SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Iscover and for subsequent procedures until 1September 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Atherosclerosis is a major pathological process causing death and disability in the Western World. The initial clinical presentation of the atherosclerotic disease depends upon the vascular bed where the atherosclerotic process is the most advanced.

Therapeutic interventions are usually aimed at the vascular territory causing the clinically symptomatic disease.

Patients who suffered from an ischaemic event such as myocardial infarction (MI), stroke or who have peripheral arterial disease with intermittent claudication, represent a group who is at the highest risk of further atherosclerotic/thrombotic events. Prevention of vascular ischaemic events can be achieved with oral anticoagulation or through inhibition of platelet aggregation. Furthermore life style modifications are encouraged (dietary changes, lipid control, exercise and smoking cessation).
Inhibition of platelet aggregation with acetyl salicylic acid (ASA), besides being more practical and safer than anticoagulation, has been shown to be effective. The meta-analysis conducted by the Antiplatelet Trialists' Collaboration (APTC) included 145 randomised trials, involving 100,000 patients at risk of vascular events. Of these, over 70,000 were considered high-risk. The results showed a risk reduction of 25% of vascular events in all high-risk subgroups. The doses of ASA were in the range of 75 to 325 mg daily. There is no evidence that higher doses of ASA confer an increased benefit.

When considering such long-term therapy, the safety and tolerability of the anti-platelet agent is a major consideration. ASA is associated with an increased risk of gastrointestinal ulceration and haemorrhage. Ticlopidine, another commonly used antiplatelet agent, has a higher rate of diarrhoea and rash versus ASA, which albeit not clinically serious, can cause drug withdrawal. Although infrequently, ticlopidine causes neutropaenia and thrombocytopaenia which can be serious and usually appear in the first three months of long-term therapy.

Iscover tablets contain clopidogrel, a new thienopyridine molecule analogue of ticlopidine, which has been developed as an inhibitor of platelet aggregation for use in the prevention of vascular ischaemic events in patients with established atherosclerotic disease.

2. Part II: Chemical and pharmaceutical aspects

Composition

Iscover is formulated as conventional tablets containing 97.875 mg of clopidogrel hydrogen sulphate equivalent to 75 mg of clopidogrel base, and conventional excipients.

The medicinal product is supplied in clear or opaque PVC/PVDC blister packs sealed with aluminium foil or all aluminium blisters packs in cardboard cartons of 28, 50, and 84 tablets.

Pharmaceutical development

Clopidogrel is the S-enantiomer of a new thienopyridine molecule analogue containing one single chiral centre. The chemical stability and compatibility of different excipients with four different clopidogrel salts were investigated. The final choice was given to clopidogrel hydrogen sulphate, which has optimal stability and compatibility.

The first pharmaceutical formulation used in the clinical trials was a capsule. In view of marketing, a tablet form was developed and was film-coated to mask the very bitter taste of the drug substance. The tablet formulation intended for marketing was considered to be optimal. Further slight modifications were introduced after the final bioequivalence study, but these did not affect the tablets dissolution characteristics.

After the Marketing Authorisation, a new crystalline form (clopidogrel hydrogen sulphate polymorphic Form II) has been identified and found to be more thermodynamically stable than the initial Form I. Consequently, the Marketing Authorisation Holder applied for a change of the formulation. Based on the submitted pharmaceutical data and demonstration of bioequivalency and equipotency, this new formulation was subsquently approved.

Method of preparation

The manufacturing formula for the film-coated tablets was provided. Validation data from 35 semi-industrial batches and 1 industrial batch demonstrated that the manufacturing process is under control and ensures both, batch-to-batch reproducibility and compliance with specifications. A revised validated manufacturing process was provided for the new formulation.

Control of starting materials

The synthetic pathway is presented as a Drug Master File. The manufacturers of the active substance are Sanofi Chimie and Orgamol LTD companies. The analytical methods used to control starting materials as well as intermediates of synthesis are acceptable and identical for both manufacturers. The impurity profile is well characterised and in line with current ICH guidelines. All other ingredients entering in the preparation of the tablets are adequately controlled.

The synthetic route, control tests and specifications of clopidogrel hydrogen sulphate are acceptable and identical for both manufacturers. The quality of the active substance is guaranteed by the established specifications and the proposed analytical methods are adequately validated.

The method of preparation of Form II for the new formulation was provided. Specifications and impurity profile were defined and stability data confirmed the good stability of the active substance under specified storage conditions.

Control tests on the finished product

The analytical methods are suitable to ensure consistent quality of the finished product. No degradation products have been detected upon storage.

Proposed specifications, methods procedures and validations, and batch analysis results ensured consistent quality for the new formulation.

Stability

Drug substance

Results from primary stability studies and additional stability data provided (3 semi and industrial batches, 24 months at 25°C/60% RH and at 30°C/60% RH) support a retest period of 3 years. For the new polymorphic form, the data obtained on 3 batches stored for 18 months at 25°C/60% RH and at 30°C/60% RH support a retest period of 3 years.

Finished product

Results from primary stability studies performed on 3 batches for 36 months at 25°C/60% RH, together with supportive stability studies clearly justified the 3 years shelf-life. The end of shelf-life specifications were adjusted to tightened values following discussion with the company. The company submitted data available at three years stability studies at 25°C/60% RH. For the new formulation, the data for three batches after 12 months and on the experience with the previous formulation justified a shelf-life of 24 months.

3. Part III: Pharmacological and toxicological aspects

Pharmacodynamics

The antiaggregating activity was evaluated in *ex vivo* and *in vitro* models. Oral and intravenous administration of clopidogrel inhibited the *ex vivo* ADP (adenosine diphosphate) induced aggregation of platelets, thereby affecting ADP-dependent activation of the GPIIb-IIIa complex, the major receptor for fibrinogen on the platelet surface. This effect was observed in all animal species investigated (mouse, rat, rabbit and baboon). The R-enantiomer was completely inactive and the S-enantiomer was

approximately twice more potent than the racemic mixture. No effect on platelet aggregation was observed when clopidogrel was tested *in vitro*. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation.

Clopidogrel exerted an antithrombotic action in various models of thrombosis in rats with a potency at least 50-fold higher than that of ticlopidine. The R-enantiomer of clopidogrel was devoid of any protective action.

The mechanism of the antiaggregating action is related to the specific inhibition of ADP (adenosine diphosphate) receptors on platelets. *In vitro* studies showed that following incubation of clopidogrel with rat liver microsomes, an active metabolite is generated which binds to platelet ADP receptors, thus inhibiting platelet aggregation induced by ADP. This metabolite has been isolated and its structure characterised as a thiol derivative of 2-oxo clopidogrel. The irreversible modification of the ADP-receptor site could be explained by the formation of a disulfur bridge between the reactive thiol and a cysteine residue of a platelet protein. The company was asked to comment further on the identity of the active metabolite, the site of, and the enzymes involved in, the metabolic activation of clopidogrel. This issue, and its relevance in terms of efficacy and possible interactions, was further discussed during the hearing held on 24th February 1998. The CPMP considered that this issue had been satisfactorily addressed by the company and that it was resolved.

Low levels of the R-enantiomer were detected in mice, rats and baboons. This racemisation of S-enantiomer was observed *in vivo*, and comparative toxicology studies revealed that clopidogrel was less toxic than the racemic compound and the R-enantiomer. Metabolic inversion was, however, insignificant in human subjects.

Safety pharmacology studies did not reveal any relevant effects to the central nervous, cardiovascular, respiratory, gastrointestinal and renal systems.

Pharmacokinetics

Metabolism and disposition of clopidogrel were assessed from several *in vitro* and *in vivo* studies.

Studies conducted in the rat with ^{14}C-labelled clopidogrel showed that 60% of clopidogrel was absorbed in the intestine within 60 minutes. Clopidogrel undergoes extensive first-pass metabolism and the main metabolite found in plasma, the carboxylic acid derivative, is inactive. The peak plasma concentration values were observed 1 to 2 hours after dosing. Administration with food decreased the maximal plasma concentration, but did not affect the AUC.

