to bleeding" are synonymous.*

## Risk Management Plan

The Office of Product Review undertook an evaluation of the Risk Management Plan (RMP) and the sponsor has addressed the recommendations outlined in the evaluation. *Would the sponsor please confirm that it has implemented all of the recommendations made?* The sponsor has undertaken to provide an updated version of the RMP to the TGA. Overall, the sponsor's response to the RMP evaluation was accepted by the RMP evaluator.

The RMP evaluator noted that the clinical evaluator has stated: "The postmarketing data indicate signals for hepatic AEs, thrombocytopenia, immunological AEs and Stevens Johnson syndrome that are not present in the clinical trial data. This may be because of the poor quality of the postmarketing data and concomitant medication with other drugs. However, these events should be added to the safety specification." In a communication to the Delegate, the RMP evaluator recommended that the sponsor be required to update the RMP to include the above safety concerns as important potential risks. *Accordingly, the sponsor should update the pharmacovigilance plan and risk minimisation plan, or provide justification of its decision not do so.*

The RMP evaluator has also made the same comments as in the previous paragraph, in relation to the following comments of the clinical evaluator: "The data contained in the submission also indicate an increased risk of injuries. This might be because haematomas and bruising might have been categorised as injuries. However, injuries should also be added to the safety specification." The RMP evaluator has recommended that the sponsor be required to update the RMP to include the above safety concerns as important potential risks and to update the pharmacovigilance plan and risk minimisation plan accordingly, or provide justification of its decision not to do so.

## Risk Benefit Analysis

### Delegate Considerations

#### *Efficacy*

There was a statistically significant reduction in the risk of stroke (fatal or non-fatal), MI (fatal or non-fatal), non-CNS systemic embolism or vascular death with clopidogrel/ASA in comparison with ASA. The relative risk reduction was 11.1%, 95% CI [2.4%, 19.1%]. The treatment effect appeared to increase over time and in proportion to time. Prior medical history and concomitant medication did not influence efficacy. The greatest contribution to the overall decrease in event rates was the decrease in stroke which appeared to be independent of stroke severity. As noted by the clinical evaluator, the clinical significance of the treatment effect is probably quite modest. The absolute difference in event rate at 36 months was 2.45%, 95% CI [0.625, 4.27%] with an associated NNT of 41. By contrast, it was shown in ACTIVE W that clopidogrel/ASA was clinically and statistically significantly worse than oral anticoagulant therapy and the study was terminated early, at 2 years. After 12 months treatment, the increase in absolute risk of clopidogrel/ASA vs oral anticoagulant therapy was 2.06%, 95% CI [1.025, 3.10%] which translates to an NNH of 49. The risks of stroke and of non-CNS systemic embolism were greatly increased on clopidogrel/ASA compared with oral anticoagulant therapy.

#### *Safety and RMP*

The rates of adjudicated major bleeding, severe bleeding, intracranial haemorrhage, fatal bleeds and haemorrhagic stroke were all higher in the clopidogrel/ASA group vs the placebo/ASA group. The absolute risk increase for adjudicated major bleeding was 2.37%, 95% CI [1.35%, 3.40%] with an associated NNH of 42. The rates of both bleeding episodes and major bleeding episodes were higher in the clopidogrel/ASA group than in the oral anticoagulant group whereas the rates of fatality due to bleeding were slightly higher in the oral anticoagulant group (0.33%) than in the clopidogrel/ASA group (0.21%). Injuries were more common with clopidogrel/ASA than with either ASA alone or anticoagulant therapy. The excess of injuries appears to be accounted for by an excess of contusions and haematomas associated with clopidogrel/ASA. The Office of Product Review has found the RMP acceptable. However, the sponsor has undertaken to provide an updated RMP. *Furthermore, the sponsor has been requested to add a number of safety concerns identified by the clinical evaluator to the important potential risks and to update both the pharmacovigilance and risk minimisation plans accordingly.*

#### *Indication*

As noted by the clinical evaluator, the currently approved indication for ASA in Australia differs from that proposed in this submission. The most relevant part of the currently approved indication and that which is transferable to the one proposed in the submission is that which states: "Prophylaxis and treatment of transient ischaemic attacks and other thromboembolic disorders". While it is impossible to quantify the exact degree of overlap of the patient populations captured by this indication and the one proposed, the Delegate was of the opinion that there would be a reasonable if not substantial degree of overlap. *However, both the sponsor and the members of the ACPM were asked for comment on this.*

There may be some concerns at the inclusion, in the proposed indications, of the following wording: "In adult patients with atrial fibrillation at increased risk of vascular events who can take VKA therapy, VKA has been shown to be associated with a better clinical benefit than aspirin alone or the combination of clopidogrel and aspirin for the reduction of stroke". The statement is an accurate reflection of clinical trial evidence, at least in the present instance, with respect to the comparison between VKA therapy and therapy with

clopidogrel/aspirin. The Delegate has no strong views against the inclusion of the statement in the Indications. However, there must be a rider added that before prescribing VKA therapy, the currently approved Product Information for the VKA therapy must be consulted. *The Delegate requested that the ACPM members indicate their views on the appropriateness or otherwise of inclusion of the statement in the Indications.*

### *Data deficiencies*

The Delegate expressed concerns that ASA 75-100 mg may not have been an appropriate comparator in ACTIVE A. It would appear that at least some of the SPAF clinical trial results were based on the use of higher doses of aspirin, for example, 325 mg. Yet there appears to have been no accounting of this in the sample size calculations for ACTIVE A. *The sponsor has been asked to show the evidence in support of the use of ASA at doses of 75-100 mg in patients with AF.* Without robust evidence which demonstrates the latter, how can ASA at such doses be an appropriate comparator? Finally, while the target population for the preventative use of low dose ASA already approved in Australia does overlap with the target population for the proposed indications, there is not precise overlap.

*The sponsor must respond to the clinical evaluator's observations of several instances of nonsensical ranges of values reported for certain demographic parameters. If these are the result of data entry errors, what are the guarantees which the sponsor can offer with regard to the integrity of the rest of the dataset.*

One of the most obvious flaws in the design of the ACTIVE A study was that there was no arm involving treatment with clopidogrel only. Clopidogrel is already approved for prevention of vascular ischaemia associated with atherothrombotic events in a patient population which does overlap at least to some degree with the proposed population of patients with AF. Thus it could be argued that clopidogrel may have been an appropriate comparator. There are no data available in the submission to compare the efficacy of clopidogrel/ASA with that of clopidogrel/placebo. As pointed out by the clinical evaluator, one should be able to demonstrate that a fixed dose combination product has efficacy which is superior to that of either of the component active entities, ASA or clopidogrel alone. It is a question not only of efficacy but of the risk benefit balance. Nothing can be surmised about the risk benefit balance of clopidogrel alone *vis a vis* the indication, nor anything about the comparison of that risk benefit balance with the risk benefit balance of clopidogrel/ASA and of ASA.

Finally, it appeared that half of the combined population of the ACTIVE A and W studies were taking irbesartan and half were not taking irbesartan. There was nothing in the data set which gave any indication as to whether or not there was any sort of interaction with irbesartan, that is, an irbesartan effect. While the Delegate thinks that it would be unlikely, there is no evidence either way.

### *Summary*

In ACTIVE A, the NNT value for the primary endpoint of stroke, MI, non-CNS systemic embolism or vascular death was 41 compared with a NNH of 42 for the safety endpoint of adjudicated major bleeding. Numerically, these balance each other. In qualitative terms, prevention of a case of stroke or MI or non-CNS bleeding or vascular death may arguably be a better outcome than causing a case of adjudicated major bleeding. However, compared with the rates on ASA alone, the rates of bleeding on clopidogrel/ASA were increased for all types of bleeding and from all sites, including intracranial and gastrointestinal. One of the prime motivators for a clinician not to use VKA in a patient with AF may well be an already existing increased risk of bleeding in the patient. What is proposed is a course of treatment which itself has an inherently high risk of causing bleeding. It seems illogical to use this product when the risk of bleeding is higher

compared to that of aspirin alone and when the ACTIVE W trial showed the efficacy of this product to be inferior to that of VKA therapy. Also balanced against this arguably better outcome are the increased rate of injuries (haematomas, contusions) on clopidogrel/ASA vs ASA, the concerns expressed by the Delegate about the use of the SPAF trials in the sample size calculations, the concerns expressed by the Delegate about the choice of ASA 75-100 mg as an appropriate comparator, the concerns expressed by the Delegate about the "eligibility" of patients to participate in ACTIVE A and about the exact nature of the "unwillingness" expressed by participants in ACTIVE A to take VKA, the difficulty in equating the populations targeted by the current approved indication for ASA and that proposed for clopidogrel/ASA, the data entry errors detected by the clinical evaluator, the fact that nothing is known about the risk benefit balance of clopidogrel when used for the proposed indication and the lack of any data concerning possible interaction effects of irbesartan. Of these latter extra concerns, the risk of injuries, all of the Delegate's concerns surrounding the choice of ASA 75-100 mg as an appropriate comparator and the lack of knowledge concerning the risk benefit balance of clopidogrel alone are the most important. Given the number of unresolved issues and that, regardless of these issues, the Delegate proposed to reject the submission. The Delegate posed the following questions to the Advisory Committee on Prescription Medicines (ACPM).

- Do members of the committee share any or all of the Delegate's concerns regarding the choice of ASA 75-100 mg as an appropriate comparator in ACTIVE A?
- Do members of the committee share the Delegate's concerns about the lack of any comparison with clopidogrel alone for the proposed indications in patients with AF?
- Do members of the committee agree with the Delegate that, based on a comparison of the NNT and NNH values, the evidence for a treatment benefit as conveyed by ACTIVE A is finely balanced or neutral?
- What are the views of the ACPM with regard to the inclusion in the proposed indications of the statement that *VKA has been shown to be associated with a better clinical benefit than aspirin alone or the combination of clopidogrel and aspirin for the reduction of stroke*?

**Response from Sponsor**

In light of the comments of the clinical evaluator and the Delegate the sponsor proposed to modify the Clinical Trials, Indication, Precautions and Dosage and Administration instructions in the Product Information (PI) to more clearly articulate that CoPlavix is an alternative option only for those AF patients who are not suitable for VKA therapy and have a low bleeding risk, and should not be considered for use in any patient for whom VKA therapy is appropriate.

The revised indication is outlined below and is more closely aligned with wording recently recommended for approval in the EU following a positive CHMP opinion.

