ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Iscover 75 mg film-coated tablets
Iscover 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Each film-coated tablet contains 3 mg of lactose and 3.3 mg of hydrogenated castor oil.

Iscover 300 mg film-coated tablets
Each film-coated tablet contains 300 mg of clopidogrel (as hydrogen sulphate).

Excipients with known effect:
Each film-coated tablet contains 12 mg of lactose and 13.2 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Iscover 75 mg film-coated tablets
Pink, round, biconvex, engraved with «75» on one side and «1171» on the other side.

Iscover 300 mg film-coated tablets
Pink, oblong, engraved with «300» on one side and «1332» on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary prevention of atherothrombotic events
Clopidogrel is indicated in:

- Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

- Adult 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 patients undergoing percutaneous coronary intervention (including patients undergoing a stent placement) or medically treated patients eligible for thrombolytic/fibrinolytic therapy.

In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)
Clopidogrel in combination with ASA is indicated in:

- Adult patients with moderate to high-risk TIA (ABCD2[1] score ≥4) or minor IS (NIHSS[2] ≤3) within 24 hours of either the TIA or IS event.

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

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology
- Adults and elderly

Iscover 75 mg film-coated tablets
Clopidogrel should be given as a single daily dose of 75 mg.

Iscover 300 mg film-coated tablets
This 300 mg tablet of clopidogrel is intended for use as a loading dose.

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 or 600 mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended (see section 4.4). Clopidogrel treatment should be 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:
  - For medically treated patients eligible for thrombolytic/fibrinolytic therapy, 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 medically treated 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).
  - When percutaneous coronary intervention (PCI) is intended:
    - Clopidogrel should be initiated at a loading dose of 600 mg in patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy. In patients ≥ 75 years old the 600 mg LD should be administered with caution (see section 4.4).
    - Clopidogrel 300 mg loading dose should be given in patients undergoing PCI within 24 hours of receiving fibrinolytic therapy.

[1] Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnoses
[2] National Institutes of Health Stroke Scale

Clopidogrel treatment should be continued at 75 mg once a day with ASA 75 mg – 100 mg daily. Combined therapy should be started as early as possible after symptoms start and continued up to 12 months (see section 5.1).

Adult patients with moderate to high-risk TIA or minor IS:
Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg-100 mg once daily). Treatment with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy.

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

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
- For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

Special populations

- Elderly patients

  Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):
  - A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended (see section 4.4).

  ST segment elevation acute myocardial infarction:
  - For medically treated patients eligible for thrombolytic/fibrinolytic therapy: in patients over 75 years of age clopidogrel should be initiated without a loading dose.

  For patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy:
  - In patients ≥ 75 years old the 600 mg LD should be administered with caution (see section 4.4).

- Paediatric population
  Clopidogrel should not be used in children because of efficacy concerns (see section 5.1).

- 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).

Method of administration
For oral use
It may be given with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 2 or section 6.1.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.4 Special warnings and precautions for use

Bleeding and haematological disorders
Due to the risk of bleeding and haematological adverse reactions, 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 (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), CYP2C19 strong inducers or other medicinal products associated with bleeding risk such as pentoxifylline (see section 4.5). Due to the increased risk of haemorrhage, triple antiplatelet therapy (clopidogrel + ASA + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or TIA (see section 4.5 and section 4.8). 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.

The use of clopidogrel 600 mg loading dose is not recommended in patients with non-ST segment elevation acute coronary syndrome and ≥75 years of age due to increased bleeding risk in this population.

Due to the limited clinical data in patients ≥75 years old with STEMI PCI, and increased risk of bleeding, the use of clopidogrel 600 mg loading dose should be considered only after an individual assessment of the bleeding risk of the patient by the physician.

Thrombotic Thrombocytopenic Purpura (TTP)
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.

Acquired haemophilia
Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Recent ischemic stroke

- *Initiation of therapy*
    - In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset.
    - There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial hemorrhage.
    - In non-minor IS patients, clopidogrel monotherapy should be started only after the first 7 days of the event.
- *Non-minor IS patients (NIHSS >4)*
  In view of the lack of data, use of dual antiplatelet therapy is not recommended (see section 4.1).
- *Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned*
  There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

Use of medicinal products that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.5).