An extensive binding of clopidogrel and the main circulating metabolite to plasma proteins was observed (87% in mice, 95% in rats and 92% in baboons). Plasma radioactivity was partly covalently bound to plasma proteins, and in the baboon the decrease of this binding was characterised by a half-life of approximately 8 days. Clopidogrel and its carboxylic acid derivative showed little affinity for red blood cells (<20 %).

Clopidogrel was widely distributed in the tissues. In a repeated dose study in rats, accumulation of radioactivity in most of the organs raised over the duration of the study (21 days). Radioactivity was slowly eliminated from the tissues, but 21 days after the suspension of clopidogrel several tissues (arterial wall, thyroid gland, cartilage, skin, spleen) maintained radioactivity levels similar to those observed on the last day of administration.

Clopidogrel undergoes extensive metabolism. Twenty metabolites were identified. The main circulating compound was the carboxylic acid derivative of clopidogrel (SR 26334), which is inactive.

The major route of elimination is biliary. The majority of radioactivity was excreted within 48 hours. A significant entero-hepatic recirculation of radioactivity was observed. It accounted for 45-95% of clopidogrel derived activity and had no effect on platelet aggregation.

In lactating rats, clopidogrel and/or its metabolites levels in milk were 0.5 to 2.6 times higher than the maternal plasma levels. Transfer of the radioactivity to the developing foetus was observed in pregnant rats.

Toxicology

Single dose toxicity of clopidogrel was evaluated in the rat, mouse and in the baboon. Repeated dose toxicity by the oral route was conducted in the mouse for up to 3 months, in the rat for up to 52 weeks and in the baboon for up to one year.

After single oral administration to rats, mice and baboons, toxicity occurred only at very high doses. The target organs were mainly the gastrointestinal tract, the kidney and the lung. After intravenous administration to rats and mice, the main target organs were the kidney and the lung.

The toxicity on the digestive tract was also shown in the repeated dose toxicity studies; in particular in rats and baboons treated orally with high doses (from 400 mg/kg/day and upwards).

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

A slight decrease in heart rate and a slight increase in QT interval were observed in rats and baboons at very high doses (1,000 mg/kg/day in rats, and 400 mg/kg/day in baboons). However, there was no prolongation of QTc-interval. An *in vitro* electrophysiological study on rabbit Purkinje fibres was submitted with the responses to the consolidated list of questions. Although the results did not reveal a proarrhythmic potential, the highest concentration tested (~ 9.6 mg/l) was only three times the C_{max} obtained in humans with the therapeutic dose (~ 2.7 mg/l). This issue and its clinical relevance were further discussed during the hearing held on 24th February 1998. The CPMP considered that this issue had been satisfactorily addressed by the company and that it was resolved.

The R-enantiomer of clopidogrel revealed a higher toxicity than the active compound, namely on the central nervous system. The impact of the toxicity of this impurity on the overall toxicological profile of clopidogrel formulation seems to be minor due to its low concentration in the test compound. Furthermore, there is no evidence of epimerisation in man.

The reproduction toxicity studies in rats and rabbits did not reveal any teratogenic or faetotoxic potential for clopidogrel even at borderline maternally toxic doses. Male and female fertility, growth and development of the F1 offspring were not affected. High doses of clopidogrel induced a slight delay in the development of the offspring of lactating rats possibly due to the effect of the drug excreted in the lactating milk. The effect was reversible after weaning. In the light of these findings, and in the absence of significant experience in pregnant women, clopidogrel is contraindicated during breast-feeding and not recommended during pregnancy.

A battery of *in vitro* studies and one *in vivo* mouse micronucleus assay did not reveal any mutagenic, genotoxic or clastogenic potential of clopidogrel. No immunogenic, antigenic, phototoxic or photoallergenic potential was observed.

The carcinogenic potential of clopidogrel was investigated in two life-span studies in the rat and in the mouse. Both studies were negative. The company was requested to discuss the clinical relevance of the increased incidence of thyroid cysts observed in the rat carcinogenicity study taking into account the high level of sustained radioactivity observed in the thyroid gland in the tissue distribution studies. The company stated that developmental cysts are embryonic vestiges and do not represent lesions with neoplastic potential. This explanation was considered satisfactory.

4. Part IV: Clinical aspects

The clinical documentation includes an extensive clinical programme of 51 clinical pharmacology studies involving 1,150 subjects and one comparative international multicentre clinical trial (the "CAPRIE" study, Clopidogrel versus ASA in Patients at Risk of Ischaemic Events) involving 19,185 patients.

Human pharmacology

The pharmacodynamic effects of clopidogrel in humans were evaluated in several studies both in healthy subjects and in patients, after single or repeated administration. The selection of the dose was

based on two surrogate markers of pharmacological activity, inhibition of ADP-induced platelet aggregation and prolongation of bleeding time.

The precise correlation between the degree of inhibition of ADP-induced platelet aggregation and the reduction in ischaemic events is unknown. Dose selection for clopidogrel therefore aimed to identify that dose which inhibits ADP-induced platelet aggregation and prolongs bleeding time to the same extent as the proven effective dose of ticlopidine (250 mg twice daily).

Results from three phase I dose ranging studies indicated that a daily dose of 75 mg of clopidogrel would give the same level of ADP-induced platelet aggregation and prolongation of bleeding time as 250 mg of ticlopidine twice daily.

These findings were confirmed in a study performed in 150 atherosclerotic patients. The pharmacological activity of repeated administration (28 days) of 5 dose levels (10-100 mg per day) was compared to ticlopidine (250 mg twice a day) and placebo. The dose of 75 mg once daily was superior to 50 mg, and comparable to 100 mg once daily in terms of inhibition of ADP-induced platelet aggregation.

Based on the results of the above studies, it was considered that a daily dose of 75 mg clopidogrel would be effective and well tolerated in the target population. Consequently this dose was chosen for the phase III clinical programme.

Clopidogrel selectively inhibits the binding of ADP to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Dose dependent inhibition of platelet aggregation is observed 2 hours after single oral dose of clopidogrel. Repeated doses of 75 mg per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between day 3 and day 7. At steady state, the average inhibition level was between 40% and 60%.

The pharmacological activity is maintained with long-term use of clopidogrel. One study showed that the level of inhibition of platelet aggregation and prolongation of bleeding time were similar at one week and after 80 days of treatment. After discontinuation, inhibition of platelet aggregation and bleeding time returned to baseline values approximately 5 days after the last dose.

These findings are consistent with the mode of action of clopidogrel, namely that the active metabolite binds irreversibly to the platelet ADP receptor, therefore affecting the platelets for the remainder of their life span.

Pharmacokinetics

The pharmacokinetic profile was evaluated in 27 clinical trials carried out in healthy volunteers and special populations with either single or repeated administration.

Clopidogrel is rapidly absorbed and extensively metabolised by the liver. However, plasma levels of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours. The main circulating metabolite, which is inactive, is the carboxylic acid derivative which represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3 mg/l after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P_{450} isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

Consequently, though useful as a marker of absorption, the relevance of conventional pharmacokinetic studies of this inactive metabolite is limited. Thus, many aspects of the behaviour of clopidogrel, in special populations or potential interactions with other drugs, were studied using the dynamic markers, inhibition of ADP-induced platelet aggregation and prolongation of bleeding time.

In vitro studies showed that clopidogrel and SR 26334 bind reversibly to plasma proteins (98 % and 94 % respectively). Due to this high level of binding and the potential for interactions with products

with a known affinity for albumin, specific *in vitro* interaction studies were performed. These studies showed that there was no potential for interaction with such products.

A low level of covalent binding to proteins was observed in *in vivo* studies. Theoretically covalent binding to proteins could result in allergic reactions, but specific immunotoxicity studies in animals did not indicate clopidogrel had the potential to cause such effects.

The elimination half-life of SR 26334 after a single and repeated administration of 75 mg once daily of clopidogrel is approximately 8 hours.

The excretion of clopidogrel following a single dose of 75 mg of ^{14}C clopidogrel given alone or at the end of a ten-day dosing period of unlabelled drug accounted for 92-98% of the radioactive dose administered, equivalent percentages excreted through the faecal and urinary routes (46 and 50% respectively). The terminal half-life of radioactivity was approximately 7 days. This relatively long half-life is consistent with the platelet turnover.