*CoPlavix is indicated 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 are not suitable for Vitamin K antagonists (VKAs), and who have a low bleeding risk (see Clinical Trials). VKAs are the recommended treatment for AF patients with a moderate to high risk of stroke. Before prescribing VKA therapy, the currently approved Product Information for the VKA therapy must be consulted. CoPlavix should only be used in patients for whom VKAs are not suitable (see Precautions; Dosage and Administration).*

*Risk factors for vascular events include:*

*· age ≥75 years*
*· age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease*
*· on treatment for systemic hypertension*
*· prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus*
*· left ventricular dysfunction with left ventricular ejection fraction <45%*
*· peripheral vascular disease*

The sponsor concurred with the conclusions of the clinical evaluator and considered the benefit risk of clopidogrel and ASA in this indication supports approval on the following grounds:

- The benefits of VKAs in prevention of stroke in AF is well established and warfarin remains the gold standard treatment, however, it is also well documented that up to 30% of appropriately indicated AF patients in Australia and globally do not currently take or do not persist with VKA therapy for a multitude of reasons beyond bleeding risk
- ASA is currently the only available therapy in clinical practice for AF patients to prevent stroke in those patients who are unsuitable for VKA therapy, albeit there being no specific indication in the product labeling. There is thus a clear unmet medical need for an additional/alternative therapy to prevent the debilitating consequences of stroke and other vascular events in patients for whom VKA therapy is not suitable
- A dose of ASA of 75-100mg is recommended in ESC AF medical guideline. It has been recommended based on a meta-analysis of clinical trial data and aspirin's pharmacological effect of near complete platelet inhibition and reduced risk of bleeding compared to higher doses (300 mg) of aspirin
- ACTIVE A demonstrated that in AF patients unsuitable for VKA therapy, clopidogrel in combination with ASA (75-100 mg) reduced the composite primary endpoint risk of stroke, MI, non-CNS embolism or vascular death by 11.1% (95% CI:2.4,19.1;0=0.013) and in particular the rate of stroke by 28.4% (95% CI: 16.8, 38.3; p=00001) compared to ASA alone.
- Recent clinical practice guidelines (2010 AF guidelines from the ESC; 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation) endorse the use of clopidogrel and ASA 75-100 mg in AF patients in whom oral anticoagulation with warfarin is considered unsuitable
- In assessing benefit risk, there is a clear benefit to using CoPlavix in this indication. Overall the clinical consequences of stroke is the most impactful on patient outcomes considering the higher risk of mortality and long term effects on patient quality of life compared to most major bleeds that do not result in increased mortality nor result in chronic disability
- The sponsor's proposal to revise the indication and to more closely align with that recommended for approval in the EU will ensure that the importance of evaluation for suitability for VKA therapy as the preferred primary treatment option is clearly communicated to prescribers and patients and that only patients unsuitable for VKA therapy with a low bleeding risk are considered for CoPlavix therapy
- In the absence of an approved indication for CoPlavix in AF patients, up to 30% of patients are at risk of debilitating stroke and the adoption of clinical practice

guidelines may result in 'off label' use, without the appropriate information being readily accessible to physicians and patients. This could potentially increase the risk of inappropriate use and would not be aligned with the concepts of quality use of medicines

### *Unmet Medical Need in AF Patients Unsuitable for VKA Therapy*

The complexity of VKA therapy and the difficulty of maintaining patients in the therapeutic range means that for some patients, this therapy is unmanageable and physicians often decide that the risks and difficulty of VKA therapy outweigh its potential benefits. The reasons are numerous: anticoagulation carries a greater risk of bleeding, regular blood taking is needed to monitor the levels of the INR, changes in lifestyle are necessary to take into account dietary restrictions and avoidance of alcohol, physical immobility from age related health problems could lead to an increase in fall risks, and the lack of caregiver commitments to ensure compliance to treatment and follow up visits. Additionally many patients begin VKA therapy and then cease taking the therapy due to difficulties maintaining INR or difficulties in accessing pathology testing to regularly monitor their INR.

Multiple surveys clearly document that there is a sizable proportion of patients in whom physicians choose not to use VKA therapy beyond bleeding risks. Most surveys in western countries document that about a third of patients who would otherwise appear to be ideal for VKA therapy are either not started on it or taken off it after an initial period of treatment. The Euro Heart Survey demonstrated that VKA therapy was used in 61% of high risk European patients.[8] An administrative database survey in the USA, evaluating 16000 Medicare patients, showed very similar results indicating that about a third of AF patients considered ideal for VKA therapy, in terms of stroke and bleeding risk, were not receiving VKA.[9] Gallagher et al analysed the General Practice Research Database in the United Kingdom, including 41910 chronic AF patients.[10] Overall, less than 50% of patients were started on VKA. Amongst elderly patients whose risk of stroke is highest, the rates of uptake were much lower. The rate of discontinuation of VKA is also high, even after patients have been successfully initiated. Gallagher et al found a 50% discontinuation rate within 3 years of starting VKA in all age groups.[10] Discontinuation rates were also high in the US Medicare survey. Although many investigators believe that better education of physicians will improve uptake of VKA therapy, this view is not supported by data from some of the most highly respected hospitals. Data from the Massachusetts General Hospital and Boston University in the east of the US and from the Kaiser Permanente Health Management System in California confirm that between a third and a half of elderly patients with AF (>65 years) do not receive VKA therapy. They also confirm that once started, rates of discontinuation exceed 25% within one year.[11,12,13]

[8] Nieuwlaat R, Capucci A, Camm AJ et al. Atrial fibrillation management: a prospective survey in ESC member countries. The Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005; 26: 2422-34.

[9] Birman-Deych E, Radford MJ, Nilasena DS, and Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006; 37: 1070-4.

[10] Gallagher AM, Rietbrock S, Plumb J and Van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemos 2008; 6: 1500–6.

[11] Hylek EM, Evans-Molina C, Shea C, Henault LE and Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007; 115: 2689-96.

[12] Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke 2006; 37: 1075-80.

In AF patients deemed unsuitable for VKA therapy there is an unmet medical need for an additional/alternative therapy to prevent the debilitating consequences of stroke and other vascular events for which they are at increased risk. CoPlavix provides a therapeutic option to meet this need.

The remainder of the response addressed a number of issues raised by the Delegate relating to the clinical trial design, including subject eligibility and choice of comparator arms as well as the overall benefit risk relevant to assessment of the treatment effect in ACTIVE A.

### *Subject Eligibility*

ACTIVE A was part of the ACTIVE clinical program that aimed to determine the place of clopidogrel in the prevention of atherothrombotic events, including stroke, in patients with AF and at least one risk factor for atherothrombotic event. The suitability of patients for ACTIVE A was assessed by study physicians who decided whether to use VKA or clopidogrel in combination with ASA based on their assessment of risks and benefits considering the individual patient case history and patient preference. In accordance with international guidelines, patients eligible for (that is, able to receive VKAs with standard clinical care) and willing to take VKA were enrolled into the ACTIVE W study. Patients whom physicians assessed to not have a good risk and benefit profile to receive VKA therapy or who were unwilling to take VKA therapy were enrolled into study ACTIVE A. The Steering Committee of the ACTIVE A study did not second guess these decisions and asked only that the physician document the reasons for the decision to enrol into ACTIVE A in the case report form. No systematic information was collected about why a physician decided that a patient was not a candidate for VKA after the initial assessment. However, all patients enrolled into study ACTIVE A because of refusal to take a VKA needed to review and sign the ACTIVE A consent form, which clearly described the proven benefits of VKAs and the fact that this was the treatment recommended in the guidelines.[14] In the sponsor's *Clinical Overview* a summary of factors influencing decisions to enrol patients in ACTIVE A was provided, including specific bleeding risks.

In summary patients were deemed ineligible for VKA therapy (and hence enrolled in ACTIVE-A) for the following reasons: 28.1% due to physicians assessment of VKA inappropriateness, 21.5% due to patient inability to comply with INR monitoring, 25.7% due to patient preference only, and 23.1% due to a specific bleeding risk. ACTIVE W demonstrated that patients should not be put on clopidogrel plus aspirin if the sole reason for not initiating VKA therapy is concern about bleeding. Therefore the proposed indication has been revised to state that CoPlavix should be used only in those patients with a low bleeding risk. Thus the benefits of clopidogrel and ASA seen in ACTIVE A can be generalised to patients in the community who are judged unsuitable for VKA.

### *Assessment Duration*

All outcome events were counted over the duration of follow up that lasted up to 5 years (from randomization to the final follow up visit), after validation by the Event Adjudication Committee. The final follow up visit was planned to be held between 1 and 30 November

[13] Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. Predictors of warfarin discontinuation in older patients with atrial fibrillation. J Am Coll Cardiol 2008; 51: A238.

[14] Fuster VF, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Cardiology Committee for Practice Guidelines (Writing Committee to Revise the Association Task Force on Practice Guidelines and the European Society of 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006; 114: 700-52.

2008. For patients who did not have a visit in November 2008, but in whom information was obtained following that period, only events occurring up to 30 November 2008 were included. For patients not having an event the censoring date was the minimum of their November 2008 visit date or 30 November 2008, or their final follow up visit or contact visit if the patient was lost to follow up.

### *Choice of Comparator*

At time of study design, the Steering Committee constituted of experts in the field of AF did not consider that clopidogrel monotherapy could be proposed to this population of AF with high risk factors for atherothrombotic or thromboembolic events. It was hypothesized that due to the synergistic effect of clopidogrel in combination with ASA, and the recent results of the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) study at time of ACTIVE design, combining the two compounds was the most beneficial alternative to prevent stroke in these patients where stroke is known to be the major complication. The CURE study demonstrated a benefit of clopidogrel in combination with ASA in acute coronary syndrome (ACS) patients for the prevention of thrombotic events with a risk reduction of 20% in vascular events. It was hypothesized based on the CURE data and on the mechanism of thrombus in AF patients that could not exclude a component of atherothrombosis, that clopidogrel in addition to ASA will provide greater benefit on vascular events. Since the CURE study also showed that increasing the dose of ASA from below 100 mg/day to over 200 mg/day increased the risk of major bleeding, in ACTIVE A it was decided to evaluate a dose of 75-100 mg/day of ASA in combination with clopidogrel. This is why for patients who could receive VKA, the comparison in study ACTIVE W was made with clopidogrel on a background of ASA versus VKA in a non-inferiority design, and for patients that could not receive VKA, clopidogrel in combination with ASA was compared to ASA in a superiority design. Current guidelines and clinical practice support aspirin in a dosage of 75 mg-100 mg as an alternative to VKA therapy for patients with lower risk of stroke and is therefore the appropriate comparator in ACTIVE A.

