National Institute of Pharmacy

Public Assessment Report

Decentralised/Mutual recognition Procedure

Name of the Product: Egitromb
DC/MRP Number: HU/H/0206/001/DC

Applicant: EGIS Pharmaceuticals PLC

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Modul 1
Information about the initial procedure

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Product name	Egitromb
Type of application:	Generic, Art 10.1 and 10.2 Dir 2001/ 83
level 1	Abridged
level 2	Initial application
level 3	Generic, Art 10.1 and 10.2 Dir 2001/ 83
level 4	Chemical substance
level 5	Prescription only
Active substance	clopidogrel hydrogen sulphate
Pharmaceutical form	film coated tablet
Strength	75 mg
MA holder	EGIS Pharmaceuticals PLC
RMS	Hungary
CMS	BG, CZ, LT, LV, PL, RO, SK
Procedure number	HU/H/0206/001/DC
Timetable	day0 2008.09.04 day70 (PrAR) 2008.11.13 day95 2008.12.08 day100 2008.12.13 day105 2008.12.18 day106 2009.02.06 day120 (DAR) 2009.02.20 day140 2009.03.12 day145 2009.03.17 day150 2009.03.22 day160 2009.04.01 day180 (DAR) 2009.04.21 day195 2009.05.06 day200 2009.05.11 day205 2009.05.16 day210 (FAR) 2009.05.21

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 2
Summary of Product Characteristics

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

1. NAME OF THE MEDICINAL PRODUCT

Egitromb 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate).
Excipients: each film-coated tablet contains 12 mg hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to almost white, round, biconvex film-coated tablets, engraved with “E 181” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

For further information please refer to section 5.1.

4.2 Posology and method of administration

- Adults and elderly
  Clopidogrel should be given as a single daily dose of 75 mg with or without food.
  In patients suffering from acute coronary syndrome:
    - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300-mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1).
    - ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300-mg loading dose in combination with

ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1).

- Paediatric patients
  The safety and efficacy of clopidogrel in children and adolescents have not yet been established.
- Renal impairment
  Therapeutic experience is limited in patients with renal impairment (see section 4.4).
- Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

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 (see section 4.8). 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, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs including Cox-2 inhibitors. 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. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

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.

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section 4.2).

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Glycoprotein IIb/IIIa inhibitors: clopidogrel 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 section 4.4).

Acetylsalicylic acid (ASA): 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 (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

Heparin: in a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

Thrombolytics: the safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

Other concomitant therapy: a number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products 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 coadministration of phenobarbital, cimetidine, or oestrogen.

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

Data from studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of cytochrome P450 2C9. This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, and GP-IIb/IIIa antagonists without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for ASA.

In CURE, the major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo+ASA (<100mg: 2.0%; 100-200mg: 2.3%; >200mg: 4.0%). The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%).

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

In CLARITY, there was an overall increase in bleeding in the clopidogrel+ASA group (17.4%) vs. the placebo+ASA group (12.9%). The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel+ASA and the placebo+ASA groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups (0.6% versus 0.5% in the clopidogrel+ASA and the placebo+ASA groups, respectively).

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare: (<10,000). Within each system organ class-adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labirynth			Vertigo	

System Organ Class	Common	Uncommon	Rare	Very rare
disorders				
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulance	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis) arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged,		

System Organ Class	Common	Uncommon	Rare	Very rare
		neutrophil count decreased, platelet count decreased		

4.9 Overdose

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC04

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GP IIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

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 5 days after treatment was discontinued.

The safety and efficacy of clopidogrel have been evaluated in 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when 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 to 16.4]; 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. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

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 [p=0.258]). 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 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤75 years.

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.

Acute coronary syndrome

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave 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=6,259) or placebo (N=6,303), both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GP IIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel and placebo was not significantly affected by the concomitant heparin therapy.

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 (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

The use of clopidogrel in CURE was associated with a decrease in the need of thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GP IIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1**,**035 (16.5%) in the clopidogrel-treated group and 1**,**187 (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. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

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

the results of the primary analysis**.** In particular, in a post-hoc analysis in 2**,**172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary end-point (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

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

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1**,**752) or placebo (n=1**,**739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day) a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before 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. The patient population included 19.7% women and 29.2% patients ≥ 65 years. 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.

Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favor of clopidogrel (95% CI: 24, 47%; p<0.001), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, n=22,961) or placebo (n=22,891), in combination with ASA (162 mg/day), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics.