Interactions

The interaction between clopidogrel and several other drugs (e.g. heparin, non-steroidal anti inflammatory drugs, theophylline and digoxine) has been investigated. The findings are reflected in the summary of product characteristics and in the package leaflet.

Hepatic microsomal studies indicated that clopidogrel could inhibit one of the cytochrome P_{450} enzymes, CYP 2C9. This could lead to elevated plasma levels of drugs, which are substrates for this isoenzyme (e.g. phenytoin, warfarin, tolbutamide and certain non-steroidal anti-inflammatory drugs such as piroxicam and diclofenac). Furthermore *in vitro* studies on human liver microsomes showed that the main circulating compound of clopidogrel could minimally inhibit one of the two main pathways through which glibenclamide is cleared. Data from the CAPRIE study indicate that phenytoin, tolbutamide and glibenclamide can be safely coadministered with clopidogrel.

Two studies were undertaken to assess the potential interaction of ASA with clopidogrel. ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution

Due to the use of too high a dose of warfarin (30-40 mg), the study to assess the potential interaction of warfarin with clopidogrel was prematurely discontinued. Although this study was inconclusive it is reasonable to assume that the risk of bleeding would be increased by the association of these two agents. Consequently, the concomitant administration of clopidogrel with warfarin can not be recommended.

The experience with the coadministration of clopidogrel with thrombolytic agents is limited. In one open uncontrolled study regrouping 116 patients, the concomitant administration of clopidogrel, rt-PA and heparin was assessed in patients with recent myocardial infarction. The incidence of moderate to severe bleeding was 1.7%. No data exist for the concomitant administration of clopidogrel with other thrombolytic agents. One interaction study of combined administration of heparin/clopidogrel and heparin/ASA resulted in one case of bleeding and 4 cases of haematoma at the injection site for the heparin/clopidogrel group (n=15) compared to no bleeding events in the heparin/ASA group (n=13). However, it should be noted that clopidogrel treatment started with a loading dose of 375 mg on day 1 followed by a dose of 75 mg daily. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Special populations

A small comparative study without control groups showed that there is no basis for expecting any differences in terms of efficacy and safety in patients with renal impairment. No dosage adjustment of clopidogrel is required. The limited relevant clinical experience regarding the therapeutic use of clopidogrel in renally impaired patients was further addressed during the hearing on 24th February 1998. However in view of the limited data and the fact that patients with severe renal impairment were

excluded from the CAPRIE study, clopidogrel should be used with caution in patients with renal impairment.

The company provided results of a pharmacokinetics/pharmacodynamics study of clopidogrel in 12 subjects with cirrhosis, compared with 12 healthy volunteers. As expected from the extensive first pass metabolism, the plasma level of clopidogrel was markedly elevated in cirrhotic patients. The inhibitory effect on platelets and the incidence of adverse events were globally comparable between the two groups. The mean inhibition of platelet aggregation was similar with a much larger variability in patients with hepatic impairment. The limited relevant clinical experience regarding the therapeutic use of clopidogrel in hepatically impaired patients was further addressed during the hearing on 24th February 1998.

Taking into consideration that patients with hepatic impairment were excluded from the CAPRIE study, that they may have bleeding diatheses, and that liver metabolism plays a key role in the generation of the active metabolite, clopidogrel is contraindicated in patients with severe liver impairment. Furthermore, clopidogrel should be used with caution in patients with moderate liver impairment who may have bleeding diatheses.

Clinical experience

Design

CAPRIE was a randomised, international multicentre double blind comparative trial designed to assess the relative efficacy of clopidogrel (75 mg once daily) and ASA (325 mg once daily) in reducing the risk of a composite outcome cluster of ischaemic stroke, myocardial infarction, or vascular death. The relative safety was also assessed.

The **primary efficacy endpoint** was based on the first occurrence of an event in the composite outcome cluster of fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction and vascular death.

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent ischaemic stroke (IS) (between 7 days and 6 months), recent myocardial infarction (MI) (<35 days), or established peripheral arterial disease (PAD).

9,599 (50.0%) were assigned to receive clopidogrel and 9,586 (50.0%) were assigned to receive ASA. The two groups were similar with respect to demographic characteristics, although there was a slight but statistically significant imbalance in the proportion of non-Caucasians in the two groups (p=0.02). The mean age was 62.5 (standard deviation 11.08) years with a range from 21 to 94 years.

The median duration of participation was between 20.4-23.9 months. 2,286 patients (23.8%) who received clopidogrel and 2,311 patients (24.1%) who received ASA permanently discontinued the study drug early. The majority of cases were due to adverse events or to patients who withdrew their consent for study participation.

Results and discussion

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to16.4]; p=0.045). This corresponds for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. The cumulative proportion of patients who experienced an event in the primary outcome cluster shows that the benefit of clopidogrel over ASA appears at an early stage of the treatment and continues to increase over time.

Two secondary endpoint clusters (ischaemic stroke, myocardial infarction, amputation, or vascular death; and vascular death alone) showed that there were more events in the ASA group than in the clopidogrel group, although the differences were not statistically significant. Analysis of total mortality as a secondary endpoint did not show a significant difference between clopidogrel (5.8%) and ASA (6.0%).

The CAPRIE trial was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups.

A test for heterogeneity of the three treatment effects was statistically significant suggesting that the true benefit may not be identical across the three clinical subgroups. In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD), the benefit appeared to be strongest (achieving statistical significance at p=0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR= 23.7%; CI : 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR= 7.3% ; CI : -5.7 to 18.7). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR= -4.0%; CI: -22.5 to 11.7).

Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

This issue of subgroup heterogeneity regarding qualifying conditions, and the implications for the therapeutic indication with regard to efficacy and especially safety (all cause mortality, vascular death, sudden death) in the myocardial infarction subgroup were further discussed during the hearing held on 24th February 1998, and during the March CPMP meeting. The final recommendation regarding initiation of clopidogrel in patients with myocardial infarction agreed by the CPMP is reflected in the agreed therapeutic indication.

Using the appropriate trials from the APTC meta-analysis (i.e. those in the same clinical syndromes), the efficacy of clopidogrel versus a putative placebo was estimated. These analyses strongly supported the superiority of clopidogrel over placebo in the overall CAPRIE population and in the IS and MI subgroup.

Oral explanations were provided during the hearing held on 24th February 1998 on the time to onset of action in view of the lack of new data to document the efficacy of clopidogrel at the first few days of an acute situation. The final recommendation agreed by the CPMP is that clopidogrel should not be initiated within the first few days following myocardial infarction, and that in view of the lack of data, clopidogrel can not be recommended in unstable angina, PTCA (stenting), CABG and acute ischaemic stroke (less than 7 days).

An unplanned subgroup-analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients $\leq$75 years. There were 243 patients with events in the clopidogrel group compared to 220 in the ASA group (efficacy odds ratio: 1.176; CI: 0.980 to 1.412). Efficacy and safety in patients over 75 years of age, together with the possible interaction with the qualifying condition of myocardial infarction, and effects on sudden deaths were addressed during the hearing held on 24th February 1998. The issue was considered as satisfactorily addressed by the CPMP and no specific recommendation was introduced in the Summary of Product Characteristics for patients over 75 years of age.

Safety

Clinical pharmacology studies

The safety profile of clopidogrel was based on the experience from the CAPRIE study and also from 51 clinical pharmacology studies including 1,150 healthy volunteers and patients receiving clopidogrel, placebo and/or another drug.

As expected from its pharmacological action, platelet clotting and bleeding disorders were more common on clopidogrel (10% at 75 mg once daily of compared to 3.9% on placebo). Haematoma and purpura, including bruising were the other most common events. Gastrointestinal tract adverse events occurred in 10.5% compared to 7.1% on placebo, though diarrhoea was the only individual event seen more frequently on clopidogrel (2.8% at 75 mg once daily compared to 0.7% on placebo). Its incidence did not increase with higher doses and was rarely severe. Rash was noted in 1% of subjects on 75 mg once daily and 2.5% at higher doses compared to 0.7% on placebo.