CYP2C8 substrates
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

Cross-reactions among thienopyridines
Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment
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).

Hepatic impairment
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).

Excipients
Iscover contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution (see section 4.4).

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). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who 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)

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).

SSRIs: since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy:

Inducers of CYP2C19
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active

metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.4).

Inhibitors of CYP2C19
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see sections 4.4 and 5.2).

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton Pump Inhibitors (PPI):
Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4).

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.
The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

Boosted anti-retroviral therapy (ART): HIV patients treated with boosted anti-retroviral therapies (ART) are at high-risk of vascular events.

A significantly reduced platelet inhibition has been shown in HIV patients treated with ritonavir-or cobicistat-boosted ART. Although the clinical relevance of these findings is uncertain, there have been spontaneous reports of HIV-infected patients treated with ritonavir boosted ART, who have experienced re-occlusive events after de-obstruction or have suffered thrombotic events under a clopidogrel loading treatment schedule. Average platelet inhibition can be decreased with concomitant use of clopidogrel and ritonavir. Therefore, concomitant use of clopidogrel with ART boosted therapies should be discouraged.

Other medicinal products: 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 co-administration of phenobarbital 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 the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

CYP2C8 substrate medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution (see section 4.4).

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 GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Rosuvastatin: Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (C_{max}) after administration of a 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on C_{max} after repeated administration of a 75 mg clopidogrel dose.

4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding
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 Iscover.

Fertility
Clopidogrel was not shown to alter fertility in animal studies.

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

Summary of the safety profile

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

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 similar for clopidogrel and ASA.

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

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups. 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.

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

In TARDIS, patients with recent ischemic stroke receiving intensive antiplatelet therapy with three medicinal products (ASA + clopidogrel + dipyridamole) had more bleeding and bleeding of greater severity when compared with either clopidogrel alone or combined ASA and dipyridamole (adjusted common OR 2.54, 95% CI 2.05-3.16, $p<0.0001$).

Tabulated list of adverse reactions

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 (<1/10,000), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
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, acquired haemophilia A, granulocytopenia, anaemia
Cardiac disorders				Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
Immune system disorders				Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*, insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)*
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances, ageusia
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious hemorrhage, hemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary hemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	Gastrointestinal hemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal hemorrhage	Gastrointestinal and retroperitoneal hemorrhage 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, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Reproductive systems and breast disorders			Gynaecomastia	

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
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, neutrophil count decreased, platelet count decreased		

* Information related to clopidogrel with frequency "not known".

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: B01AC-04.

Mechanism of action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The safety and efficacy of clopidogrel have been evaluated in 7 double-blind studies involving over 100,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT, CHANCE, POINT and ACTIVE-A 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 ischemic 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 ischemic events (combined end point of myocardial infarction, ischemic 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 ischemic 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, ischemic 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 ischemia. Patients were required to have either ECG changes compatible with new ischemia 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 GPIIb/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 hemorrhage 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 GPIIb/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 ischemia) 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 endpoint (CV death, MI, stroke or refractory ischemia). 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, GPIIb/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).

ST-segment Elevation Myocardial Infarction

In patients with acute ST-segment elevation MI (STEMI), safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY, a prospective subgroup analysis of CLARITY (CLARITY PCI) 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.

CLARITY PCI sub-group analysis involved 1,863 STEMI patients undergoing PCI. Patients receiving 300 mg loading dose (LD) of clopidogrel (n=933) had a significant reduction in incidence of cardiovascular death, MI or stroke following PCI compared to those receiving placebo (n=930) (3.6% with clopidogrel pre-treatment versus 6.2% with placebo, OR: 0.54; 95% CI: 0.35-0.85; p=0.008). The patients receiving 300 mg LD of clopidogrel had a significant reduction in incidence of cardiovascular death, MI or stroke through 30 days following PCI compared to those receiving placebo (7.5% with clopidogrel pre-treatment versus 12.0% with placebo, OR: 0.59; 95% CI: 0.43-0.81; p=0.001). However, this composite endpoint when assessed in the overall population of the CLARITY study was not statistically significant as a secondary endpoint. No significant difference was observed in the rates of major or minor bleeding between both the treatments (2.0% with clopidogrel pre-treatment versus 1.9% with placebo, p>0.99). The findings of this analysis support the early use of clopidogrel loading dose in STEMI and the strategy of routine clopidogrel pretreatment in patients undergoing PCI.