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 reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

5.2 Pharmacokinetic properties

After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main 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. 3mg/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 P450 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.

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. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

After repeated doses of 75 mg clopidogrel per day, 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 to levels observed in other studies with healthy subjects. 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. In addition, clinical tolerance was good in all patients.

The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75 mg/day was safe and well tolerated. Clopidogrel C_{max} for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

5.3 Preclinical safety data

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.
At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Silicified microcrystalline cellulose:
- Microcrystalline cellulose
- Colloidal anhydrous silica

Low-substituated hydroxypropylcellulose
Hydrogenated castor oil

Coating:
Opadry Y-1-7000 white:
- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

OPA/Al/PVdC//Al blisters in a carton containing 28, 84, 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

Modul 3
Package leaflets

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Egitromb 75 mg film-coated tablets
clopidogrel (as hydrogen sulphate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT EGITROMB IS AND WHAT IT IS USED FOR

Egitromb belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood, smaller than red or white blood cells, which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Egitromb is taken to prevent blood clots (thrombi) forming in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Egitromb to help prevent blood clots and reduce the risk of these severe events because:
- You have a condition of hardening of arteries (also known as atherosclerosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or
- You have experienced a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. You should also be given acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever as well as to prevent blood clotting) by your doctor.

2. BEFORE YOU TAKE EGITROMB

Do not take Egitromb
- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of Egitromb;

- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain;
- If you suffer from severe liver disease.

If you think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Egitromb.

Take special care with Egitromb

If any of the situations mentioned below apply to you, you should tell your doctor before taking Egitromb:

- if you have a risk of bleeding such as
  - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer)
  - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body)
  - a recent serious injury
  - a recent surgery (including dental)
  - a planned surgery (including dental) in the next seven days
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred within the last seven days
- if you are taking another type of medicine (see 'Taking other medicines')
- if you have kidney or liver disease.

While you are taking Egitromb:

- You should tell your doctor if a surgery (including dental) is planned.
- You should also tell your doctor immediately if you develop a medical condition that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see 'POSSIBLE SIDE EFFECTS').
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see 'POSSIBLE SIDE EFFECTS').
- Your doctor may order blood tests.
- You should tell your doctor or pharmacist if you notice any side effect not listed in the 'POSSIBLE SIDE EFFECTS' section of this leaflet or if you notice that a side effect gets serious.

Egitromb is not intended for use in children or adolescents.

Taking other medicines

Some other medicines may influence the use of Egitromb or vice versa.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The use of oral anticoagulants (medicines used to reduce blood clotting) with Egitromb is not recommended.

You should specifically tell your doctor if you take a non-steroidal anti-inflammatory drug, usually used to treat painful and/or inflammatory conditions of muscle or joints, or if you take heparin or any other medicine used to reduce blood clotting.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed Egitromb in combination with acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever. An occasional use of acetylsalicylic acid (no more than 1,000 mg in any 24 hour period) should generally not cause a problem, but prolonged use in other circumstances should be discussed with your doctor.

Taking Egitromb with food and drink
Food/meals have no influence. Egitromb may be taken with or without food.

Pregnancy and breast-feeding
It is preferable not to use this product during pregnancy and breast-feeding.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Egitromb. If you become pregnant while taking Egitromb, consult your doctor immediately as it is recommended not to take clopidogrel while you are pregnant.

While taking Egitromb, consult your doctor about the breast-feeding of a baby.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Egitromb is unlikely to affect your ability to drive or to use machines.

Important information about some of the ingredients of Egitromb
Egitromb contains hydrogenated castor oil. Hydrogenated castor oil may cause stomach upset or diarrhoea.

3. HOW TO TAKE EGITROMB

Always take Egitromb exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Egitromb (4 tablets of 75 mg) once at the start of treatment. Then, the usual dose is one 75-mg tablet of Egitromb per day to be taken orally with or without food, and at the same time each day.

You should take Egitromb for as long as your doctor continues to prescribe it.

If you take more Egitromb than you should
Contact your doctor or the nearest emergency department because of the increased risk of bleeding.

If you forget to take Egitromb
If you forget to take a dose of Egitromb, but remember within 12 hours of your usual time, take your tablet straightaway and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for the forgotten individual doses.