ASA has been studied for the prevention of ischaemic events in a large variety of doses, from <50 mg/day to >1200 mg/day. As shown by the Antiplatelet Trialists Collaboration Meta-analysis, there is strong evidence that doses of ASA between 75 and 1500 mg/day are equally effective against vascular events.[15,16] The ASA doses used in placebo controlled trials of ASA in patients with AF also have varied considerably. The three largest trials used ASA doses from 75 mg to 1200 mg/day. The only trial (SPAF) to report a significant benefit from ASA against stroke in AF used a relatively high dose of ASA (325 mg), and due to internal heterogeneity and early termination its result may be exaggerated.[17] The equally large EAFT study observed a nonsignificant relative risk reduction of 11% in stroke with a similar dose of ASA (300 mg). The relative risk reductions for stroke in previous AF trials according to the dose of ASA used were provided.

When aspirin alone was compared with placebo or no treatment in seven trials, treatment with aspirin was associated with a nonsignificant 19% (95% CI –1% to –35%) reduction in the incidence of stroke. There was an absolute risk reduction of 0.8% per year for primary

[15] Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. 1. Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81-106.

[16] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. [Erratum in: BMJ 2002; 324: 141.] BMJ 2002; 324: 71-86.

[17] Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. Circulation 1991; 84: 527-539.

prevention trials and 2.5% per year for secondary prevention by using aspirin. Aspirin was also associated with a 13% (95% CI –18% to –36%) reduction in disabling strokes and a 29% (95% CI –6% to –53%) reduction in non-disabling strokes. When only strokes classified as ischaemic were considered, aspirin resulted in a 21% (95% CI –1% to –38%) reduction in strokes. When data from all comparisons of antiplatelet agents and placebo or control groups were included in the metaanalysis, antiplatelet therapy reduced stroke by 22% (95% CI 6–35).

New 2010 ESC AF guidelines support the usage of ASA in dosages 75-100 mg as an alternative to VKA in low risk patients. To the sponsor's knowledge, however, ASA is not indicated in any country for this indication. The ACTIVE A protocol referring to guidelines at the time stated: "These have uniformly recognized that both warfarin (including other oral anticoagulants) and ASA are effective antithrombotic agents in AF, with a preference for warfarin. Warfarin (or other oral anticoagulant therapy) is recommended for AF patients with risk factors for stroke who do not have an excessive risk of bleeding. ASA is recommended only for patients with either a lower than average risk of stroke or a higher risk of serious bleeding." In accordance with the new ESC guidelines, 75-100 mg is now one of the recommended dosages of aspirin to be used in this particular population: "Pharmacologically, near complete platelet inhibition is achieved with aspirin 75 mg. Furthermore, low dose aspirin (100 mg) is safer than higher doses (such as 300 mg), given that bleeding rates with higher doses of aspirin are significant. Thus, if aspirin is used, it is reasonable to use doses in the lower end of the allowed range (75–100 mg daily)." Use of low dose ASA in ACTIVE A is thus consistent with best practice.

Additionally in the just released 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, based on the ACTIVE A data, a new recommendation is included: "The addition of clopidogrel to aspirin (ASA) to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation". On the basis of the above the sponsor considered that ACTIVE A is an appropriately designed study and the choice of comparator arms and dosage of ASA reflect best clinical practice allowing a robust evaluation of the treatment outcomes relevant to use in the general community.

### *Benefit risk assessment*

In ACTIVE A, the benefit of clopidogrel in combination with ASA was seen primarily in the reduction of stroke (risk reduction ratio [RRR] 28.4%, 95% confidence interval [CI]: 16.8, 38.3; p = 0.00001), with 112 fewer strokes. Most strokes in patients with AF are large and result in major disability and morbidity. This was also true in ACTIVE A, where almost two thirds of all strokes had a modified Rankin score of 3-6 indicating major disability or death. The benefit of adding clopidogrel to aspirin was seen for all severities of strokes, as measured by the modified Rankin score. There were 46 fewer non-disabling 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) with the addition of clopidogrel to ASA. In the context of existing clinical practice and the unmet medical need for alternative therapies for AF patients unsuitable for VKA therapy, the sponsor provided an indirect comparison of the 2007 meta-analysis and the ACTIVE A results which supports the conclusion that there is a 39% relative reduction for stroke with warfarin compared to ASA, a 28% relative risk reduction for stroke with clopidogrel in combination with ASA compared to ASA, and a 22% relative reduction for stroke with ASA alone.

The assessment of net clinical benefit for antithrombotic therapy is challenging as it requires balancing multiple risks and benefits which have different clinical importance. Most strokes result in long term disability or death, but most major bleeds, even if they require blood transfusion, do not result in chronic disability and have a lower rate of mortality. Thus, simply adding strokes and major bleeds give a misleading picture of the net benefit. Therefore, it makes clinical sense to look to assess clinical benefit by looking at a composite outcome which includes stroke, MI and severe bleeds. Another useful composite outcome that assesses the more severe outcomes is that of disabling stroke and intracranial bleeding. There was a net benefit in favour of adding clopidogrel to ASA when considering stroke/MI versus major bleeding or severe bleeding.

While the prevention of any stroke may be appropriately balanced against severe bleeding, the prevention of specifically disabling or fatal stroke should be weighed against the risk of intracranial haemorrhage in evaluating the benefit/risk relationship, since intracranial haemorrhage is the most devastating of bleeding complications. Such an analysis demonstrates that the benefit/risk relationship is positive for clopidogrel in combination with ASA compared to ASA alone in patients with disabling or fatal stroke (Rankin 3 to 6), as well as in patients with stroke of any severity when weighed against the risk of intracranial bleeding.

Overall, the large ACTIVE program in AF patients, with its two separate but interrelated trials totaling 14, 260 patients at risk for vascular events and stroke, showed conclusive results that allows physicians to provide the most suitable treatment for AF on a patient by patient basis. For suitable patients VKA therapy is the treatment of choice, as recommended by international guidelines and confirmed by the ACTIVE W results. The ACTIVE A study showed that for patients who cannot receive a VKA, clopidogrel in combination with ASA is a suitable alternative therapy considering that as shown by literature data on real life experience, many AF patients do not currently receive any therapy despite their substantial level of risk for stroke.

**Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission for an extension of indications.

In making this recommendation, the committee considered that safety and efficacy of the products in combination have not been satisfactorily established for the proposed indication. While superior efficacy of the proposed treatment was demonstrated in the prevention of stroke, the rate of major bleeding was reported to be statistically significantly higher and the minor bleeding rate was also trending higher; this created a negative risk benefit profile. The risk of haemorrhage is a real possibility. Vitamin K antagonists were demonstrated to have a more positive safety profile. The relative efficacy of clopidogrel versus clopidogrel and aspirin was not clear.

The ACPM was concerned at the need for cessation of the proposed treatment prior to surgery and the lack of any possibility of reversal in an emergency and also with the lack of data in renal failure.

The committee also noted the excess in trade names (and the lack of dosage quantum in those trade names) in the application and the subsequent possibility of confusion among both prescribers and patients.

## Outcome

Based on a review of safety and efficacy, TGA proposed to recommend rejection of the proposed extension of indications for the combination of clopidogrel (100 mg) and aspirin

(75 mg/100 mg). The sponsor therefore elected to withdraw the PI amendments relating to the proposed extension of indications for the fixed dose combination, whilst implementing other PI amendments to harmonize the PI with the approved PI for clopidogrel (Plavix). The grounds for withdrawal were based on the sponsor not intending to undertake any additional clinical studies in the AF population, especially since the proposed indication has already been approved in the European Union and Canada where the application was submitted for Plavix (clopidogrel) rather than the fixed dose combination CoPlavix (clopidogrel and aspirin). Hence, no new data to address the questions raised by the Delegate and ACPM to demonstrate the relative benefit of clopidogrel alone in combination with aspirin vs. the combination of clopidogrel and aspirin could be provided.

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

# PRODUCT INFORMATION

## COPLAVIX® 75MG/75MG & COPLAVIX® 75MG/100MG

## NAME OF THE MEDICINE

### Non-proprietary Name

CoPlavix® 75mg/75mg containing clopidogrel 75 mg (as clopidogrel hydrogen sulfate) and aspirin 75 mg

CoPlavix® 75mg/100mg containing clopidogrel 75 mg (as clopidogrel hydrogen sulfate) and aspirin 100 mg

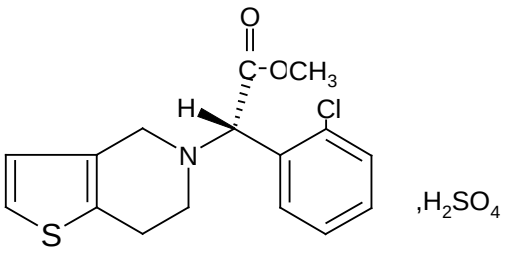
### Chemical Structure

Clopidogrel

Clopidogrel hydrogen sulfate is designated chemically as methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate sulfate (1:1).

The empirical formula of clopidogrel hydrogen sulfate is $C_{16}H_{16}ClNO_2S.H_2SO_4$ and its molecular weight is 419.9.

Clopidogrel hydrogen sulfate has the following chemical structure:



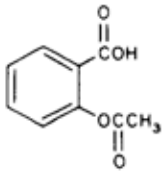

*CAS Number*

120202-66-6 (Clopidogrel hydrogen sulfate),

113 665-84-2 (Clopidogrel base).

Aspirin

Aspirin (or acetylsalicylic acid) is designated chemically as 2-acetoxybenzoic acid and has the following chemical structure.




The empirical formula is $C_9H_8O_4$ and its molecular weight is 180.2.

*CAS Number*

50-78-2.

## DESCRIPTION

### Clopidogrel

Clopidogrel hydrogen sulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It is freely soluble in methanol, sparingly soluble in methylene chloride and is practically insoluble in ethyl ether. It has a specific optical rotation of about + 56°.

### Aspirin

Aspirin is a white crystalline powder or colourless crystals, odourless or almost odourless, slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether. It melts at about 135°C.

### CoPlavix

CoPlavix tablets are film coated and for both strengths each tablet contains mannitol, macrogol 6000, cellulose – microcrystalline, castor oil – hydrogenated, hydroxypropylcellulose, maize starch, stearic acid, silica – colloidal anhydrous. The coating contains lactose, hypromellose, titanium dioxide, glycerol triacetate, a colourant and carnauba wax. The colourant is yellow iron oxide in CoPlavix 75mg/75mg and red iron oxide in CoPlavix 75mg/100mg.

## PHARMACOLOGY

### Pharmacodynamics

Clopidogrel

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Platelets have an established role in the pathophysiology of atherosclerotic disease and thrombotic events. Long term use of anti-platelet drugs has shown consistent benefit in the prevention of ischaemic stroke, myocardial infarction and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet ADP receptors, P2Y12, thus inhibiting platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover (approximately 7 days).

Statistically significant and dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 7 days after treatment was discontinued.