The clinical pharmacology studies showed that adverse events commonly seen with ticlopidine such as diarrhoea and rash were less common with clopidogrel. Severe cases were rare. More importantly

there was no evidence of clinically relevant thrombocytopaenia, neutropaenia or impairment of liver function.

CAPRIE study

The extent of exposure to clopidogrel 75 mg once daily as well as to ASA 325 mg once daily in the CAPRIE study provided a strong basis for a reliable comparison of the safety profile of the two drugs.

The mean treatment duration was 19.5 months (Standard deviation 10.18 months for both treatment groups) allowing over 15,500 patient years experience with each drug. Only 56 patients were lost to follow-up: 30 on clopidogrel and 26 on ASA.

A comparable rate of adverse events was reported under the two treatments: 86.3% on the clopidogrel group and 86.5% patients on the ASA group reported at least one adverse event. This was expected given the length of the treatment and the severity of the underlying condition.

The overall frequency of serious adverse events was similar for both treatment groups (40.4% on clopidogrel and 41.1% on ASA). The incidence of death resulting from an adverse event that began under treatment was similar in both treatment groups: 4.1% and 4.3% on clopidogrel and ASA respectively. Very few deaths were considered as related to the study drug : 11 on clopidogrel and 13 on ASA.

Gastrointestinal adverse events were statistically more frequent in the ASA group ($p<0.001$). Diarrhoea was rarely severe and was reported at a higher frequency on clopidogrel compared to ASA (4.5% vs. 3.4%).

Cardiovascular system ($p=0.002$), central and peripheral nervous ($p=0.016$), heart rate and rhythm ($p=0.011$) and red blood cell ($p=0.024$) disorders were significantly more frequent in the ASA group than in the clopidogrel group.

There was no statistically significant difference between treatments groups in the incidence of adverse events in the urinary, biliary and hepatic systems.

There were no differences between treatments groups in the frequency of potentially clinically significant liver function abnormalities (AST, ALT and alkaline phosphatase), although the clopidogrel group had a small mean increase in total bilirubin (0.01-0.03 mg/dl) relative to ASA.

Skin and appendage disorders were more frequent in the clopidogrel group ($p<0.001$) than in the ASA group. Specifically, rash was experienced by significantly more patients in the clopidogrel group than in the ASA group ($p=0.012$). Patients in the clopidogrel group experienced significantly more pruritus ($p<0.001$).

Hyperuricaemia ($p=0.015$) was experienced by significantly more patients in the ASA group. Asthenia ($p=0.017$) and gout ($p=0.026$) were experienced by significantly more patients in the clopidogrel group.

The percentage of patients with a platelet, bleeding or clotting disorder did not differ significantly between treatment groups. However significantly more patients experienced purpura (bruising) in the clopidogrel group (5.27%) than in the ASA group (3.68%) ($p<0.001$).

The overall incidence of neutropaenia was low and did not differ between groups. Neutropaenia was seen in 0.08% of the clopidogrel group and in 0.15% of the ASA group. Only 4 cases (0.04%) on clopidogrel and 2 cases (0.02%) on ASA had severe low neutrophil count below 0.450×10^9/l. Two cases of agranulocytosis occurred in patients taking clopidogrel.

No significant difference between clopidogrel and ASA was found either in the frequency of thrombocytopaenia (<100 G/L) 0.33% in both groups, or the frequency of severe (<80 G/L) thrombocytopaenia (0.16% vs. 0.08%).

One serious unexpected case of aplastic anaemia occurred during the CAPRIE study and seemed probably related to clopidogrel. The patient however was also on other medication known to be associated with haemotoxic effects. The patient was not rechallenged with clopidogrel.

The overall incidence of any bleeding did not differ statistically significantly between the two groups (9.3 % in both groups). The occurrence of gastrointestinal bleeding was slightly but significantly higher in the ASA group (2.7%versus 2%, $p=0.002$). Three patients died from gastrointestinal

bleeding (one in the clopidogrel group and two in the ASA group). There was no statistically significant difference in the incidence of intracranial bleeding.

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

Of the 75 patients in the clopidogrel group with eye bleeding only five had a severe event. In the ASA group, 46 patients experienced eye bleeding with only one patient having a severe event.

A substantial number of patients (clopidogrel n=382, ASA n=387) underwent cardiac catheterisation with angiography, PTCA or stenting. A slight excess of bleeding events (clopidogrel n=46, ASA n=38) or haematoma (clopidogrel n=18, ASA n=14) was seen in the clopidogrel treatment group as compared to the ASA group. Another clinical study has evaluated the safety of clopidogrel compared to aspirin in patients undergoing PTCA. In this study a higher incidence of bleeding or haematoma was observed in the clopidogrel group (5/15 patients versus 0/13). It should however be noted that clopidogrel was given as loading dose of 375 mg followed by 75 mg once daily.

5. Overall conclusion and benefit/risk assessment

Benefit risk assessment

The CAPRIE trial showed that clopidogrel at a dose of 75 mg once daily is an effective antithrombotic agent which reduced by 8.7% (p=0.045) compared to ASA (325 mg once daily) the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) in patients with clinical evidence of atherosclerosis. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to16.4]; p=0.045), which corresponds for every 1,000 patients treated for 2 years, to 10 [CI:0 to 20] additional patients being prevented from experiencing a new ischaemic event.

The safety profile shows that clopidogrel is at least as well tolerated as ASA. Overall clopidogrel was well tolerated, having an adverse event profile comparable to ASA, but with better gastrointestinal tolerability. Only rash, purpura (bruising) and diarrhoea were notable in the clopidogrel group but were rarely severe. There is no evidence that clopidogrel shares the risk, seen with ticlopidine, of neutropaenia or thrombocytopaenia. The company has additionally been requested to provide as a follow-up to the marketing authorisation together with the periodic safety update reports an analysis of the haematological effects of clopidogrel.

Conclusion

The quality of the medicinal product is considered satisfactory. No major objections on the chemical and pharmaceutical aspects of the dossier prevent the approval of the medicinal product. However a number of follow-up measures have been addressed by the applicant.

The pharmacodynamic activity of clopidogrel was adequately evaluated. Clopidogrel is a prodrug. The active metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The overall animal toxicological profile of clopidogrel (hydrogen sulphate salt form) was adequately evaluated and no major findings were described at doses at least up to 100 mg/kg/day in all species. The systemic exposure of the several animal species to that dose as compared to the human exposure expected at therapeutic dose of 75 mg/day is satisfactorily higher and does not suggest safety concerns in relation to the human use of the drug.

Although the explanation provided by the company regarding the increased incidence of thyroid cysts in rats may be acceptable, no further explanation was provided on the high level of sustained radioactivity observed in the tissue distribution studies. Therefore, the company is requested to provide as a post marketing surveillance follow-up measure clinical safety data on the thyroid function.

Clinical efficacy is based on the results of the CAPRIE trial which showed that clopidogrel at a dose of 75 mg once daily reduces by 8.7% (p=0.045) the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) in patients with clinical evidence of atherosclerosis, over ASA (325 mg once daily). Overall clopidogrel was well tolerated, having an adverse event profile comparable to ASA, but with better gastrointestinal tolerability.

The CPMP considered the benefit/risk ratio to be favourable and issued on 25 March 1998 a positive opinion for granting a marketing authorisation for Iscover.

6. New indication in Acute Coronary Syndrome

Introduction

Acute coronary syndromes (ACS) (unstable angina or non-Q-wave MI) is defined as any clinical syndrome of acute cardiac ischaemia related to coronary artery disease (CAD), including those with or without persistent ST segment elevation. ACS patients with persistent ST segment elevation (i.e. rapidly evolving into Acute MI) require urgent recanalisation (either by thrombolytic or mechanical reperfusion), and were not prospectively evaluated in CURE and, therefore, are beyond the scope of this variation. In contrast, non-ST segment elevation ACS (NSTEACS), which includes the closely related conditions of Unstable Angina (UA) and non-ST segment elevation MI (NSTEMI), do not benefit from urgent recanalisation. These NSTEACS share similar pathogenesis and clinical presentation, and require similar clinical management to prevent transmural MI and other serious cardiovascular events. Apart from symptomatic treatment, the aim of therapeutic interventions in NSTEACS patients is to prevent thrombosis extending to complete coronary occlusion and MI. Anti-platelet therapy is a logical therapeutic approach given the key pathophysiological role of platelets.