If you stop taking Egitromb
Do not stop the treatment. Contact your doctor or pharmacist before stopping.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Egitromb can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots and/or confusion (see 'Take special care with Egitromb').
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

The most common side effect (affects 1 to 10 patients in 100) **reported with Egitromb is bleeding.** Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine**.** In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

If you experience prolonged bleeding when taking Egitromb
If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see 'Take special care with Egitromb').

Other side effects reported with Egitromb are:

Common side effects (affects 1 to 10 patients in 100): Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (affects 1 to 10 patients in 1,000): Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, abnormal touch sensation.

Rare side effect (affects 1 to 10 patients in 10,000): Vertigo.

Very rare side effects (affects less than 1 patient in 10,000): Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions; swelling in the mouth; blisters of the skin; skin allergy; inflammation of the mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; taste disorders.

In addition, your doctor may identify changes in your blood or urine test results.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE EGITROMB

Keep out of the reach and sight of children.

Do not use Egitromb after the expiry date which is stated on the carton and on the blister. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.
Do not use Egitromb if you notice any visible sign of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Egitromb contains

The active substance is clopidogrel. Each tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

The other ingredients are silicified microcrystalline cellulose (microcrystalline cellulose, colloidal anhydrous silica), low-substituated hydroxypropylcellulose, hydrogenated castor oil in the tablet core, and Opadry Y-1-7000 white (hypromellose (E464), titanium dioxide (E171), macrogol 400) in the tablet coating.

What Egitromb looks like and contents of the pack

Egitromb 75 mg film-coated tablets are white to almost white, round, biconvex film-coated tablets engraved with “E 181” on one side.
They are supplied in cartons containing 28, 84 or 100 tablets in OPA/Al/PVdC//Al blisters.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

To be completed nationally.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

This medicinal product is authorised in the Member States of the EEA under the following names:

Hungary	Egitromb 75 mg film-coated tablets
Bulgaria	Egitromb 75 mg film-coated tablets
Czech Republic	Egitromb 75 mg film-coated tablets
Latvia	Egitromb 75 mg film-coated tablets
Lithuania	Egitromb 75 mg film-coated tablets
Poland	Egitromb 75 mg film-coated tablets
Romania	Egitromb 75 mg film-coated tablets
Slovakia	Egitromb 75 mg film-coated tablets

This leaflet was approved in

Modul 4
Labelling

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Egitromb 75 mg film-coated tablets
clopidogrel (as hydrogen sulphate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate)

3. LIST OF EXCIPIENTS

Contains hydrogenated castor oil. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
[84 film-coated tablets]
[100 film-coated tablets]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp.:

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

EGIS Pharmaceuticals PLC
H-1106 Budapest, Keresztúri út 30-38.
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

Reg. No.:

13. BATCH NUMBER

Batch No.:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

To be completed nationally**.**

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Egitromb 75 mg film-coated tablets
clopidogrel (as hydrogen sulphate)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

EGIS

3. EXPIRY DATE

Exp.:

4. BATCH NUMBER

Batch No.:

5. OTHER

Modul 5
Scientific discussion during the initial procedure

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This decentralised application concerns a generic version of clopidogrel hydrogen sulphate, under trade names Clopidogrel-EGIS, Egitromb, Clopidogrel Jenson. In this Assessment Report, the name Egitromb is used.

The originator's product Plavix® 75 mg film-coated tablets by Sanofi Pharma Bristol-Myers Squibb SNC were centrally registered on 15-07-1998 (EU/1/98/069).

With Hungary as the Reference Member State in this Decentralized Procedure, EGIS Pharmaceuticals PLC is applying for the Marketing Authorisations for Egitromb *(HU/H/206/01/DC)*; Clopidogrel EGIS *(HU/H/207/01/DC)* and Clopidogrel Jenson *(HU/H/208/01/DC).*

Clopidogrel, the active ingredient of Clopidogrel 75 mg film-coated tablets, is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex.

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04.

Therapeutic indications

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

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

Posology and method of administration

Adults and elderly

Clopidogrel should be given as a single daily dose of 75 mg with or without food.

In patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.
- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a loading dose in combination with ASA and with or without thrombolytics. For patients greater than 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting

- Paediatric patients

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

- Renal impairment
  Therapeutic experience is limited in patients with renal impairment (see section 4.4).

- Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the medicinal product.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

Special warnings and precautions for use

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients.

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

This is an application according to Article 10 (1) and 10(2) of Directive 2001/83/EC (generic application).

The dossier was submitted in CTD format.

The overviews concerning non-clinical and clinical aspects are well written and of high quality.