Aspirin

Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and the production of thromboxane $A_2$, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

**Pharmacokinetics**

Clopidogrel

Clopidogrel After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Clopidogrel mean peak plasma levels (approximately 2.2 - 2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is a prodrug which is extensively hydrolysed in the liver by HCEl (human carboxylesterase1). In vitro and in vivo, clopidogrel is metabolised according to two main metabolic pathways:

- One mediated by esterases and leading to hydrolysis into its carboxylic acid derivative, which is inactive and is the main circulating metabolite (about 85% of the circulating compound in plasma). Mean peak plasma levels of this metabolite (approx. 3600 ng/ml after single 75 mg oral dose) occurred approximately 45 minutes after dosing. *In vitro* in the presence of ethyl alcohol, the rate of clopidogrel hydrolysis was decreased, and some of the clopidogrel was converted to ethyl clopidogrel.
- One mediated by multiple cytochromes P450 in the gastrointestinal tract and liver leading to the active metabolite(s) of clopidogrel, a thiol derivative, which is generated through formation of 2 oxo clopidogrel. This metabolic pathway is mediated by multiple Cytochrome P450 isoenzymes, i.e., CYP3A4, CYP3A5, CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP2B6. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. Clinical studies have indicated that individuals with loss of function variants of CYP2C9 and CYP2C19 are more likely to have lower concentrations of the active metabolite and higher residual platelet activity; clopidogrel is therefore less likely to be efficacious in these poor metabolisers.

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

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

Following an oral dose of $^{14}$C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120 hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half life of approximately 6 hours. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (≥75 years) as compared to young healthy volunteers. However, these higher plasma levels were not associated with differences in platelet aggregation and bleeding time.

Plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 mL/min) and healthy subjects, after repeated doses of 75 mg/day. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day.

Aspirin

*Absorption*

Following absorption, the aspirin in CoPlavix is hydrolysed to salicylic acid, with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of aspirin are essentially undetectable 1.5 to 4 hours after dosing. Administration of aspirin with meals did not significantly modify its bioavailability.

*Distribution*

Based on available data, aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its

binding is concentration dependent (nonlinear). At low concentrations (<100 µg/mL), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk and foetal tissues.

*Metabolism and Elimination*

The aspirin in CoPlavix is rapidly hydrolysed by HCE2 (human carboxylesterase 2) in the intestine and the liver to salicylic acid, with a half-life of 0.3 to 0.4 hours for aspirin doses from 75 to 100 mg. This salicylic acid has a plasma half-life of approximately 2 hours. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations, due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic aspirin doses (10 to 20 g), the plasma half-life may be increased to over 20 hours. At high aspirin doses, the elimination of salicylic acid follows zero-order kinetics (i.e. the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid.

Clopidogrel/Aspirin Bioequivalence

CoPlavix 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to the clopidogrel 75 mg tablets in terms of clopidogrel $C_{max}$ and AUC, and/or carboxylic acid metabolite. For aspirin, CoPlavix® 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to aspirin 75 mg and 100 mg, respectively, in terms of aspirin AUC, and salicylic acid $C_{max}$ and AUC. In terms of $C_{max,}$ aspirin was not bioequivalent with the $C_{max}$ being 1.3- to 1.6-fold higher for CoPlavix than for the aspirin tablets. However, a slight difference in aspirin $C_{max}$ is not considered to be clinically significant (See CLINICAL TRIALS).

*Pharmacogenetics*

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 µM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg

regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

**Table 1: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metaboliser Status**

| | DOSE | ULTRARAPID (N=10) | EXTENSIVE (N=10) | INTERMEDIATE (N=10) | POOR (N=10) |
|---|---|---|---|---|---|
| $AUC_{last}$ (ng.h/mL) | 300 mg (Day 1) | 33 (11) | 39 (24) | 31 (14) | 14 (6) |
| | 600 mg (Day 1) | 56 (22) | 70 (46) | 56 (27) | 23 (7) |
| | 75 mg (Day 5) | 11 (5) | 12 (6) | 9.9 (4) | 3.2 (1) |
| | 150 mg (Day 5) | 18 (8) | 19 (8) | 16 (7) | 7 (2) |
| IPA (%)[a]* | 300 mg (24 h) | 40 (21) | 39 (28) | 37 (21) | 24 (26) |
| | 600 mg (24 h) | 51 (28) | 49 (23) | 56 (22) | 32 (25) |
| | 75 mg (Day 5) | 56 (13) | 58 (19) | 60 (18) | 37 (23) |
| | 150 mg (Day 5) | 68 (18) | 73 (9) | 74 (14) | 61 (14) |

Values are mean (SD)

*a* * Inhibition of platelet aggregation with 5μM ADP; larger value indicates greater platelet inhibition

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 μM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), and TRITON-TIMI 38 (n=1477) and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

**Special Populations**

Geriatric Patients

Plasma concentrations of the main circulating metabolite of clopidogrel are significantly higher in the elderly (≥ 75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients

CoPlavix is contraindicated in severe renal impairment. After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although

inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75 mg of clopidogrel per day. Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment. Therefore CoPlavix should be used with caution in this population.. (see 'PRECAUTIONS').

Patients with Hepatic Impairment

CoPlavix is contraindicated in severe hepatic impairment. Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. CoPlavix should therefore be used with caution in this population (see 'PRECAUTIONS').

CYP2C9 AND CYP2C19 poor metabolisers

Clinical studies have indicated that individuals with loss of function variants of CYP2C9 and CYP2C19 are more likely to have lower concentrations of the active metabolite and higher residual platelet activity; clopidogrel is therefore less likely to be efficacious in these poor metabolisers.

Gender

No significant difference was observed in the plasma levels of the main circulating metabolite of clopidogrel between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Ethnicity

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see PHARMACOLOGY, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

## CLINICAL TRIALS

The safety and efficacy of clopidogrel and aspirin has been evaluated in patients in three double-blind studies: the CURE, CLARITY, and COMMIT studies, which compared clopidogrel to placebo, both given in combination with aspirin and other standard therapy.

The **CURE** study included 12,562 patients with acute coronary syndrome (unstable angina or non-ST-elevation myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, n = 6244) or placebo (n = 6287), both given in combination with aspirin (75-325 mg once daily) and other standard therapies (oral anti-coagulants and long term NSAIDs were not permitted). Patients were treated for up to one year.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p = 0.00009) for the clopidogrel-treated group. The benefits of clopidogrel were seen within a few hours and maintained throughout the course of the study (up to 12 months). The primary outcome was reduced to a similar extent within the first 30 days (relative risk reduction of 22 %), from 30 days to one year (relative risk reduction of 19%), and for the entire one year study (relative risk reduction of 20%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1035 (16.5%) in the clopidogrel-treated group and 1187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p = 0.0005) for the clopidogrel-

treated group, a benefit which was consistent for each component, indicating that clopidogrel reduced a range of atherothrombotic events.

In the course of the study, patients who underwent cardiac revascularisation (surgical or percutaneous coronary intervention with or without coronary stent implantation), received similar benefit from clopidogrel + aspirin (including standard therapies) as those who did not have a cardiac revascularisation.

The results obtained in populations with different characteristics (e.g. unstable angina or non-ST-elevation MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering drugs, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of aspirin (75-325 mg once daily).

In patients with ST-segment elevation acute myocardial infarction, safety and efficacy of clopidogrel have been evaluated in two randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The randomised, double-blind, placebo-controlled **CLARITY** trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomised to receive either clopidogrel (300 mg loading dose, followed by 75 mg/day; n = 1752) or placebo (n = 1739), together with aspirin (150 to 325 mg loading dose followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

The primary endpoint was the occurrence of the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the predischarge angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge, if prior to Day 8.

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% were 65 years or over. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta-blockers, 54.7% ACE inhibitors and 63% statins.

The number of patients who reached the primary endpoint was 262 (15.0%) in the clopidogrel-treated group and 377 (21.7%) in the placebo group, representing an absolute reduction of 6.7% and a 36% reduction in the odds of the endpoint in favour of treatment with clopidogrel (95% CI: 0.53, 0.76; $p<0.001$), as shown in Table 2, mainly related to a reduction in occluded infarct-related arteries.

The benefit of clopidogrel on the primary endpoint was consistent across all prespecified subgroups, including patients' age, gender, infarct location and type of fibrinolytic or heparin used.

**Table 2: Event Rates for the Primary Composite Endpoint in the CLARITY Study**

| | Clopidogrel + aspirin N = 1753 | Placebo + aspirin N = 1739 | OR | 95% CI |
|---|---|---|---|---|
| Number (%) of patients reporting the composite endpoint | 262 (15.0%) | 377 (21.7%) | 0.64 | 0.53, 0.76 |
| Occluded IRA | | | | |
| N (subjects undergoing angiography) | 1640 | 1634 | | |
| n (%) patients reporting endpoint | 192 (11.7%) | 301 (18.4%) | 0.59 | 0.48, 0.72 |
| Death | | | | |
| n (%) patients reporting endpoint | 45 (2.6%) | 38 (2.2%) | 1.18 | 0.76, 1.83 |
| Recurrent MI | | | | |
| n (%) patients reporting endpoint | 44 (2.5%) | 62 (3.6%) | 0.69 | 0.47, 1.02 |

The total number of patients with a component event (occluded IRA, death or recurrent MI) is greater than the number of patients with a composite event because some patients had more than a single type of component event.

The randomised, double-blind, placebo-controlled, 2x2 factorial design **COMMIT** trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected myocardial infarction with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients were randomised to receive clopidogrel (75 mg/day) or placebo, in combination with aspirin (162 mg/day), for 28 days or until hospital discharge, whichever came first.

The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The patient population included 27.8% women, 58.4% 60 years or over (26% 70 years or over) and 54.5% patients who received fibrinolytics, 68% who received ACE-inhibitors and 10.9% who received non-trial beta-blockers (as well as half of the patients who received metoprolol as study medication).