The objectives of the therapeutic management of patients with NSTEACS are:

1. *Immediate treatment* of the ischaemic symptoms: chest pain and haemodynamic instability, with or without associated cardiac rhythm disturbances.
2. *Early and long-term prevention* of atherothrombotic events, not only of those complicating the culprit coronary lesion which triggered the ACS (related MI), but also those complicating atherosclerotic lesions in other vascular beds of these "vascular" patients (e.g., AMI, strokes…).

Prior to CURE, ASA alone was the front line pharmacological treatment for patients with NSTEACS, with a recommendation to start therapy as soon as possible and to continue it indefinitely. For those patients intolerant to ASA, a thienopyridine (ticlopidine) was recommended as an effective alternative. Both European and North American Recommendations for the treatment of ACS are based on a considerable amount of information from sound clinical trials, and can be considered as evidence-based guidelines. The American College of Cardiology and the American Heart Association (ACC/AHA Guidelines for the Management of Patients with UA and NSTEMI, 2000) propose the following (Recommendations Class I for Antithrombotic therapy):

- Possible ACS: ASA (75-325 mg/day)
- Likely or Definite ACS: ASA + Subcutaneous low molecular weight heparin or Intravenous heparin
- Definite ACS with continuing ischaemia or other high risk features (eg. diabetes, recent MI, elevated troponin T or I) or planned interventions: ASA + Intravenous heparin + Intravenous platelet GPIIb/IIIa receptor antagonists.

The Recommendations of the European Society of Cardiology Task Force are similar, suggesting that high-risk patients (recurrent pain, ST segment elevation or depression, elevated troponin, patients with haemodynamic instability, major arrhythmias or early post infarction UA) should receive platelet GPIIb/IIIa receptor antagonists in addition to ASA and heparin. In low risk patients (no recurrence of chest pain within the observational period, no elevation of troponin or other biochemical markers of myocardial necrosis, without ST-segment depression or elevation but rather negative T waves, flat T waves or normal ECG), platelet GPIIb/IIIa receptor antagonists are not suggested and discontinuation of heparin should be considered, if a second troponin measurement is negative.

Patients with NSTEMI and ACS may be at increased risk of cardiac death and AMI (8 to 16%, one month after the episode); beyond the first month the risk exists but shows a progressive decrease. At present, the place of thienopyridines in ACS is a second choice of antiplatelet therapy, if patients are

intolerant to ASA; if a stent procedure takes place, ticlopidine in addition to ASA is indicated as a first line therapy. From a pharmacological basis it is reasonable to hypothesise that the combination of clopidogrel with ASA would provide better efficacy for the prevention of adverse outcomes in NSTEACS patients, since clopidogrel blocks the ADP platelet receptor, a pathway complementary to that of ASA.

The present application seeks approval for the indication of clopidogrel as a first line therapy together with ASA, both for early and long-term treatment, in all patients presenting with ACS.

Clinical aspects

Pharmacology: dose regimen

Inhibition of ADP-induced platelet aggregation is the most appropriate way to measure the pharmacodynamic activity of this clopidogrel *in vivo*. Although inhibition of platelet aggregation is noted 2 hours after the administration of 75 mg of clopidogrel, a steady-state level of inhibition (40-60%) is reached only 3 - 7 days after the first dose.

The dose regimen of ASA to be used as background therapy in every patient in CURE, whereby investigators chose a dose within the established therapeutic range of 75 to 325 mg once daily, was selected according to the existing clinical documentation and international recommendations (Recommendations of the Task Force of the European Society of Cardiology. Eur Heart J 2000; 21(17): 1406-32). This strategy was later supported by the results of a pharmacology study in healthy subjects demonstrating the additive activity of clopidogrel and ASA on the final inhibition of platelet aggregation induced by collagen and the earlier inhibition of ADP-induced platelet aggregation with a clopidogrel loading dose.

The long-term benefit of clopidogrel 75 mg once daily dose was clinically assessed in the CAPRIE trial, which demonstrated superior efficacy to ASA in atherosclerotic patients at risk. An initial 300 mg loading dose was used in order to reach a steady-state level of pharmacodynamic activity earlier. Further data (eg: CLASSICS study comparing ASA +clopidrogrel 300mg on day 1 followed by 75mg daily to ASA + ticlopidine 250mg twice, in the prevention of acute coronary closure after a stent) supported this dosing strategy.

Clinical data

The claimed indication is based on the results of the CURE (Clopidrogrel in Unstable Angina to Prevent Recurrent Event) study. This was a multinational trial comparing the efficacy and safety of clopidogrel 75 mg daily after an initial loading dose of 300 mg to matching placebo in patients with NSTEACS (Unstable angina or Non-ST segment Elevation Myocardial Infarction) treated with ASA (75-325 mg/day, left to the investigators' decision) and other concomitant therapy for a minimum of 3 months and a maximum of 12 months.

The primary objective was to evaluate the efficacy of clopidogrel relative to placebo in preventing ischaemic complications. The secondary objective was to evaluate the safety of clopidogrel in this setting. Patients over 21 years of age presenting with ischaemic symptoms suspected to represent an ACS (defined as UA or MI without ST segment elevation greater than 1 mm) and electrocardiogram (ECG) changes compatible with new ischaemia or already elevated cardiac enzymes or troponin I or T were randomised within 24 hours of onset of the most recent episode of chest pain/ischaemic symptoms. These inclusion criteria were adopted following a protocol modification to include the requirement of ECG changes and/or cardiac marker elevation for all patients, independently of age, in order to further secure the diagnosis of coronary disease. *Follow-up* was a minimum of 3 months and maximum of 12 months. The dose was 4 tablets on Day 1 and 1 tablet once daily starting on Day 2. *Exclusion criteria* included known contraindications to ASA and/or clopidogrel and factors affecting the evaluation of the effect of the study drug such as concomitant use of oral anticoagulants, antithrombins (other than heparins), open-label use of thienopyridines (clopidogrel or ticlopidine) and dipyridamole.

There were two composite co-primary *endpoints*. The first endpoint was the first occurrence of any of the following outcomes: cardiovascular (CV) death, MI, or stroke over the duration of the follow-up; the second endpoint was the first occurrence of CV death, MI, stroke or refractory ischaemia over the duration of the follow-up. All primary outcome events were blindly adjudicated by an Independent Adjudication Committee (IAC). Refractory ischaemia during initial hospitalisation had very stringent criteria:

- recurrent chest pain or
- ischaemic symptoms lasting longer than 5 minutes while on optimal therapy and leading to:
  - additional intervention (thrombolysis for threatened MI, cardiac catheterisation, insertion of intra-aortic balloon pump) or
  - revascularisation procedure, (i.e. PTCA/stent or CABG surgery) or
  - transfer for these procedures by midnight of the next day.

The post-discharge definition, "rehospitalisation for UA", was less stringent and included any hospital stay for at least 24 hours with clinical symptoms of typical prolonged chest pain unresponsive to the patient's usual medication associated with ECG changes consistent with acute myocardial ischaemia.

Other planned outcomes were: i) CV death, total death, MI, and stroke (subdivided as ischaemic, haemorrhagic or of uncertain type) considered separately; ii) severe ischaemia during initial hospitalisation; iii) recurrent angina during initial hospitalisation; iv) mechanical or pharmacological coronary revascularisation (percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass graft [CABG surgery] or thrombolytic therapy).

Safety criteria for evaluation were the occurrence of life-threatening bleeding and serious adverse events (SAEs). Life-threatening and major bleeding events were adjudicated by the IAC and were defined as follows:

- Life-threatening bleeding: fatal bleeding or bleeding leading to a drop in haemoglobin $\geq$5 g/dl, or significant hypotension with need for inotropes, or surgery (other than vascular site repair), or symptomatic intracranial hemorrhage, or transfusion of 4 or more units of red blood cells or equivalent whole blood.
- Major bleeding: significantly disabling, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood.
- Minor bleeding: any other bleeding requiring temporary/permanent discontinuation of study drug.