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.

<u>Clopidogrel 600 mg Loading Dose in Acute Coronary Syndrome Patients Undergoing PCI</u>

CURRENT-OASIS-7 (*Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies in Ischemic Syndromes*)
This randomized factorial trial included 25,086 individuals with acute coronary syndrome (ACS) intended for early PCI. Patients were randomly assigned to either double-dose (600 mg on Day 1, then 150 mg on Days 2–7, then 75 mg daily) versus standard-dose (300 mg on day 1 then 75 mg daily) clopidogrel, and high-dose (300–325 mg daily) versus low-dose (75–100 mg daily) ASA. The 24,835 enrolled ACS patients underwent coronary angiography and 17,263 received PCI. Among the 17,263 patients receiving PCI treatment, when compared with the standard dose, double-dose clopidogrel reduced the rate of the primary endpoint (3.9% vs 4.5% adjusted HR= 0.86, 95% CI 0.74-0.99, p=0.039) and significantly reduced stent thrombosis (1.6% vs 2.3%, HR: 0.68; 95% CI: 0.55 0.85; p=0.001). Major bleeding was more common with double-dose than with standard-dose clopidogrel (1.6% vs 1.1%, HR=1.41, 95% CI 1.09-1.83, p=0.009). In this trial, clopidogrel 600 mg loading dose has shown consistent efficacy in patients age ≥75 years of age and patients <75 years of age.

ARMYDA-6 MI (*The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty - Myocardial Infarction*)
This randomized, prospective, international, multicenter trial evaluated pre-treatment with a 600 mg versus 300 mg clopidogrel LD in the setting of urgent PCI for STEMI. Patients received a clopidogrel 600 mg LD (n=103) or clopidogrel 300 mg LD (n=98) prior to PCI, then were prescribed 75 mg/day from the day after PCI up to 1 year. Patients receiving a 600 mg LD of clopidogrel had a significantly reduced infarct size compared to those receiving a 300 mg LD. There was less frequent thrombolysis in MI flow Grade <3 after PCI in 600 mg LD (5.8% versus 16.3%, p=0.031), improved LVEF at discharge (52.1 ±9.5% versus 48.8 ±11.3%, p=0.026), and 30-day major adverse cardiovascular events were fewer (5.8% versus 15%, p=0.049). No increase in bleeding or entry-site complications were observed (secondary endpoints at Day 30).

HORIZONS-AMI (*Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction*)
This post-hoc analysis trial was conducted to evaluate whether a 600 mg clopidogrel LD provides faster and greater inhibition of platelet activation. The analysis examined the impact of a LD of 600 mg compared with 300 mg on 30-day clinical outcomes in 3,311 patients from the main trial (n=1,153; 300 mg LD group; n=2,158; 600 mg LD group) before cardiac catheterization followed by 75 mg/day dose for ≥6 months post-discharge. The results showed significantly lower 30-day unadjusted rates of mortality (1.9% versus 3.1%, p=0.03), reinfarction (1.3% versus 2.3%, p=0.02), and definite or probable stent thrombosis (1.7% versus 2.8%, p=0.04) with the 600 mg LD without higher bleeding rates. By multivariable analysis, a 600 mg LD was an independent predictor of lower rates of 30-day major adverse cardiac events (HR: 0.72 [95% CI: 0.53–0.98], p=0.04). Major bleeding rate (non-CABG related) was 6.1% in 600 mg LD group and 9.4% in 300 mg LD group (p=0.0005). Minor bleeding rate was 11.3% in 600 mg LD group and 13.8% in 300 mg LD group (p=0.03).