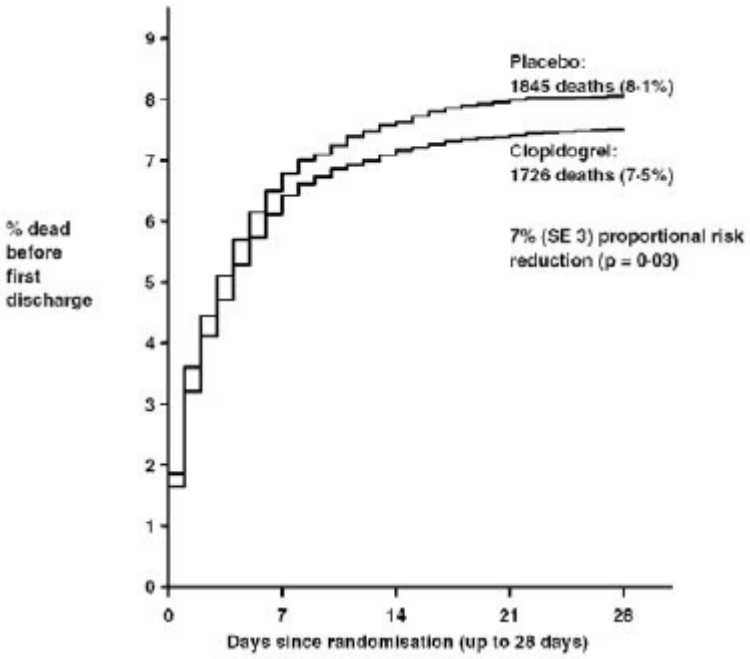
As shown in the Table 3 and Figures 1 and 2 below, clopidogrel significantly reduced the relative risk of death from any cause by 7% (p = 0.029) and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002), representing an absolute risk reduction of 5 and 9 patients per 1000 treated (0.5 and 0.9%), respectively.

**Table 3: Outcome Events in the COMMIT Analysis**

| Event | Clopidogrel +aspirin n = 22961 | Placebo +aspirin n = 22891 | Odds ratio (95% CI) | p-value |
|---|---|---|---|---|
| Composite endpoint: | | | | |
| Death, MI or Stroke | 2121 (9.2%) | 2310 (10.1%) | 0.91 (0.86, 0.97) | 0.002 |
| Death | 1726 (7.5%) | 1845 (8.1%) | 0.93 (0.87, 0.99) | 0.029 |
| Non-fatal MI | 270 (1.2%) | 330 (1.4%) | 0.81 (0.69, 0.95) | 0.011 |
| Non-fatal Stroke | 127 (0.6%) | 142 (0.6%) | 0.89 (0.70, 1.13) | 0.33 |

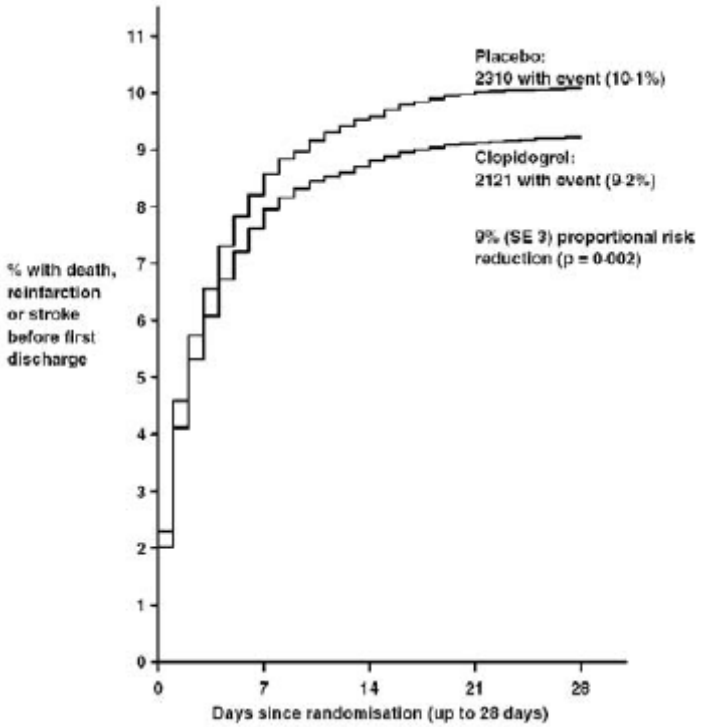
Note: 9 patients (2 clopidogrel and 7 placebo) suffered from both a non-fatal stroke and a non-fatal MI, hence the apparent disparity between composite endpoint and the sum of death, non-fatal MI and non-fatal stroke. Values for non-fatal MI and non-fatal stroke exclude patients who died of any cause.

**Figure 1: Cumulative Event Rates for Death in the COMMIT Study***




* All treated patients received aspirin.

**Figure 2: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study ***




* All treated patients received aspirin.

The benefit associated with clopidogrel on the combined endpoint was consistent across age, gender and with or without fibrinolytics and was observed as early as 24 hours.

The bioequivalence of CoPlavix to reference clopidogrel and aspirin tablets has been demonstrated in three open-label, randomized, single-dose, 2-sequence, 2-period, 2-treatment crossover studies. One study was performed with CoPlavix 75 mg/75 mg (BDR4659) and two with CoPlavix 75 mg/100 mg (BDR5000 and BEQ10600). Study BEQ10600 (CoPlavix 75 mg/100 mg) evaluated bioequivalence in 121 young healthy subjects based on clopidogrel and its inactive carboxylic acid metabolite, and aspirin and salicylic acid. Studies BDR4659 (CoPlavix® 75 mg/75 mg) and BDR5000 (CoPlavix 75 mg/100 mg) evaluated bioequivalence in 40 young healthy subjects based on clopidogrel inactive carboxylic acid metabolite, and aspirin and salicylic acid.

CoPlavix 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to the clopidogrel 75 mg tablets in terms of clopidogrel $C_{max}$ and AUC, and/or carboxylic acid metabolite. For aspirin, CoPlavix® 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to aspirin 75 mg and 100 mg, respectively, in terms of aspirin AUC, and salicylic acid $C_{max}$ and AUC. The 90% CIs for these parameters were entirely within the bioequivalence interval [0.80-1.25].

In terms of $C_{max}$, aspirin was not bioequivalent in the 3 studies, with the $C_{max}$ being 1.3- to 1.6-fold higher for CoPlavix than for the aspirin tablets. However, considering the large number of aspirin formulations on the market and the clinical studies evaluating the benefit/risk of clopidogrel in combination with ASA (see above), a slight difference in ASA $C_{max}$ is not considered to be clinically significant.

**Table 4: Mean (coefficient of variation %) exposure of clopidogrel and its inactive carboxylic acid metabolite after a single oral dose of CoPlavix 75 mg/75 mg or 75 mg/100 mg and Plavix 75 mg**

| Compound | PK parameter | CoPlavix 75 mg/75 mg | | | CoPlavix 75 mg/100 mg | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | BDR4659 | | | BDR5000 | | | BEQ10600 | | |
| | | CoPlavix | Plavix | 90%CI | CoPlavix | Plavix | 90%CI | CoPlavix | Plavix | 90%CI |
| Clopidogrel | $C_{max}$ (ng/mL) | Not assessed | | | Not assessed | | | 2.49 (306) | 2.23 (255) | 0.94; 1.23 |
| | AUC (ng.h/mL) | Not assessed | | | Not assessed | | | 2.74 (210)[a] | 2.72 (189)[a] | 0.92; 1.15 |
| Carboxylic acid metabolite | $C_{max}$ (ng/mL) | 3319 (26) | 3105 (27) | 0.99; 1.17 | 3042 (25) | 2810 (26) | 0.98; 1.20 | 3640 (30) | 3590 (30) | 0.96; 1.06 |
| | AUC (ng.h/mL) | 9215 (29) | 8947 (27) | 0.98; 1.07 | 8059 (19) | 8004 (26)[a] | 0.98; 1.07 | 9830 (25) | 9860 (27) | 0.98; 1.02 |

[a]n=39; [b]n=110, [c]n=111

**Table 5: Mean (coefficient of variation %) exposure of aspirin and salicylic acid after a single oral dose of CoPlavix 75 mg/75 mg or 75 mg/100 mg and aspirin 75 mg or 100 mg**

| Compound | PK parameter | CoPlavix 75 mg/75 mg | | | CoPlavix 75 mg/100 mg | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | BDR4659 | | | BDR5000 | | | BEQ10600 | | |
| | | CoPlavix | Aspirin | 90%CI | CoPlavix | Aspirin | 90%CI | CoPlavix | Aspirin | 90%CI |
| Aspirin | $C_{max}$ (ng/mL) | 1207 (25) | 738 (26) | 1.51; 1.78 | 1492 (26) | 964 (23) | 1.41; 1.69 | 1580 (31) | 1230 (35) | 1.22; 1.39 |
| | AUC (ng.h/mL) | 936 (17) | 826 (22)[a] | 1.10; 1.20 | 1131 (16)[a] | 1007 (21)[b] | 1.08; 1.19 | 1440 (24)[c] | 1300 (22)[d] | 1.07; 1.13 |
| Salicylic acid | $C_{max}$ (ng/mL) | 3533 (16) | 3094 (17) | 1.10; 1.20 | 4878 (14) | 4189 (16) | 1.12; 1.22 | 5390 (22) | 5030 (21) | 1.04; 1.10 |
| | AUC (ng.h/mL) | 12217 (21)[a] | 11778 (19) | 1.00; 1.06 | 17791 (32) [a] | 17225 (30) | 1.01; 1.05 | 21700 (29)[c] | 20900 (28) | 1.02; 1.04 |

[a]: n=39; [b]: n=37; [c]: n=116; [d]: n=111

## INDICATIONS

CoPlavix is a fixed-dose combination product.

CoPlavix is intended as continuation of therapy in patients with acute coronary syndrome already initiated with separate clopidogrel and aspirin products:

- Unstable angina or non-ST-elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischaemia). CoPlavix is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).
- ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, CoPlavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke in medically treated patients eligible for thrombolytic therapy.

## CONTRAINDICATIONS

Due to the presence of both components of the product, CoPlavix is contraindicated in case of:

Hypersensitivity to clopidogrel, salicylates or any of the excipients.

Severe liver impairment.

Active pathological bleeding such as haemophilia, intracranial haemorrhage or gastrointestinal bleeding.

Peptic ulcer or erosive gastritis

Breast-feeding (see 'PRECAUTIONS'-Use in Lactation).

In addition, due to the presence of aspirin, its use is also contraindicated in case of:

Known allergy to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and in patients with the syndrome of asthma with rhinitis and/or nasal polyps.

Severe renal impairment.

Third trimester of pregnancy (see Pregnancy).

## PRECAUTIONS

### General

Clopidogrel and aspirin prolong bleeding time, and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions, as follows:

If a patient is to undergo elective surgery and an anti-platelet effect is not desired, CoPlavix should be discontinued 7 days prior to surgery.

If the patient is at high risk of ophthalmic bleeding due to intraocular lesions clopidogrel should be used with extra caution.

CoPlavix should be used with caution in patients who have lesions with a propensity to bleed. Drugs that might induce such lesions (such as NSAIDs) are not recommended in patients taking CoPlavix (see 'PRECAUTIONS'-Interactions with other medicines).

CoPlavix should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, as this may be due to gastric ulceration which may lead to gastric bleeding.

Gastrointestinal side effects, including stomach pain, heartburn, nausea, vomiting and gastrointestinal bleeding, may occur. Although minor upper gastrointestinal symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous gastrointestinal symptoms.