The CRO that performed the bioequivalence study explicitly states to be in compliance with GCP/GLP regulations.
GMP compliance of the manufacturer of the API and the product is demonstrated by the applicant.

II. QUALITY ASPECTS

II.1 Introduction

Clopidogrel film-coated tablets containing 97.86 mg clopidogrel hydrogensulphate (equivalent to 75 mg clopidogrel base) as active substance have been developed for the prevention of atherothrombotic events (myocardial infarction, ischaemic stroke, acute coronary syndrome: Non-ST segment elevation acute coronary syndrome or ST segment elevation acute myocardial infarction, in combination with ASA).
Product with the same active substance has been first marketed in 1998 via Centralised Procedure. Thus, generic medicinal products are claimed to be "essentially similar" to the reference medicinal products Plavix 75 mg film-coated tablet (Sanofi Pharma Bristol-Myers Squibb SNC).
The film-coated tablets will be marketed in a dosage strengths of 75 milligrams (expressed to clopidogrel base) and packaged in OPA/Al/PVC//Al blisters and box.

II.2 Drug Substance

Data on the quality and manufacture of the active substance was provided in the applicant's dossier via European DMF procedure. A letter of access to the DMF was submitted.

INN name: Clopidogrel hydrogensulphate
Chemical name: Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S)-, sulphate (1:1)
The active substance is a white to cream coloured powder and freely soluble in methanol. It shows polymorphism.
The molecule has a chiral center and exhibits isomerism (R and S isomer). The manufacturer consistently produces the S-isomer, and the R-isomer is controlled in the drug substance as an impurity.
The proposed manufacturing process has been adequately described, critical steps and accompanying in-process controls have been defined to ensure quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.
Evidence of the structure has been confirmed by thermal analysis, UV-, FT-IR, NMR and mass spectroscopy, X-ray powder diffraction, optical rotation and by elemental analysis.
Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in relation to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.
The substance complies with the requirements of the EMEA guideline on genotoxic impurities.
The substance is not official in the Ph.Eur. Therefore, an in-house specification has been set for clopidogrel bisulphate, which includes tests for appearance, specific optical rotation, identification (IR, XRD), assay (titration and HPLC), purity, including enantiomeric purity (HPLC), residual solvents (GC), loss on drying, heavy metals and sulphated ash.
The specification is in accordance with the Ph.Eur. general monograph on Substances for pharmaceutical use and the ICH Q6A guideline.
The specifications reflect all relevant quality attributes of the active substance and were found to be suitable for the control of the quality of the drug substance. The limits set are properly justified.
Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are well characterised.
Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.
During the stability studies no significant changes in any parameters were observed. The proposed retest period of 36 months is supported by the supplemented stability data of 24 months with the storage condition: "Store at 5 °C in the original packaging".
GMP compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the pharmaceutical development was to develop a manufacturing process for a generic oral dosage form containing 75 mg clopidogrel as active ingredient that meets the general requirements of the Ph. Eur. regarding tablets and that has a similar in-vitro dissolution profile to the reference medicinal product (Plavix film-coated tablet, Sanofi Pharma Bristol Myers Squibb SNC).
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided. The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.
The excipients used in the finished product are microcrystalline cellulose, colloidal anhydrous silica, low-substituted hydroxy-propyl cellulose, hydrogenated castor oil. The white film-coating contains hypromellose, titanium dioxide and macrogol 400. All excipients used comply with their respective European Pharmacopoeia monograph, with exception of low-substituted hydroxy-propyl cellulose, which comply with a satisfactory in-house monograph. Compliance of the product with the general monograph of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.
The film-coated tablet is white or almost white and slightly biconvex. There is a stylized E 181 engraving on one side of the film-coated tablet, the other side has no mark.
The tablets are packaged in cold blister (OPA/Al/PVC foil fastened with Aluminium foil) and in a paper box.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.
A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated
The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the European pharmacopoeia and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented. Certificates of analysis were also provided for the working standard used.
The container closure system of the product is as follows: OPA/Al/PVC//Al blisters.
The PVC layer of the blister foil that is in direct contact with the finished medicinal product complies with the requirements of the relevant Ph. Eur. chapters and also with Directive 2002/72/EEC regarding the food contact safety and with Directive 78/142/EEC Annex 1 regarding the VC-monomer content.
The heat seal laquer of the aluminium foil that is also in direct contact with the film-coated tablets is stated to satisfy section 31 paragraph 1 of the German Foodstuffs and Consumer Article Regulations and also the requirements of 21 CFR section 175.300 of the US FDA regulations and the Council of Europe Resolution AP (96)5, Strasbourg 1996.
Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions is approved.
The pharmaceutical data in the SPC, PIL and label are acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of clopidogrel are well known. As clopidogrel is a widely used, well-known active substance, further studies are not required.