Long Term (12 Months) Treatment with Clopidogrel in STEMI Patients after PCI

CREDO (*Clopidogrel for the Reduction of Adverse Events During Observation*)
This randomized, double-blind, placebo-controlled trial was conducted in the United States and Canada to evaluate the benefit of long-term (12 month) treatment with clopidogrel after PCI. There were 2,116 patients randomized to receive a 300 mg clopidogrel LD (n=1,053) or placebo (n=1,063) 3 to 24 hours before PCI. All patients also received 325 mg of aspirin. Thereafter, all patients received clopidogrel 75 mg/day through Day 28 in both groups. From Day 29 through 12 months, patients in clopidogrel group received 75 mg/day clopidogrel and in control group received placebo. Both groups received ASA throughout the study (81 to 325 mg/day). At 1-year, significant reduction in the combined risk of death, MI or stroke was observed with clopidogrel (26.9% relative reduction, 95% CI: 3.9%-44.4%; p=0.02; absolute reduction 3%) compared to placebo. No significant increase in the rate of major bleeding (8.8% with clopidogrel versus 6.7% with placebo, p=0.07) or minor bleeding (5.3% with clopidogrel versus 5.6% with placebo, p=0.84) at 1-year was observed. The major finding of this study is that continuation of clopidogrel and ASA for at least 1-year leads to a statistically and clinically significant reduction in major thrombotic events.

EXCELLENT (*Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting*)
This prospective, open-label, randomized trial was conducted in Korea to evaluate whether 6-month dual antiplatelet therapy (DAPT) would be noninferior to 12-month DAPT after implantation of drug-eluting stents. The study included 1,443 patients undergoing implantation who were randomized to receive 6-month DAPT (ASA 100–200 mg/day plus clopidogrel 75 mg/day for 6 months and thereafter ASA alone up to 12 months) or 12-month DAPT (ASA 100–200 mg/day plus clopidogrel 75 mg/day for 12 months). No significant difference was observed in the incidence of target vessel failure (composite of cardiac death, MI or target vessel revascularization) which was primary end point between 6-month and 12-month DAPT groups (HR: 1.14; 95% CI: 0.70 1.86; p=0.60). Also, the study showed no significant difference in the safety end point (composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between 6-month and 12-month DAPT groups (HR: 1.15; 95% CI: 0.64-2.06; p=0.64). The major finding of this study was that 6-month DAPT was non-inferior to 12-month DAPT in the risk of target vessel failure.

De-escalation of $P2Y_{12}$ Inhibitor Agents in Acute Coronary Syndrome
Switching from a more potent $P2Y_{12}$ receptor inhibitor to clopidogrel in association with aspirin after acute phase in Acute Coronary Syndrome (ACS) has been evaluated in two randomized investigator-sponsored studies (ISS) – TOPIC and TROPICAL-ACS – with clinical outcome data.

The clinical benefit provided by the more potent $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, in their pivotal studies is related to a significant reduction in recurrent ischemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischemic benefit was consistent throughout the first year, greater reduction in ischemic recurrence after ACS was observed during the initial days following the treatment initiation. In contrast, *post-hoc* analyses demonstrated statistically significant increases in the bleeding risk with the more potent $P2Y_{12}$ inhibitors, occurring predominantly during the maintenance phase, after the first month

post-ACS. TOPIC and TROPICAL-ACS were designed to study how to mitigate the bleeding events while maintaining efficacy.

TOPIC (*Timing Of Platelet Inhibition after acute Coronary syndrome*)
This randomized, open-label trial included ACS patients requiring percutaneous coronary intervention (PCI). Patients on aspirin and a more potent $P2Y_{12}$ blocker and without adverse event at one month were assigned to switch to fixed-dose aspirin plus clopidogrel (de-escalated dual antiplatelet therapy (DAPT)) or continuation of their drug regimen (unchanged DAPT).

Overall, 645 of 646 patients with ST-elevation-MI (STEMI) or non-ST-elevation-MI (NSTEMI) or unstable angina were analyzed (de-escalated DAPT (n=322); unchanged DAPT (n=323)). Follow-up at one year was performed for 316 patients (98.1%) in the de-escalated DAPT group and 318 patients (98.5%) in the unchanged DAPT group. The median follow-up for both groups was 359 days. The characteristics of the studied cohort were similar in the 2 groups.