Patients should be told about the signs and symptoms of gastrointestinal side effects and what steps to take if they occur. Patients should be told that it may take longer than usual for bleeding to stop when they take CoPlavix, and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking CoPlavix before any surgery is scheduled and before any new drug is taken.

In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding. Therefore, use of the combination of clopidogrel and aspirin should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

To prevent gastric irritation due to aspirin, CoPlavix should be taken with or after food.

Due to the presence of aspirin, caution is required in patients with a history of asthma or allergic disorders (as they are at increased risk of hypersensitivity reactions) or with gout (as low doses of aspirin increase urate concentrations).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The hypoglycaemic effect of chlorpropamide may be enhanced by the concurrent administration of aspirin. Large doses of aspirin may have intrinsic hypoglycaemic activity when given to diabetic patients, but the effects on carbohydrate metabolism are complex and it may cause hyperglycaemia

Tinnitus is a premonitory sign of salicylism but may not be detected in patients with hearing loss

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

CoPlavix is to be used under medical supervision only.

**Coronary Artery Bypass Surgery**

When coronary artery bypass surgery is to be performed, clopidogrel and aspirin should be suspended at least 7 days before surgery to reduce the risk of bleeding (see 'ADVERSE EFFECTS').

**Cytochrome P450 2C19 (CYP2C19)**

Pharmacogenetics: In patients who are CYP2C19 poor metabolizers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function (see Pharmacokinetics, Pharmacogenetics). Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider the alternative treatment strategies in patients identified as CYP2C19 poor metabolisers (see Dosage and Administration, Pharmacogenetics).

**Ischaemic Stroke**

In view of the lack of data, clopidogrel cannot be recommended in acute ischaemic stroke (less than 7 days).

**Haematological**

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

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have also been reported very rarely in patients taking clopidogrel (see 'ADVERSE EFFECTS').

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. With chronic administration, occult blood loss may lead to iron deficiency anaemia. As a dual anti-platelet agent, CoPlavix should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery.

**Renal Impairment**

Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment. Therefore CoPlavix should be used with caution in this population. Patients should be observed closely for signs of salicylism. See also 'CONTRAINDICATIONS' for severe renal impairment.

**Hepatic Impairment**

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. CoPlavix should therefore be used with caution in this population. See also 'CONTRAINDICATIONS' for severe hepatic impairment.

**Carcinogenicity**

There was no evidence of carcinogenic effects when clopidogrel was given in the diet for 78 weeks to mice and 104 weeks to rats at doses up to 77 mg/kg per day (representing an exposure ≈ 18 times the anticipated patient exposure, based on plasma AUC for the main circulating metabolite in elderly subjects).

Carcinogenicity studies have not been conducted with aspirin

**Genotoxicity**

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by the oral route in mice).

Aspirin was not genotoxic in bacterial reverse mutation assays or in a recessive lethal mutation assay in Drosophila. However, there are conflicting results on the clastogenicity of aspirin in mammalian cells.

**Effects on Fertility**

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day.

Aspirin had antispermatogenic effects by inhibiting prostaglandin formation in Long-Evans rats at 250 mg/kg/day PO, but did not affect the fertility of male Wistar rats at 300 mg/kg/day IP. The clinical relevance of these observations is unknown.

**Use in Pregnancy (Category C)**

No clinical data on exposure to clopidogrel plus aspirin during pregnancy are available. Clopidogrel plus aspirin should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel in combination with aspirin. Due to the present of aspirin clopidogrel plus aspirin is contraindicated during the third trimester of pregnancy.

Clopidogrel and/or its metabolites are known to cross the placenta in pregnant rats and rabbits. However, teratology studies in rats and rabbits at doses up to 500 mg and 300 mg/kg/day PO, respectively, revealed no evidence of embryotoxicity or teratogenicity.

Reproduction toxicity data show that aspirin is teratogenic in several laboratory animals.

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the foetal ductus arteriosus, prolong labour and delay birth. Aspirin increases bleeding time both in the newborn infant and in the mother because of its anti-platelet effects.

CoPlavix should not be used in women during pregnancy unless the potential benefits outweigh the risks.

**Use in Lactation**

Breast-feeding is contraindicated during treatment with CoPlavix (see 'CONTRAINDICATIONS'). Studies in rats have shown that clopidogrel and/or its metabolites are excreted in breast milk. Salicylates are excreted in breast milk. Chronic high doses of aspirin can cause adverse effects in the infant.

**Interactions with alcohol**

The effect of alcohol on the safety and efficacy of the combination of clopidogrel and aspirin has not been investigated in clinical trials. Concurrent ingestion of alcohol and aspirin may enhance occult blood loss and gastric irritation. In prolonged aspirin administration, occult blood loss may lead to iron deficiency anaemia. Aspirin inhibits ethanol dehydrogenase, a major enzyme in the first pass elimination of alcohol.

*In vitro,* the metabolism of clopidogrel has been shown to be altered in the presence of ethanol, such that clopidogrel is hydrolysed (inactivated) more slowly, and ethyl clopidogrel formed; the toxicity of ethyl clopidogrel has not been fully investigated.

**Interactions with other medicines**

Aspirin

A pharmacodynamic interaction between clopidogrel and aspirin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to one year. See also 'PRECAUTIONS' - General

CoPlavix should not be administered simultaneously with other salicylate containing preparations, uricosuric agents or NSAIDs.

Oral Anticoagulants (including warfarin)

The concomitant administration of CoPlavix with oral anticoagulants, including warfarin, is not recommended since it may increase the intensity of bleeding (see PRECAUTIONS).

Glycoprotein IIb/IIIa inhibitors

CoPlavix should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors (see PRECAUTIONS). As a pharmacodynamic interaction between CoPlavix and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

Injectable Anticoagulants

A pharmacodynamic interaction between CoPlavix and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Anti-platelet agents (such as eptifibatide, ticlopidine, tirofiban)

The effects of CoPlavix and other drugs which inhibit platelet aggregation may be additive, leading to an increased risk of bleeding.

Thrombolytics

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparins are co-administered with aspirin. The safety of concomitant administration of CoPlavix with thrombolytic agents has not been formally established and should be undertaken with caution.

Methotrexate

Due to the presence of aspirin, methotrexate and CoPlavix should be used together with caution, as aspirin can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity. Salicylates can also displace methotrexate from albumin.

Non Steroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin may increase the risk of gastrointestinal side effects, including bleeding, when administered with NSAIDs. Aspirin displaces diclofenac from its binding sites, reducing diclofenac effectiveness.

The concomitant administration of ibuprofen with aspirin may limit the beneficial cardiovascular effects of aspirin in patients with increased cardiovascular risk.

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

Uricosuric agents (e.g. probenecid)

Caution is required because aspirin may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Drugs metabolised by Cytochrome P450 2C9

At high concentrations *in vitro*, clopidogrel inhibits cytochrome P450 (2C9) and at lower concentrations inhibits CYP2B6 and CYP2C19. Accordingly, CoPlavix may interfere with the metabolism of bupropion, lansoprazole, omeprazole, pantoprazole, diazepam, phenytoin, tamoxifen, tolbutamide, warfarin, fluvastatin, and many NSAIDs, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is co-administered with CoPlavix.

Other concomitant therapy

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this is uncertain. Concomitant use of drugs that inhibit CYP2C19 (e.g., omeprazole) should be discouraged.

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

Care should be observed when coadministering aspirin and methotrexate, chlorpropamide, corticosteroids, sulfinpyrazone, probenecid and spironolactone. The hypoglycaemic effect of chlorpropamide may be enhanced by the concurrent administration of aspirin

Hydrocortisone may increase the renal clearance of salicylate and when hydrocortisone is discontinued, serum salicylate levels may rise significantly. Aspirin may antagonise the diuretic effect of spironolactone. The rate and extent of aspirin absorption is increased by caffeine. The rate of excretion is increased by urinary alkalinisers. Aspirin at high doses reduces the uricosuric effects of probenecid and sulfinpyrazone.

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

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

*Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics*

Concomitant use of a renin-angiotensin system inhibiting drug (angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including aspirin or COX-2 inhibitors) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy and periodically thereafter.

*Interactions with higher dose aspirin*

Interactions with the following medicines with higher (anti-inflammatory) doses of aspirin have been reported: alendronate, ACE inhibitors, anticonvulsants (phenytoin and valproic acid), beta blockers, systemic corticosteroids, diuretics, selective serotonin reuptake inhibitors (SSRIs), spironolactone, verapamil, hypoglycaemic agents and zafirlukast.

More than 30,000 patients entered into clinical trials with clopidogrel plus aspirin at maintenance doses lower than or equal to 325 mg, received a variety of concomitant medications, including diuretics, beta blockers, ACE inhibitors, calcium channel antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists, without evidence of clinically significant adverse interactions.

**Effects on ability to drive and use machines**

CoPlavix has no or negligible influence on the ability to drive and use machines.

## ADVERSE EFFECTS

### Clopidogrel

Clinical Studies Experience

Clopidogrel has been evaluated for safety in more than 44,000 patients, including over 30,000 patients treated with clopidogrel plus aspirin, and over 12,000 patients treated for 1 year or more. The clinically relevant adverse events observed in CURE, CLARITY, COMMIT, CHARISMA, ACTIVE-A and ACTIVE-W are discussed below.

CURE, CLARITY AND COMMIT

*Haemorrhagic disorders*

In CURE, there was a significant difference between the two treatment groups for non life-threatening major bleeds (1.6% clopidogrel + aspirin vs. 1.0% placebo + aspirin), primarily gastrointestinal and at arterial puncture sites, and minor bleeds (5.1% clopidogrel + aspirin vs. 2.4% placebo + aspirin). The major bleeding event rate for clopidogrel + aspirin was dose-dependent on aspirin (<100 mg: 2.6%; 100-200 mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo + aspirin (<100 mg: 2.0%; 100-200 mg: 2.3%; >200 mg: 4.0%).

The administration of clopidogrel + aspirin as compared to placebo + aspirin, was not associated with an increase in life-threatening or fatal bleeds (event rates 2.2% vs. 1.8% and 0.2% vs. 0.2%, respectively). The incidence of intra-cranial bleeding was 0.1% in both groups.

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel + aspirin vs. 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + aspirin group (17.4%) versus the placebo + aspirin group (12.9%), with the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in haemoglobin > 5 g/dL) being similar between groups (1.3% versus 1.1% in the clopidogrel + aspirin and the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel + aspirin and in the placebo + aspirin groups, respectively) and intracranial haemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of non-cerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups, as shown in Table 6.