Overview based on literature review (referring to 32 publications up to year 2006) is appropriate. The non-clinical overview has been written by a certified toxicologist. The Expert Report is dated as July 2008.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) submitted by the applicant is found acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Clinical and Biopharmaceutical Overview has been written by a medical doctor expert. The clinical report refers to 25 publications up to year 2008. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

Absorption
After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/L) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Biotransformation
Clopidogrel is extensively metabolised by the liver and the main 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 P450 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.
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.

Elimination
Following an oral dose of 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

Reduced renal function
After repeated doses of 75 mg clopidogrel per day, 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 to levels observed in other studies with healthy subjects. 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 clopidogrel per day. In addition, clinical tolerance was good in all patients

Reduced hepatic function
The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75 mg/day was safe and well tolerated. Clopidogrel Cmax for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

Bioequivalence - Clinical study reports

To support the application, the applicant has submitted two bioequivalence studies with study codes MC-0090 and MC-0101.

Results of study MC-0090 were not suitable for evaluation due to analytical problems.

The objective of MC-0101 was to determine the relative bioavailability of one 75 mg clopidogrel hydrogen sulphate film-coated tablet (EGIS Pharmaceuticals PLC, Hungary) versus one 75 mg Plavix® film-coated tablet in 54 healthy non-smoking Caucasian male volunteers under fasting conditions.

Study design
MC-0101 was a single-centre, open-label, randomised, two-treatment, two-period, two-sequence crossover bioequivalence study performed under fasting conditions. The treatment phases were separated by a washout period of 7 days. Fifty-four healthy, adult, male Caucasian non-smokers aged between 18 and 55 years have been enrolled in the study. There was 4 dropouts and 2 withdrawals in the study (Subject 54 was withdrawn for adverse events after drug administration in Period 1; Subject 46 was withdrawn due to influenza vaccination prior to drug administration in Period 2; Subjects 22 and 51 elected to withdraw from the study due to personal reasons prior to drug administration in Period 2; Subjects 31 and 44 did not show up for Period 2 confinement). 48 subjects completed both periods. Pharmacokinetic and statistical evaluation was performed in these 48 subjects while safety data were evaluated for all 54 subjects who received at least one treatment. After a supervised overnight fast of at least 10 hrs, blood samples were collected prior to study drug administration and 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 1.17, 1.33, 1.67, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 12.0, 16.0, and 24.0 hours post-dose in each period.

Test formulation:
Clopidogrel EGIS 75 mg film-coated tablets
Manufacturer: EGIS Pharmaceuticals PLC, Hungary
Active ingredient: clopidogrel hydrogen sulphate
Batch No.: 01017 0905
Date of manufacturing: September, 2005 Batch size: 100 000 tablets/batch

Reference formulation:
Plavix 75 mg film-coated tablets
Manufacturer: Sanofi Whintrop Industrie, France
Active ingredient: clopidogrel hydrogen sulphate
Batch No.: 1421
Expiry date: November, 2007
Purchased from: Hungary

Results:

Pharmacokinetics:

SUMMARY OF RESULTS
CLOPIDOGREL
N = 48

Pharmacokinetic Parameters

Parameters		Test (Clopidogrel Hydrogen Sulphate (A)) Mean	SD	CV (%)	Reference (Plavix (B)) Mean	SD	CV (%)
AUC_{0-t}	(pg·h/mL)	1826.64	2060.84	112.82	2066.72	2420.63	117.12
AUC_{0-inf}*	(pg·h/mL)	1822.21	2058.93	112.99	2122.40	2486.03	117.13
C_{max}	(pg/mL)	1140.35	1588.10	139.26	1231.24	1750.29	142.16
Residual area*	(%)	4.56	3.16	69.23	5.48	4.60	84.05
T_{max}	(h)	0.950	0.472	49.73	0.870	0.324	37.24
T_{max}**	(h)	0.833	0.503	-	0.833	0.333	-
K_{el}*	(h^{-1})	0.2050	0.1630	79.50	0.1862	0.1556	83.55
$T_{½ el}$*	(h)	4.51	2.19	48.60	5.24	2.86	54.55

* For these parameters, N = 46.
** Medians and interquartile ranges are presented.