The primary outcome, a composite of cardiovascular death, stroke, urgent revascularization, and BARC (Bleeding Academic Research Consortium) bleeding ≥2 at 1 year post ACS, occurred in 43 patients (13.4%) in the de-escalated DAPT group and in 85 patients (26.3%) in the unchanged DAPT group ($p<0.01$). This statistically significant difference was mainly driven by fewer bleeding events, with no difference reported in ischemic endpoints ($p=0.36$), while BARC ≥2 bleeding occurred less frequently in the de-escalated DAPT group (4.0%) versus 14.9% in the unchanged DAPT group ($p<0.01$). Bleeding events defined as all BARC occurred in 30 patients (9.3%) in the de-escalated DAPT group and in 76 patients (23.5%) in the unchanged DAPT group ($p<0.01$).

TROPICAL-ACS (*Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes*)
This randomized, open-label trial included 2,610 biomarker-positive ACS patients after successful PCI. Patients were randomized to receive either prasugrel 5 or 10 mg/d (Days 0-14) (n=1306), or prasugrel 5 or 10 mg/d (Days 0-7) then de-escalated to clopidogrel 75 mg/d (Days 8-14) (n=1304), in combination with ASA (<100 mg/day). At Day 14, platelet function testing (PFT) was performed. The prasugrel-only patients were continued on prasugrel for 11.5 months.

The de-escalated patients underwent high platelet reactivity (HPR) testing. If HPR≥46 units, the patients were escalated back to prasugrel 5 or 10 mg/d for 11.5 months; if HPR<46 units, the patients continued on clopidogrel 75 mg/d for 11.5 months. Therefore, the guided de-escalation arm had patients on either prasugrel (40%) or clopidogrel (60%). All patients were continued on aspirin and were followed for one year.

The primary endpoint (the combined incidence of CV death, MI, stroke and BARC bleeding grade ≥2 at 12 months) was met showing non-inferiority. Ninety-five patients (7%) in the guided de-escalation group and 118 patients (9%) in the control group (p non-inferiority=0.0004) had an event. The guided de-escalation did not result in an increased combined risk of ischemic events (2.5% in the de-escalation group vs 3.2% in the control group; p non-inferiority=0.0115), nor in the key secondary endpoint of BARC bleeding ≥2 ((5%) in the de-escalation group versus 6% in the control group ($p=0.23$)). The cumulative incidence of all bleeding events (BARC class 1 to 5) was 9% (114 events) in the guided de-escalation group versus 11% (137 events) in the control group ($p=0.14$).

<u>Dual Antiplatelet Therapy (DAPT) in Acute Minor IS or Moderate to High-risk TIA</u>

DAPT with combination clopidogrel and ASA as a treatment to prevent stroke after an acute minor IS or moderate to high-risk TIA has been evaluated in two randomized investigator-sponsored studies (ISS) – CHANCE and POINT – with clinical safety and efficacy outcome data.

CHANCE (*Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events*)
This randomized, double-blinded, multicenter, placebo-controlled clinical trial included 5,170 Chinese patients with acute TIA (ABCD2 score ≥4) or acute minor stroke (NIHSS ≤3). Patients in both groups received open-label ASA on day 1 (with the dose ranging from 75 to 300 mg, at the discretion of the

treating physician). Patients randomly assigned to the clopidogrel–ASA group received a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg of clopidogrel per day on days 2 through 90, and ASA at a dose of 75 mg per day on days 2 through 21. Patients randomly assigned to the ASA group received a placebo version of clopidogrel on days 1 through 90 and ASA at a dose of 75 mg per day on days 2 through 90.

The primary efficacy outcome was any new stroke event (ischemic and hemorrhagic) in the first 90 days after acute minor IS or high-risk TIA. This occurred in 212 patients (8.2%) in the clopidogrel-ASA group compared with 303 patients (11.7%) in the ASA group (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.57 to 0.81; P<0.001). IS occurred in 204 patients (7.9%) in the clopidogrel–ASA group compared with 295 (11.4%) in the ASA group (HR, 0.67; 95% CI, 0.56 to 0.81; P<0.001). Hemorrhagic stroke occurred in 8 patients in each of the two study groups (0.3% of each group). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel–ASA group and in eight (0.3%) in the ASA group (P = 0.73). The rate of any bleeding event was 2.3% in the clopidogrel–ASA group as compared with 1.6% in the ASA group (HR, 1.41; 95% CI, 0.95 to 2.10; P = 0.09).