Any life-threatening/major bleeding had to be reported as a SAE by the Investigator, with the exception of haemorrhagic stroke, which was a study outcome. Any other bleeding event was to be reported on the minor bleeding form of the case report form, but not on the adverse event (AE) form.

An initial sample size of 9,000 patients was planned, but after a review of the first 3,500 patients, the study sample size was increased to 12,500 patients due to a lower than expected event rate. Regarding the *statistical methods*, the main efficacy analysis was an intention-to-treat (ITT) analysis including all patients randomized in the study regardless of whether they actually received study drug. The relative efficacy of clopidogrel and placebo was assessed by comparing the survival curves for the 2 treatments using the logrank test. Treatment effect, measured by the hazard ratio and its associated 95% confidence interval (CI), was derived by employing Cox's proportional hazards model. In order to maintain an overall type I error rate of 5%, the primary outcomes were tested at adjusted alpha levels. Statistical significance was claimed if the computed p-value for the first cluster of CV death, MI or stroke was $\leq$ 0.045 (0.044 adjusted for two interim analyses) or the p-value for the cluster including refractory ischemia was $\leq$ 0.01. The safety analyses were based on the ITT population. Statistical comparisons of safety data were made using Pearson's Chi-squared tests.

Results

The study enrolled a total of 12,562 patients. Only 13 patients (6 clopidogrel, 7 placebo) were declared lost-to-follow-up. Slightly more patients permanently discontinued study drug prematurely in the clopidogrel group (21.1% vs. 18.8% with placebo), primarily due to the difference in AE-related study drug discontinuations (5.8% clopidogrel vs 3.9% placebo). The mean duration of study participation was 9.4 months and the total number of patient-years on study drug was 4318 for clopidogrel and 4376 for placebo. Demographic data and medical/surgical history were well balanced between the 2 treatment groups, i.e. age, sex, time to onset of pain to randomisation, heart rate, arterial blood pressure, diagnosis at entry (UA, MI), medical history, ECG, medication(s) at time of randomisation.

Regarding *efficacy*, clopidogrel significantly reduced the risk of the first co-primary endpoint compared to placebo (p=0.00009). A total of 582 (9.3%) patients in the clopidogrel group versus 719 (11.4%) patients in the placebo group experienced the first co-primary outcome. The relative risk reduction (RRR) was 19.6% (95% CI: 10.3%, 27.9%). The relative risk of the second co-primary endpoint was also significantly reduced with clopidogrel (RRR 13.7%; 95% CI: 6.2%, 20.6%, p=0.0005).

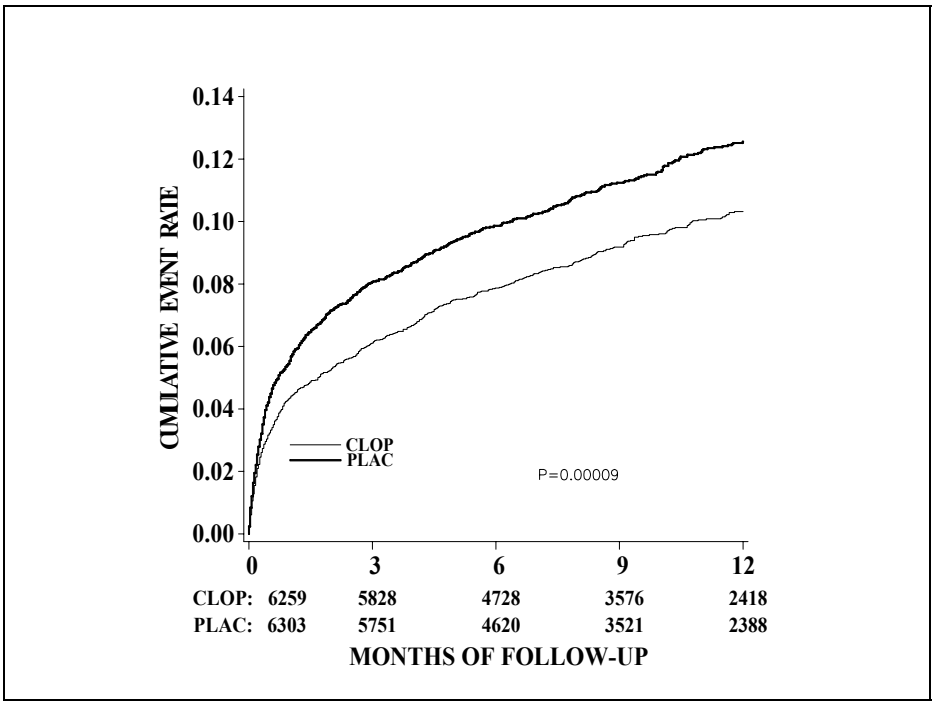
Table 1 Primary Outcome Events – Number (%) of Patients and Relative Risk Reduction

	Clopidogrel (N = 6259)	Placebo (N = 6303)	RRR (%) (95% CI)	p-Value
1st co-primary outcome (CV death/MI/Stroke)	582 (9.30%)	719 (11.41%)	19.6 (10.3, 27.9)	0.00009
2nd co-primary outcome (CV death/MI/Stroke/ Refractory ischaemia)	1035 (16.54%)	1187 (18.83%)	13.7 (6.2, 20.6)	0.00052
Primary Outcome Events: individual outcome events				
CV death	318 (5.08)	345 (5.47)	7.5 (-7.7, 20.6)	
MI (fatal or not)	324 (5.18)	419 (6.65)	23.0 (11.0, 33.4)	
Stroke (fatal or not)	75 (1.20)	87 (1.38)	13.6 (-17.1, 36.6)	
Refractory ischemia:				
- initial hospitalisation	85 (1.36)	126 (2.00)	32.1 (10.8, 48.3)	
- rehospitalisation for	470 (7.51)	469 (7.44)	-0.7 (-14.4, 11.4)	
UA	359 (5.74)	390 (6.19)	7.6 (-6.6, 20.0)	
SP death *				

*Total number of deaths during the Study Period (includes CV and non-CV death).

The benefit of clopidogrel was consistent for each individual outcome event (CV death, MI, stroke) and for the total number of deaths during the study period (SP deaths). This was evident early after randomisation and was maintained over the course of the study (up to 12 months). The predominant and only statistically significant benefit was the reduction of MI, mainly in the first 30 days. This is also the period with greater risk of cardiac death and acute MI. The positive trend in the beneficial effect of clopidogrel was not maintained in the post-discharge refractory ischaemia, probably related to its less stringent definition.

The cumulative event rates for the first co-primary efficacy endpoint against time are shown below:

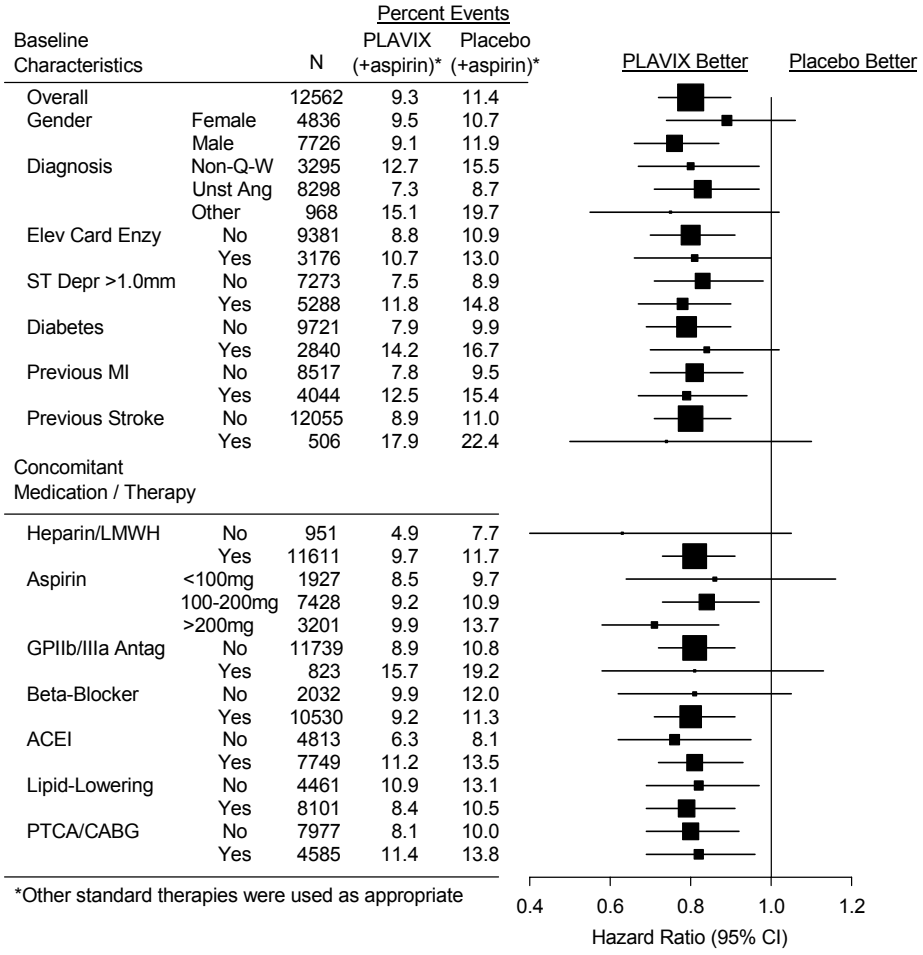


The cumulative event rates for the second co-primary efficacy endpoint are similar to the above. The co-primary event rate curves started to diverge very early after randomisation, with a significant difference in the first and second co-primary outcomes as early as 7 days and 24 hours respectively after randomisation. The curves continue to diverge throughout the course of the trial (up to 12 months), with a RRR for the first co-primary outcome of 22.0% (p = 0.002) during the first 30 days after randomisation and 17.4% (95% CI, 3.9-28.9%) beyond 30 days (up to 1 year). However, after 3 months the event curves cease to deviate and tend towards a plateau, suggesting that the number of additional events after 3 months is similar in both groups. The results thus confirm that the majority of treatment effect was obtained in the first 3 months, as expected from the physiopathology of ACS.

In view of the conspicuous decrease in efficacy after the first 3 months and given the significant incidence of bleeding with clopidogrel, the CPMP requested the MAH to focus on patients who discontinued treatment and carrry out *post-hoc* analyses of the co-primary endpoints event rates according to the time of discontinuation, ie. 2-3-4 months (as well as before and after). The results demonstrate the loss of protection with clopidogrel when the treatment is discontinued after 2 months or later. Indeed, when clopidogrel is discontinued during the 3rd month or later, patients experience the first co-primary event twice as frequently as in the placebo group (4.6% vs 2.3%).

A consistent effect on the RRR of the first co-primary endpoint was observed regardless of the patient or disease characteristics, as shown in post-hoc subgroup analyses – see figure below. Although the data suggest that the effect in women and diabetics may be less than that observed in males and non-diabetics, the relevant subgroups are probably too small to observe a statistically significant benefit in this post-hoc analysis.

Figure 1. Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study



Given the higher bleeding risk with clopidogrel in the CABG and PCI group, the CPMP requested the MAH to perform a specific benefit analysis in these patients. The results shown below indicate that the efficacy of clopidogrel was independent of PCI and/or CABG cardiac interventions. Nonetheless, the RRR for the 1st co-primary outcome in the the 9901 patients treated conservatively was slightly inferior to that observed in the overall patient population (17% vs 20%), clearly inferior to patients undergoing PTCA (~30%) and higher than in patients undergoing CABG surgery (~10%), suggesting that patients undergoing PTCA seem have the most benefit.

Interaction Variable	Subgroup	No. With Event/No. in subgroup (%) Clopidogrel	Placebo	Hazard Ratio (95% CI)	p-Value for Interaction
PTCA/CABG surgery	**No**	324/4002 (8.1)	397/3975 (10.0)	0.80 (0.69, 0.92)	0.844
	Yes	258/2257 (11.4)	322/2328 (13.8)	0.82 (0.69,0.96)	
PTCA	**No**	456/4943 (9.2)	542/4958 (10.9)	0.83 (0.74, 0.94)	0.240
	Yes	126/1316 (9.6)	177/1345 (13.2)	0.71 (0.57,0.90)	
CABG surgery	**No**	434/5245 (8.3)	547/5236 (10.4)	0.78 (0.69, 0.89)	0.276
	Yes	148/1014 (14.6)	172/1067 (16.1)	0.90 (0.72, 1.12)	

A further risk/benefit assessment carried out in the highest risk patients, such as those treated with GPIIb/IIIa antagonists during the first month, those undergoing PCI during the first month, and those

receiving GPIIb/IIIa antagonists during the first month and undergoing PCI, evidenced that these patients seemed to receive more benefit from the dual clopidogrel + ASA therapy, and the risk of bleeding in these subgroups was similar between both treatment arms (with the exception for the PCI group where bleedings did not require permanent or temporary discontinuation of the study drug).

Regarding possible effects of concomitant therapies, there was an increased frequency in the incidence of the 1st co-primary outcome in both groups with increasing doses of ASA. Despite this apparent ASA dose effect, the efficacy of clopidogrel was independent of the ASA dose (p for interaction = 0.133). There were no differences in the ASA dose distribution between treatment groups.

Fewer clopidrogrel-treated patients required concomitant GPIIb/IIIa antagonists but the efficacy of clopidogrel was independent of these concomitant therapies. Regarding other concomitant cardiovascular therapies (beta blockers, ACEIs and lipid lowering drugs), statistical analyses demonstrated that they did not interact with the efficacy of clopidogrel.

Analysis of the other efficacy endpoints showed that, consistently with the decrease in MI and refractory ischaemia during initial hospitalisation, fewer patients in the clopidogrel group required GPIIb/IIIa antagonists (5.9% vs 7.2% for placebo, p = 0.0031) or thrombolytics (1.13% vs 2.00% for placebo, p = 0.0001). Similarly, fewer patients in the clopidogrel group underwent PCI and/or CABG during the initial hospitalisation (20.8% vs 22.7% for placebo, p = 0.01). However, no significant differences in interventional cardiology were observed during the overall study follow-up between treatment groups. Fewer patients in the clopidogrel group presented with radiological evidence of heart failure during the initial hospitalisation (3.66% vs 4.44% for placebo, p = 0.026). As regards unstable angina, the rehospitalisation rates were similar in both treatment groups.

Safety

There was no statistically significant difference between the two treatment groups in the rate of life threatening bleeding; in particular, no excess in fatal bleeding or intracranial haemorrhage was observed in the clopidogrel group. Life-threatening bleeding was mainly observed during the 1st month of treatment at surgical, gastrointestinal or puncture sites in both treatment groups. There was a significant excess in all other types of bleeding with clopidogrel, as shown in the table below.

Summary of bleeding results

Outcome	No (%) With Event		% Difference clopidogrel – placebo (95% CI)	p-Value
	Clopidogrel (N = 6259)	Placebo (N = 6303)		
Life-threatening bleeding Fatal bleeding Non-fatal bleeding	135 (2.16) 11 (0.18) 125 (2.00)	112 (1.78) 15 (0.24) 99 (1.57)	0.38 (-0.12, 0.88) -0.06 (-0.24, 0.11) 0.43 (-0.05, 0,91)	0.1251
Major bleeding	100 (1.60)	65 (1.03)	0.57 (0.15, 0.98)	0.0053
Minor bleeding*	322 (5.14)	153 (2.43)	2.72 (2.04, 3.40)	<0.00001
Other bleeding**	727 (11.62)	421 (6.68)	4.94 (3.91, 5.96)	

*The total does include some events (6 cases in the clopidogrel group and 2 cases in the placebo group) reported as life-threatening or major bleeding, but adjudicated to minor bleeding.