Clopidogrel Hydrogen Sulphate (A) vs Plavix (B)

	AUC_{0-t}	AUC_{0-inf}*	C_{max}
Ratio[1]	96.39%	94.58%	101.89%
90 % Geometric C.I.[2]	87.85 % to 105.75 %	85.99 % to 104.04 %	92.44 % to 112.31 %
Intra-Subject CV	27.53 %	27.71 %	28.96 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Clopidogrel Hydrogen Sulphate (A) - Plavix (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data
* For this parameter, N = 46.

Conclusion:
Based on the submitted bioequivalence study Clopidogrel-EGIS mg film-coated tablet is considered bioequivalent with Plavix 75 mg film-coated tablets.

IV.3 Pharmacodynamics

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

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 5 days after treatment was discontinued.

IV.4 Discussion on the clinical aspects

The application contains an adequate review of published clinical data. They are summerized in sections IV.5 and IV.6.

Pharmacovigilance system

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance (QPPV) and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Since the reference product (Plavix) has been on the market since 1998, and its safety profile is well established, the applicant proposes to use the routine pharmacovigilance activities as described in Volume 9A. There is no information on any safety concern requiring additional risk minimisation activities with the reference medicinal product.

Periodic Safety Update Report (PSUR)

According to the well established safety profile of the reference product a three yearly submission schedule is considered appropriate. The PSURs will be prepared based on the EU Birth Date of clopidogrel (15th July 1998).

IV.5 Clinical efficacy

Platelets are vital components of normal haemostasis and key participants in pathologic thrombosis.
Inhibition of platelet aggregation with acetyl salicylic acid (ASA), besides being more practical and safer than anticoagulation, has been shown to be effective.
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. Although infrequently, ticlopidine causes neutropenia and thrombocytopenia, which can be serious and usually appear in the first three months of long-term therapy.
Clopidogrel is a 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.

Clopidogrel is indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction (MI) (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease (PAD); in combination with ASA in patients suffering from either non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, or in ST-segment elevation acute myocardial infarction (STEMI), in medically treated patients eligible for thrombolytic therapy. The efficacy of clopidogrel in the above-mentioned indications is well known.

<u>CAPRIE study</u>
The approval for the prevention of atherothrombotic events in patients with clinical evidence of atherosclerosis was based on the results of the CAPRIE trial. The CAPRIE trial showed that

clopidogrel at a dose of 75 mg 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 (i.e. myocardial infarction, ischaemic stroke and vascular death) in patients with established atherothrombosis (MI, ischaemic stroke, PAD). Overall clopidogrel was well tolerated, having an adverse event profile comparable to ASA, but with better gastrointestinal tolerability. Rash, purpura (bruising) and diarrhoea were notable in the clopidogrel group but were rarely severe. There were no evidence on the basis of the results of CAPRIE that clopidogrel shares the risk, have seen with ticlopidine, of neutropenia or thrombocytopenia.

CURE study

The non-ST segment elevation acute coronary syndrome (NSTE-ACS, i.e. unstable angina /UA/ or non-Q-wave myocardial infarction) indication was based on the results of the CURE trial. Regarding efficacy, the results showed a clinically and statistically significant reduction in the first and secondary co-primary endpoint at the end of scheduled 12-months of treatment. This was 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, were in agreement with the overall protective effect. The only notable exception was the slight non-significant increase in rehospitalisation for unstable angina. 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. 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, was 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 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 surgery in patients who stopped therapy more than 5 days prior to surgery, but in patients who remained on therapy within 5 days of CABG, the bleeding event rate was significantly higher with clopidogrel. The section 4.8 of the SmPC reflects these safety results.
This study demonstrated a significant reduction of atherothrombotic events in patients with non-ST segment elevation acute coronary syndrome treated with dual antiplatelet (clopidogrel+ASA) therapy 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. The section 4.2 of the SmPC reflects the facts that the optimal treatment duration 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.