POINT (*Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke*)
This randomized, double-blinded, multicenter, placebo-controlled clinical trial included 4,881 international patients with acute TIA (ABCD2 score ≥4) or minor stroke (NIHSS ≤3). All patients in both groups received open-label ASA on day 1 to 90 (50-325 mg depending upon the discretion of the treating physician). Patients randomly assigned to the clopidogrel group received a loading dose of 600 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel per day on days 2 through 90. Patients randomly assigned to the placebo group received clopidogrel placebo on days 1 through 90.

The primary efficacy outcome was a composite of major ischemic events (IS, MI, or death from an ischemic vascular event) at day 90. This occurred in 121 patients (5.0%) receiving clopidogrel plus ASA compared with 160 patients (6.5%) receiving ASA alone (HR, 0.75; 95% CI, 0.59 to 0.95; P = 0.02). The secondary outcome of IS occurred in 112 patients (4.6%) receiving clopidogrel plus ASA compared with 155 patients (6.3%) receiving ASA alone (HR, 0.72; 95% CI, 0.56 to 0.92; P = 0.01). The primary safety outcome of major hemorrhage occurred in 23 of 2,432 patients (0.9%) receiving clopidogrel plus ASA and in 10 of 2,449 patients (0.4%) receiving ASA alone (HR, 2.32; 95% CI, 1.10 to 4.87; P = 0.02). Minor hemorrhage occurred in 40 patients (1.6%) receiving clopidogrel plus ASA and in 13 (0.5%) receiving ASA alone (HR, 3.12; 95% CI, 1.67 to 5.83; P < 0.001).

CHANCE and POINT Time Course Analysis
There was no efficacy benefit of continuing DAPT beyond 21 days. A time-course distribution of major ischemic events and major hemorrhages by treatment assignment was done to analyze the impact of the short-term time-course of DAPT.

Table 1 - Time course distribution of major ischemic events and major hemorrhages by treatment assignment in CHANCE and POINT

		No. of events			
Outcomes in CHANCE and POINT	Treatment assignment	Total	1st week	2nd week	3rd week
Major ischemic events	ASA (n=5,035)	458	330	36	21
	CLP+ASA(n=5,016)	328	217	30	14
	Difference	130	113	6	7
Major Hemorrhage	ASA (n=5,035)	18	4	2	1
	CLP+ASA(n=5,016)	30	10	4	2
	Difference	-12	-6	-2	-1

Atrial fibrillation

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

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

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

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age ≥75 years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction <45%; or documented peripheral vascular disease. The mean $CHADS_2$ score was 2.0 (range 0-6).

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

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

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

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

Paediatric population
In a dose escalation study of 86 neonates or infants up to 24 months of age at risk for thrombosis (PICOLO), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kg in neonates and infants and 0.15 mg/kg only in neonates. The dose of 0.2 mg/kg achieved the mean percent inhibition of 49.3% (5 µM ADP-induced platelet aggregation) which was comparable to that of adults taking Iscover 75 mg/day.

In a randomised, double-blind, parallel-group study (CLARINET), 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomised to receive clopidogrel 0.2 mg/kg (n=467) or placebo (n=439) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac-related

intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group) (see section 4.2). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups. In the long-term safety follow-up of this study, 26 patients with the shunt still in place at one year of age received clopidogrel up to 18 months of age. No new safety concerns were noted during this long-term follow-up.

The CLARINET and the PICOLO trials were conducted using a constituted solution of clopidogrel. In a relative bioavailability study in adults, the constituted solution of clopidogrel showed a similar extent and slightly higher rate of absorption of the main circulating (inactive) metabolite compared to the authorised tablet.

5.2 Pharmacokinetic properties

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

Distribution
Clopidogrel and the main circulating (inactive) 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.

Biotransformation
Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The C_{max} of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing.

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

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

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

2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

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

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

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

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

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

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

Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Renal impairment
After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment
After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

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

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:

Mannitol (E421)
Macrogol 6000
Microcrystalline cellulose
Hydrogenated castor oil
Low substituted hydroxypropylcellulose

Coating:

Hypromellose (E464)
Lactose monohydrate
Triacetin (E1518)
Titanium dioxide (E171)
Red iron oxide (E172)

Polishing agent:

Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

In PVC/PVDC/aluminium blisters, store below 30°C.
In all aluminium blisters, this medicinal product does not require any special storage conditions.