** Minor bleeding forms which did not lead to study drug discontinuation.

Over half of the bleedings observed in both treatment groups were identified during the first month of treatment. More than half of major bleedings occurred after 30 days (see table). A total of 177 patients (2.8%) in the clopidogrel group had a transfusion (= 2 units) compared with 137 patients (2.2%) in the placebo group (p=0.019)

Number of patients with adjudicated bleeding events up to 30 days and beyond 30 days

	Period ≤ 30 days		Period > 30 days	
	Clopidogrel (N = 6259)	Placebo (N = 6303)	Clopidogrel (N = 6259)	Placebo (N = 6303)
Life-threatening bleeding	81 (1.29)	62 (0.98)	54 (0.86)	50 (0.79)
Major bleeding	48 (0.77)	39 (0.62)	52 (0.83)	26 (0.41)

Data from subgroup analyses according to interventions confirms that invasive surgical procedures increase the risk of bleeding in both treatment groups, but do not support any further differential between clopidogrel and placebo.

Summary of Adjudicated Life-Threatening/Major Bleeding According to Interventions

Interaction Variable	Subgroup	No. With Event/No. in subgroup (%) Clopidogrel	Placebo	p-Value for Interaction
PTCA/CABG surgery	No	97/4002 (2.42)	56/3975 (1.41)	0.1125
	Yes	134/2257 (5.94)	113/2328 (4.85)	
PTCA	**No**	185/4943 (3.74)	128/4958 (2.58)	0.3287
	YES	46/1316 (3.50)	41/1345 (3.05)	
CABG surgery	**No**	134/5245 (2.55)	89/5236 (1.70)	0.4746
	Yes	97/1014 (9.57)	80/1067 (7.50)	

A number of covariate analyses taking into account patient characteristics and concomitant therapies were performed on the adjudicated bleedings. Elderly patients and kidney-impaired patients experienced more adjudicated bleeding (both factors are well-known to increase the risk of bleeding), although the relative rate of adjudicated bleeding with combined treatment was independent of the patient characteristics. Similarly, the relative rate of adjudicated bleeding with clopidogrel was independent of the following therapies: dose of ASA, heparins, GPIIb/IIIa antagonists and oral Anticoagulant and Non-Steroidal Anti-Inflammatory Drugs (NSAID).

The overall rate of SAEs leading to non-CV death was similar between the 2 treatment groups. Similarly, there was no apparent difference in the rate of non-haemorrhagic SAEs. In addition, there was no difference in non-haemorrhagic AEs between treatment groups, except for an increased frequency of rash and fatigue with clopidogrel. This excess of rash explains the higher rate of permanent discontinuation of study drug due to non-haemorrhagic AEs in the clopidogrel group. Of note, no cases of thrombotic thrombocytopenic purpura, agranulocytosis or aplastic anaemia were reported in any group.

Discussion

The CURE trial is a well designed, well conducted generally consitent study, performed according to the current standards and represents a major attempt to demonstrate benefit in the use of clopidogrel in the prevention of atherotrombotic events in patients with ACS. The choice of primary endpoints for CURE is adequate and in general agreement with current CPMP recommendations, and the observed individual outcomes were defined according to stringent criteria and reflect medical practice. The lack of formal dose-exploration studies is acceptable as there is sufficient evidence of efficacy from previous trials to support the chosen dose regimen. The main criticism to the study is the failure to establish optimal treatment durations.

Regarding *efficacy*, the results show a clinically and statistically significant reduction in the first and secondary co-primary endpoints at the end of scheduled 12 months of treatment. This is mainly due to the significant reduction in the occurrence on MI and refractory ischaemia following initial hospitalisation. The trends observed for CV death and stroke, although not significant, are in agreement with the overall protective effect. The only notable exception is the slight non-significant increase in rehospitalisation for UA. Analysis of the cumulative event rate curves for both co-primary endpoints clearly shows that the maximum benefit of the clopidogrel + ASA is observed up to the first 3 months of treatment. Thereafter, the number of additional events tends to even out in both treatment groups.

In the light of the significantly increased risk of haemorrhage with clopidogrel – see efficacy discussion, this conspicuous difference in efficacy between the initial 3 months and the subsequent treatment period (up to the studied 12 months) has prompted extensive discussions by the CPMP as to whether dual therapy should be stopped after the first 3 months. However, it is difficult to compare the two treatment groups after the first 3 months of therapy, since any post-hoc analysis on comparative event rates at fixed time points after randomisation compares populations no longer balanced for risk, since the clopidogrel group becomes increasingly enriched with higher risk patients over time and given the discontinuations of high-risk patients in the ASA arm due to the occurrence of events. Nonetheless, despite the high risk population "enrichment' in the clopidogrel arm, patients in this group experience fewer first co-primary events during any period after randomisation, provided treatment is continued. Moreover, it would appear that the initial CV protection was not maintained when clopidogrel was prematurely discontinued, although this observation is based on a post-hoc analysis. The results of the trial and the concerns raised during its assessment have been adequately reflected in section 5.1 with the inclusion of the results for the different time intervals and a clear statement regarding the benefit observed beyond 3 months of treatment in relation to the increased risk of haemorrhage. Similarly, section 4.2 has been amended to reflect the facts that the optimal duration of treatment has not been established and that the trial data support use up to 12 months although the maximum benefit was seen up to 3 months.

During the CPMP discussions it was acknowledged that the proposed wording of the indication section was too complicated and should be simplified for the benefit of the prescriber. For the sake of consistency and although outside the scope of this variation procedure, the wording of the indication approved at the time of the granting of the MA has also been simplified, following the consent of the MAH. Thus, the indication has been reworded to make it clearer and to reflect the intention behind the administered treatment - as opposed to the observed outcome(s), which in the case of clopidogrel is the prevention of atherothrombotic events. Hence, the information on outcomes and relevant findings pertaining to the trials supporting the approved indications has been inserted primarily in sections 5.1 and 4.8. These changes are in line with the European Commission Guideline on the Summary of Product Characteristics (December 1999).

There was consistent benefit of clopidogrel across all groups, including both high-risk and low-risk patients, except for the post-discharge refractory ischaemia group, as shown through different subgroup analyses. Benefits were observed regardless of other medications utilised i.e. beta-blockers, statins, ACE inhibitors, and heparin. This information is reflected in section 5.1.

Regarding *safety*, the lack of significant excess in life-threatening bleeding and in non-CV mortality observed in the clopidogrel arm, and the similar incidence of intracranial bleeding in both groups, is reassuring. There was, however, a significant increase in all other types of bleeding in the clopidogrel arm. The risk of bleeding for both arms decreased during the course of the trial and, as expected, the major bleeding event rate for both treatment arms was dose-dependent on ASA. 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, and in patients who remained on therapy within five days of bypass graft surgery, the event rate was significantly higher in the clopidogrel arm. All of these findings have been included in section 4.8 of the SPC and do not reveal any new safety concerns.

In conclusion, the CURE study demonstrated a significant reduction of atherothrombotic events in patients with non-ST segment elevation ACS treated with clopidogrel + ASA versus ASA alone.

However, although a 12-month treatment period has been validated, the optimal duration of treatment has not been established, given that the maximum benefit was observed in the initial 3 months and the risk of bleeding is significantly higher with clopidogrel + ASA.

7. Post-Marketing Safety

Warnings and interactions
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. As with other antiplatelet agents, clopidogrel 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 ASA, nonsteroidal anti-inflammatory drugs, 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.

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 hemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Adverse Drug reactions
Bleeding is the most commonly reported adverse drug reaction, with most cases reported during the first month. Some cases were reported with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage). Cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with ASA, or clopidogrel with ASA and heparin.

Very rare cases of Thrombotic Thrombocytopenic Purpura (TTP) (1/200,000 exposed patients), severe thrombocytopenia, agranulocytosis, anaemia and aplastic anaemia/pancytopenia have been reported. Hypersensitivity reactions, including skin reactions (maculopapular or erythematous rash, urticaria, Stevens Johnson Syndrome...) and/or pruritus, have been reported. Very rare cases of bronchospasm, angioedema or anaphylactoid reactions, fever, arthralgia, myalgia and arthritis have been reported.

Cases of renal disorders, abnormal creatinine levels, abnormal liver function test and hepatitis have been very rarely reported. In addtion, very rare cases of taste disorders, confusion, hallucinations, pancreatitis, colitis, vasculitis and hypotension have been observed.