Stent-CURE (post-hoc analysis of the CURE trial)

A post-hoc analysis of the CURE trial in the subset of patients who underwent an intra-coronary stent placement following percutaneous coronary intervention (PCI) has supported a rewording of the NST-ACS indication, i.e. the insertion of a sentence pointing out that patients with stent after PCI are included in the target population. Acknowledging the widely generalised use of clopidogrel and the recommendation of treatment guidelines to use clopidogrel in NSTEMI patients with PCI and subsequent stenting, the addition of this sentence was considered to be a clarification of the existing indication rather than a new indication. Importantly, the Stent-CURE outcomes showed a similar positive benefit/risk ratio for the subset of NSTE-ACS patients undergoing stent placement after PCI as for the overall NSTE-ACS population investigated in the CURE trial. It is well known, that clopidogrel is routinely used in patients receiving a stent after PCI. The same recommendations on treatment duration as for the overall NSTE-ACS population apply to PCI patients.

COMMIT and CLARITY trials

The extension of acute coronary syndrome indication (ST elevation myocardial infarction, STEMI) based on two placebo-controlled, randomised, controlled trials. The difference in the designs and outcomes between the two trials makes them, to a certain extent, complementary. The results for all major endpoints and subgroup analyses are either favourable to clopidogrel or show a favourable

trend, ruling out any heterogeneity, which is reassuring. The differences in background clinical care and the high mortality rate, leading to concerns regarding the relevance of the Chinese population studied in COMMIT to European STEMI population, therefore CLARITY trial was regarded as the more relevant trial, despite the fact that the results in the primary endpoint were mainly related to a reduction in a surrogate endpoint (infarct related artery, IRA). This was counterbalanced by the positive findings on hard endpoints reported in the huge COMMIT trial. Therefore, the approved indication reflects the population treated in CLARITY. The well-established safety profile of clopidogrel is not challenged by the data provided in these two new trials. In CLARITY, the incidences of major bleeding were similar in both treatment groups and consistent across patients subgroups defined by patient characteristics or concomitant therapy. The incidences of fatal bleeding and intracranial haemorrhage were low and similar in both groups. The significant overall increase in bleeding in the clopidogrel group is reflected in section 4.8 of the SmPC. In the COMMIT trial, the overall rate of non-cerebral major bleeding or cerebral bleeding was low and similar in both groups. No untoward safety findings were reported.

IV.6 Clinical safety

The safety of clopidogrel has been already assessed during the initial NSTE-ACS indication evaluation.
The results in Stent-CURE do not differ from those observed in the overall CURE population, which was previously assessed in the context of the NSTE-ACS indication. Despite the methodical weakness of post-hoc subgroup analysis, the CHMP was of the opinion that the safety data of Stent-CURE are reliable, since they match the overall CURE outcomes such as in case of the efficacy results. Since the Stent-CURE population, i.e. patients undergoing a stent placement represent a group of high-risk patients, the possibility of a specific safety monitoring programme was discussed by the CHMP. Taking into account the extensive clinical and post-marketing experience in the treatment of NSTEMI with clopidogrel and the well-known safety profile of clopidogrel, it was deemed unnecessary.

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies were collected and analyzed.
Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.
Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment. ***(Plavix SmPC;4.8)***

Discussion on the clinical aspects

For generics: brief explanation that abridged applications avoid the need for repetitive tests on animals and humans. Reference to the reference medicinal product. For these applications the bioequivalence studies are pivotal and should be described.

The application contains an adequate review of published clinical data.
Based on the submitted bioequivalence study Clopidogrel-EGIS mg film-coated tablet is considered bioequivalent with Plavix 75 mg film-coated tablets.

Pharmacovigilance system

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance (QPPV) and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Since the reference product (Plavix) has been on the market since 1998, and its safety profile is well established, the applicant proposes to use the routine pharmacovigilance activities as described in Volume 9A. There is no information on any safety concern requiring additional risk minimisation activities with the reference medicinal product.

Periodic Safety Update Report (PSUR)

According to the well established safety profile of the reference product a three yearly submission schedule is considered appropriate. The PSURs will be prepared based on the EU Birth Date of clopidogrel (15th July 1998).

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate review of published clinical data and the bioequivalence with reference medicinal product has been shown.

Treatments were well tolerated in the two bioequivalence studies. No major side effects and no relevant differences in safety profiles were observed between the preparations.

Quality data demonstrate the consistent quality, batch to batch and throughout the period of validity.

Approval is recommended from both the clinical and quality point of view, without specific obligations and follow-up measures.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Module 6: Steps taken after the initial procedure with an influence on the Public Assessment Repor (Type II variations, PSURs, commitments) Scope	Procedure number	Type of modification [1]	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
Y/N (version)						