**Table 6: Number of Patients with Bleeding Events in COMMIT**

| Type of bleeding | Clopidogrel + aspirin (n = 22,961) | Placebo + aspirin (n = 22,891) | p-value |
|---|---|---|---|
| Major * non-cerebral or cerebral bleeding | 134 (0.6%) | 125 (0.5%) | 0.59 |
| Major non-cerebral | 82 (0.4%) | 73 (0.3%) | 0.48 |
| Fatal | 36 (0.2%) | 37 (0.2%) | 0.90 |

| | | | |
|---|---|---|---|
| Haemorrhagic stroke | 55 (0.2%) | 56 (0.2%) | 0.91 |
| Fatal | 39 (0.2%) | 41 (0.2%) | 0.81 |
| Other non-cerebral bleeding (non major) | 831 (3.6%) | 721 (3.1%) | 0.005 |
| Any non-cerebral bleeding | 896 (3.9%) | 777 (3.4%) | 0.004 |

*Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion

*Haematological disorders*

In CURE and CLARITY, the numbers of patients with thrombocytopenia or neutropenia were similar in both groups.

Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other signs of infection.

*Gastrointestinal*

In CURE, there was no significant difference in the incidence of non-haemorrhagic gastrointestinal effects in the clopidogrel or placebo groups.

In CLARITY, the incidence of gastrointestinal adverse events was 6.9% for clopidogrel treated patients, compared to 7.2% in placebo treated patients.

In COMMIT, 2 patients reported gastrointestinal adverse events in the clopidogrel treated group, compared to one in the placebo treated group.

*Rash*

In CURE, rash occurred in more patients in the clopidogrel group. In CLARITY, 0.7% of patients in the clopidogrel group reported a rash, compared to 0.5% in the placebo group.

Treatment Discontinuation

In CURE, the overall incidence of discontinuation due to adverse events was greater in the clopidogrel group than in the placebo group (366 [5.8%] and 247 [3.9%] patients, respectively), with the main differences being in events in the platelet, bleeding and clotting disorders (1.1% versus 0.7%) and skin disorders (0.7% versus 0.3%). The increase in the rate of study drug discontinuation due to non-haemorrhagic adverse events was primarily due to the increase in rash seen in the clopidogrel group. There was no apparent difference between the 2 treatment groups in the rates of discontinuations due to other adverse events.

In CLARITY, the overall incidence of discontinuation due to adverse events was greater in the placebo group compared with the clopidogrel group (6.9% for clopidogrel treated patients compared to 8.6% for placebo treated patients).

In COMMIT, the overall incidence of discontinuation due to adverse events was similar in each treatment group (2.4% for clopidogrel treated patients compared to 2.2% for placebo treated patients).

ACTIVE Studies

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 treatment with VKA was more effective than the combination of clopidogrel and aspirin. The rate of major bleeding episodes was higher in the clopidogrel + aspirin group than in the VKA group: 101 (3.03%) subjects compared with 93 (2.76%).

The ACTIVE-A study demonstrated when preventing atherothrombotic and thromboembolic events including stroke, the rate of major bleeding was greater in the clopidogrel + aspirin group 251 (6.7%) than in the placebo + aspirin group 162 (4.3%).

CAPRIE & CHARISMA

The following safety data is extracted from clinical studies for different indications of clopidogrel.

*Haemorrhagic disorders*

In CAPRIE a study conducted in 19,185 patients with established atherosclerosis or history of atherothrombosis as manifested by myocardial infarction, ischaemic stroke or peripheral arterial disease, who randomised to clopidogrel 75 mg/day or aspirin 325 mg/day, and followed for 1 to 3 years, the overall incidence of any bleeding in patients treated with either clopidogrel or aspirin was similar (9.3%). The incidence of severe bleeds was 1.4% in the clopidogrel group and 1.6% in the aspirin group.

The overall incidence of other bleeding disorders was higher in the clopidogrel group (7.3%) compared to aspirin (6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs. 0.4%). The most frequent events reported were purpura/bruising and epistaxis. Other less frequently reported events were haematoma, haematuria and eye bleeding (mainly conjunctival).

Gastrointestinal haemorrhage was significantly less frequent with clopidogrel (1.99%) compared to aspirin (2.66%). The incidence of intracranial haemorrhage was 0.35% for clopidogrel compared to 0.49% for aspirin.

In CHARISMA, a study conducted in patients with coronary artery disease, cerebrovascular disease or peripheral arterial disease as well as patients with a combination of atherothrombotic risk factors only, all receiving a background therapy with low dose aspirin (75-162 mg), there was an excess in moderate and severe bleeding, as adjudicated to the GUSTO definitions, in the clopidogrel group (see Table 7). This represented a number needed to treat, to harm, of 84 in 23 months of follow-up.

**Table 7: Number of Patients with Bleeding Events in CHARISMA**

| Type of bleeding (GUSTO) | Number (%) with event | | Difference Clopidogrel – Placebo (%) (95% CI) |
|---|---|---|---|
| | Clopidogrel + aspirin (N=7802) | Placebo + aspirin (N=7801) | |
| Any | 2827 (36.2) | 1616 (20.7) | 15.52 (14.12, 16.91) |
| Severe/moderate | 290 (3.7) | 197 (2.5) | 1.19 (0.65, 1.74) |

*Haematological disorders*

In CAPRIE, Clopidogrel was not associated with an increase in the incidence of thrombocytopenia compared to aspirin. Very rare cases of platelet count <30 x $10^9$/L have been reported.

Severe neutropenia (<0.45 x $10^9$/L) was observed in four patients (0.04%) that received clopidogrel and in two patients that received aspirin. Two of the 9599 patients who received clopidogrel and none of the patients who received aspirin had a neutrophil count of zero. One of the clopidogrel treated patients was receiving cytostatic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel.

One case of aplastic anaemia occurred on clopidogrel treatment.

The incidence of severe thrombocytopaenia (<80 G/L) was 0.2% on clopidogrel and 0.1% on aspirin; very rare cases of platelet count <=30 G/L have been reported.

*Gastrointestinal*

In CAPRIE, overall the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel was significantly lower than in those receiving aspirin. The incidence of peptic, gastric, or duodenal ulcers was 0.68% for clopidogrel and 1.15% for aspirin. Cases of diarrhoea were reported at a higher frequency in the clopidogrel group (4.46%) compared to the aspirin group (3.36%).

*Rash*

In CAPRIE, there were significantly more patients with rash in the clopidogrel group (4.2%) compared to the aspirin group (3.5%).

*Treatment Discontinuation*

In the clopidogrel and aspirin treatment groups of the CAPRIE study, discontinuation due to adverse events occurred in approximately 13% of patients after 2 years of treatment.

Adverse events occurring in ≥ 2.5% of patients on clopidogrel in the CAPRIE and CURE controlled clinical trials are shown in Table 8 regardless of relationship to clopidogrel.

**Table 8: Adverse events occurring in ≥ 2.5% of patients receiving clopidogrel in CAPRIE and CURE**

| | CAPRIE | | CURE | |
|---|---|---|---|---|
| | % Incidence (% discontinuation) | | % Incidence (% discontinuation) | |
| **BODY SYSTEM/EVENT** | **Clopidogrel n = 9599** | **Aspirin n = 9586** | **Clopidogrel + aspirin n = 6259** | **Placebo + aspirin n= 6303** |
| **Body as a Whole - general disorders** | | | | |
| Chest pain | 8.3 (0.2) | 8.3 (0.3) | 2.7 (0.02) | 2.8 (0.0) |
| Accidental/inflicted injury | 7.9 (0.1) | 7.3 (0.1) | 1.1 (0.06) | 1.2 (0.03) |
| Influenza like symptoms | 7.5 (<0.1) | 7.0 (<0.1) | 1.1 (0.0) | 1.1 (0.0) |
| Pain | 6.4 (0.1) | 6.3 (0.1) | 1.3 (0.02) | 1.4 (0.0) |
| Fatigue | 3.3 (0.1) | 3.4 (0.1) | 1.5* (0.02) | 1.0 (0.0) |
| **Cardiovascular disorders - general** | | | | |
| Hypertension | 4.3 (<0.1) | 5.1* (<0.1) | 0.9 (0.0) | 0.9 (0.0) |
| **Central and peripheral nervous system disorders** | | | | |
| Headache | 7.6 (0.3) | 7.2 (0.2) | 3.1 (0.08) | 3.2 (0.10) |
| Dizziness | 6.2 (0.2) | 6.7 (0.3) | 2.4 (0.08) | 2.0 (0.02) |
| **Gastrointestinal** | | | | |
| Abdominal pain | 5.6 (0.7) | 7.1* (1.0) | 2.3 (0.26) | 2.8 (0.27) |
| Dyspepsia | 5.2 (0.6) | 6.1* (0.7) | 2.0 (0.08) | 1.9 (0.02) |
| Diarrhoea | 4.5* (0.4) | 3.4 (0.3) | 2.1 (0.11) | 2.2 (0.13) |
| Nausea | 3.4 (0.5) | 3.8 (0.4) | 1.9 (0.18) | 2.3 (0.08) |
| **Metabolic and nutritional disorders** | | | | |
| Hypercholesterolemia | 4.0 (0) | 4.4 (<0.1) | 0.1 (0.0) | 0.2 (0.0) |
| **Musculoskeletal system disorders** | | | | |
| Arthralgia | 6.3 (0.1) | 6.2 (0.1) | 0.9 (0.0) | 0.9 (0.0) |
| Back pain | 5.8 (0.1) | 5.3 (<0.1) | 1.0 (0.03) | 1.2 (0.0) |
| **Myo-, endo-, pericardial and valve disorders** | | | | |
| Angina pectoris | 10.1 (0.6) | 10.7 (0.4) | 0.1 (0.0) | 0.1 (0.0) |
| Coronary artery disorder | 6.2 (0.3) | 5.6 (0.3) | 0.03 (0.0) | 0.06 (0.0) |
| **Platelet, bleeding and clotting disorders** | | | | |
| Purpura | 5.3* (0.3) | 3.7 (0.1) | 0.3 (0.0) | 0.1 (0.0) |
| Epistaxis | 2.9 (0.2) | 2.5 (0.1) | 0.2 (0.08) | 0.1 (0.02) |
| **Psychiatric disorders** | | | | |
| Depression | 3.6 (0.1) | 3.9 (0.2) | 0.7 (0.02) | 0.7 (0.0) |

| | CAPRIE | | CURE | |
|---|---|---|---|---|
| | % Incidence (% discontinuation) | | % Incidence (% discontinuation) | |
| **BODY SYSTEM/EVENT** | **Clopidogrel n = 9599** | **Aspirin n = 9586** | **Clopidogrel + aspirin n = 6259** | **Placebo + aspirin n= 6303** |
| **Resistance mechanism disorders** | | | | |
| Infection | 4.7 (<0.1) | 4.2 (0.1) | 1.3 (0.0) | 1.2 (0.0) |
| **Respiratory system disorders** | | | | |
| Upper respiratory tract infection | 8.7 (<0.1) | 8.3 (<0.1) | 1.1 (0.0) | 1.0 (0.0) |
| Dyspnoea | 4.5 (0.1) | 4.2. (0.1) | 1.9 (0.0) | 1.9 (0.02) |
| Rhinitis | 4.2 (0.1) | 4.2 (<0.1) | 0.2 (0.0) | 0.1 (0.0) |
| Bronchitis | 3.7 (0.1) | 3.7 (0) | 1.1 (0.0) | 1.5 (0.0) |
| Coughing | 3.1 (<0.1) | 2.7 (<0.1) | 1.3 (0.0) | 1.2 (0.0) |
| **Skin and appendage disorders** | | | | |
| Rash | 4.2* (0.5) | 3.5 (0.2) | 1.3 (0.29) | 1.1 (0.14) |
| Pruritis | 3.3* (0.3) | 1.6 (0.1) | 0.5 (0.11) | 0.5 (0.05) |
| **Urinary system disorders** | | | | |
| Urinary tract infection | 3.1 (0) | 3.5 (0.1) | 1.5 (0.0) | 1.4 (0.0) |
| **Vascular (extracardiac) disorders** | | | | |
| Claudication intermittent | 3.8 (0.2) | 3.8 (0.2) | 0.1 (0.02) | 0.1 (0.0) |
| Peripheral ischaemia | 3.2 (0.2) | 3.4 (0.2) | 0.4 (0.03) | 0.3 (0.0) |
| Cerebrovascular disorder | 2.6 (0.3) | 2.9 (0.3) | 0.3 (0.03) | 0.4 (0.03) |

* indicates statistical significance ($p \leq 0.05$)

Incidence of discontinuation, regardless of relationship to therapy is shown in parentheses.

Clinically relevant adverse reactions not listed above pooled from CAPRIE, CURE, CLARITY and COMMIT studies with an incidence of ≥ 0.1% as well as all serious and clinically relevant adverse reactions are listed below according to the World Health Organisation classification. Their frequency is defined using the following conventions: *common*: > 1/100 (1%) and < 1/10 (10%); *uncommon*: ≥ 1/1000 (0.1%) and < 1/100 (1%) and *rare*: ≥ 1/10000 (0.01%) and < 1/1000 (0.1%).

*Central and peripheral nervous system disorders*

*Uncommon*: headache, dizziness, paraesthesia,

*Rare:* Vertigo

*Gastrointestinal system disorders*

*Common:* dyspepsia, abdominal pain, diarrhoea

*Uncommon:* nausea, gastritis, flatulence, constipation, vomiting, gastric, peptic or duodenal ulcer

*Platelet, bleeding and clotting disorders*

*Uncommon:* Bleeding time increased, decreased platelets

*Skin and appendages disorders*

*Uncommon:* rash, pruritus

*White cell and RES disorders*

*Uncommon:* Leucopenia, decreased neutrophils, eosinophilia

**Post-Marketing Experience**

In addition to clinical study experience with clopidogrel either alone or in combination with aspirin, the following is a list of adverse reactions reported with clopidogrel or aspirin.

Bleeding is the most common reaction reported in the post-marketing experience with clopidogrel or aspirin.

The following have been reported spontaneously from worldwide post-marketing experience with clopidogrel:

Note *very common* ≥ 1/10 (≥ 10%)
*common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
*uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1.0%)
*rare* ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
*very rare* < 1/10,000 (< 0.01%)

Musculoskeletal, connective and bone

*Very rare:* Arthralgia, arthritis, myalgia[1]

Immune system disorders

*Very rare:* anaphylactoid reactions, serum sickness

Vascular disorders

*Very rare:* vasculitis, hypotension

Blood and lymphatic system disorders

*Very rare:* serious cases of bleeding, mainly skin, musculo-skeletal (haemarthrosis, haematoma), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), epistaxis, haematuria and haemorrhage of operative wound. Fatal haemorrhage, especially intracranial, gastrointestinal and retroperitoneal haemorrhage. Cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with aspirin or clopidogrel with aspirin and heparin (see 'Interactions with Other Medicines').

Very rare cases of thrombotic thrombocytopenic purpura (TTP) have been reported

Aplastic anaemia, neutropenia, pancytopenia, agranulocytosis, granulocytopenia, anaemia

*Uncommon*: eosinophilia, leucopenia, decreased neutrophils, decreased platelets, increased bleeding time

Skin and Subcutaneous tissue disorders

*Very rare:* maculopapular or erythematous rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), eczema, lichen planus

Psychiatric

*Very rare:* confusion, hallucinations

Nervous System disorders

*Very rare*: taste disturbances

Hepatobiliary disorders

*Very rare:* hepatitis, acute liver failure

Gastrointestinal disorders

*Very rare:* colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

Respiratory, thoracic and mediastinal disorders

*Very rare*: bronchospasm, interstitial pneumonitis

Renal and Urinary disorders

*Very rare:* glomerulopathy

Investigations

*Very rare*: blood creatinine increase, abnormal liver function tests

General disorders and administration site conditions

*Very rare:* fever, syncope

**Aspirin**

In addition to some of the adverse reactions listed above, aspirin is associated with the following adverse effects.

Aspirin produces a prolongation of the bleeding time and may produce epigastric distress, nausea and vomiting, gastric or duodenal ulcers and erosive gastritis which may lead to serious gastrointestinal bleeding. These side effects are more likely to occur when higher doses are administered, although they may also occur when low doses are used.

Gastro-duodenal ulcer/perforations, upper gastro-intestinal symptoms such as gastralgia (see Precautions).

Iron deficiency anaemia may develop as a result of occult gastrointestinal bleeding when aspirin is used for long periods of time.

Aspirin may cause haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

Aspirin may cause tinnitus, dizziness, vertigo or hearing loss.

Aspirin sensitivity is most commonly manifested by asthma, vasomotor rhinitis, urticaria, angioneurotic oedema and allergic dermatological reactions, hypoglycaemia, gout. As well as anaphylactic shock, aggravation of allergic symptoms of food allergy.

Low doses of aspirin have been reported to cause retention of uric acid, whereas high dosage may increase excretion.

Aspirin may cause acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics).

## DOSAGE AND ADMINISTRATION

### Adults

CoPlavix is given as a single tablet (75mg/75mg or 75mg/100mg) once a day taken with adequate water.

Acute Coronary Syndrome

CoPlavix is used following an initial loading dose of 300 mg clopidogrel in combination with aspirin in patients with acute coronary syndrome:

- Unstable angina or non-ST-elevation myocardial infarction:
  - Treatment should be initiated with a single 300 mg loading dose of clopidogrel plus aspirin (75 mg to 325 mg).
  - Long-term daily treatment should be continued with one CoPlavix tablet (75mg/75mg or 75mg/100mg) once a day taken with adequate water.
- ST-segment elevation acute myocardial infarction:
  - Treatment should be initiated with or without a 300-mg loading dose of clopidogrel in combination with aspirin and with or without thrombolytics as soon as possible after symptoms start. There are no data on the use of a 300-mg loading dose in elderly patients (aged 75 years or more) with ST-segment acute myocardial infarction, as no patients over 75 years old were included in the CLARITY study and no loading dose was used in the COMMIT study.

- Daily treatment should continue with one CoPlavix tablet (75mg/75mg or 75mg/100mg) once a day with adequate water. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting.

In patients who have had percutaneous coronary intervention with stent insertion, clopidogrel and aspirin should be continued for as long as is currently recommended in evidence-based guidelines for the type of stent and circumstances of implantation or for as long as otherwise indicated, taking into account the overall atherothrombotic risk profile of the patient.

Should doses of aspirin greater than 100 mg be required for daily maintenance therapy, clopidogrel and aspirin products should be administered separately.

**Pharmacogenetics**

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. A higher dose of clopidogrel (600 mg loading dose followed by 150 mg once daily) in poor metabolisers increases antiplatelet response (see Pharmacokinetics, Pharmacogenetics). Consider the use of higher clopidogrel doses in patients who are poor CYP2C19 metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

**Renal Impairment**

Experience is limited in patients with mild to moderate renal impairment (see 'PRECAUTIONS'). CoPlavix should not be used in patients with severe renal impairment (see 'CONTRAINDICATIONS').

**Hepatic Impairment**

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see 'PRECAUTIONS'). CoPlavix should not be used in patients with severe hepatic impairment (see 'CONTRAINDICATIONS').

No dosage adjustment is necessary for elderly patients (see 'PHARMACOLOGY'-Special Populations).

**Children and Adolescents**

Safety and efficacy in subjects below the age of 18 have not been established.

There is a possible association between aspirin and Reye's syndrome when aspirin is given to children. Reye's syndrome is a very rare disease which can be fatal.

## OVERDOSAGE

There is no information concerning overdosage with CoPlavix.

In animals, clopidogrel at single oral doses ≥ 1500 mg/kg caused necrotic-haemorrhagic gastritis, oesophagitis and enteritis in mice, rats and baboons. Necrotic tubulopathy and tubulo-interstitial nephritis were also noted in mice.

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

Aspirin overdosage is manifested by the following symptoms:

Moderate overdosage: tinnitus, hearing loss, dizziness, headaches, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

Severe overdosage: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycaemia, haemorrhage

In case of severe aspirin overdose, the following actions should be undertaken: admission to hospital is necessary, control of acid-base balance, possibility of haemodialysis or peritoneal dialysis if necessary.

Apart from general measures, treatment of aspirin overdosage consists chiefly of measures to accelerate the excretion (forced alkaline diuresis) and to restore the acid-base and electrolyte balance. Infusions of sodium bicarbonate and potassium chloride solutions may be given.

For advice on the management of overdosage, please contact the Poisons Information Centre on 13 11 26.

## PRESENTATION AND STORAGE CONDITIONS

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

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

Store below 25°C.

CoPlavix 75mg/75mg tablets are registered in blister packs containing 2*, 4*, 7*, 14*, 28*, 30*, 50*, 56*, 84*, 98*, 100*, 112* and 280* tablets.

CoPlavix 75mg/100mg tablets are registered in blister packs containing 2*, 4*, 7, 14*, 28*, 30, 50*, 56*, 84*, 98*, 100*, 112* and 280* tablets.

Store below 25°C

♦ Presentations currently not marketed

## NAME AND ADDRESS OF SPONSOR

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park, NSW 2113

## POISON SCHEDULE OF THE MEDICINE

Schedule 4.

## DATE OF APPROVAL

14 September 2009

Date of most recent amendment: 7 April 2011

CoPlavix is a registered trademark of sanofi-aventis.

**Therapeutic Goods Administration**

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Reference/Publication #