6.5 Nature and content of container

Iscover 75 mg film-coated tablets
PVC/PVDC/Aluminium blisters or all aluminium blisters in cardboard cartons containing 7, 14, 28, 30, 84, 90 and 100 film-coated tablets.

PVC/PVDC/Aluminium or all aluminium unit-dose blister packs in cardboard cartons containing 50x1 film-coated tablets.
Iscover 300 mg film-coated tablets
Aluminium unit-dose blisters in cardboard cartons containing 4x1, 10x1, 30x1 and 100x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBERS

Iscover 75 mg film-coated tablets
EU/1/98/070/001 - Cartons of 28 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/002 - Cartons of 50x1 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/003 - Cartons of 84 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/004 - Cartons of 100 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/005 - Cartons of 30 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/006 - Cartons of 90 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/007 - Cartons of 14 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/011 - Cartons of 7 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/013 - Cartons of 28 film-coated tablets in all aluminium blisters
EU/1/98/070/014 - Cartons of 50x1 film-coated tablets in all aluminium blisters
EU/1/98/070/015 - Cartons of 84 film-coated tablets in all aluminium blisters
EU/1/98/070/016 - Cartons of 100 film-coated tablets in all aluminium blisters
EU/1/98/070/017 - Cartons of 30 film-coated tablets in all aluminium blisters

EU/1/98/070/018 - Cartons of 90 film-coated tablets in all aluminium blisters
EU/1/98/070/019 - Cartons of 14 film-coated tablets in all aluminium blisters
EU/1/98/070/020 - Cartons of 7 film-coated tablets in all aluminium blisters

Iscover 300 mg film-coated tablets
EU/1/98/070/008 - Cartons of 4x1 film-coated tablets in all aluminium unit-dose blisters
EU/1/98/070/009 - Cartons of 30x1 film-coated tablets in all aluminium unit-dose blisters
EU/1/98/070/010 - Cartons of 100x1 film-coated tablets in all aluminium unit-dose blisters
EU/1/98/070/012 - Cartons of 10x1 film-coated tablets in all aluminium unit-dose blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 July 1998
Date of latest renewal: 19 June 2008

10. DATE OF REVISION OF THE TEXT

<DD month YYYY>

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

- Iscover 75 mg film-coated tablets

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc cedex
France

Delpharm Dijon

Sanofi S.r.l.
Strada Statale 17, Km 22
67019 Scoppito (AQ) – Italy

- Iscover 300 mg film-coated tablets

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc cedex
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Iscover 75 mg film-coated tablets
clopidogrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

3. LIST OF EXCIPIENTS

It also contains: hydrogenated castor oil and lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets
50x1 film-coated tablets
84 film-coated tablets
90 film-coated tablets
100 film-coated tablets
14 film-coated tablets
7 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C (for PVC/PVDC/aluminium blisters)
Or No special storage conditions (for all aluminium blisters)

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/070/001 28 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/002 50x1 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/003 84 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/004 100 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/005 30 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/006 90 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/007 14 film-coated tablets in PVC/PVDC/Alu blisters

EU/1/98/070/011 7 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/070/013 28 film-coated tablets in all aluminium blisters
EU/1/98/070/014 50x1 film-coated tablets in all aluminium blisters
EU/1/98/070/015 84 film-coated tablets in all aluminium blisters
EU/1/98/070/016 100 film-coated tablets in all aluminium blisters
EU/1/98/070/017 30 film-coated tablets in all aluminium blisters
EU/1/98/070/018 90 film-coated tablets in all aluminium blisters
EU/1/98/070/019 14 film-coated tablets in all aluminium blisters
EU/1/98/070/020 7 film-coated tablets in all aluminium blisters

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Iscover 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON BLISTERS
(BLISTER / 7, 14, 28 or 84 tablets)

1. NAME OF THE MEDICINAL PRODUCT

Iscover 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch:

5. OTHER

Calendar days
Mon
Tue
Wed
Thu
Fri
Sat
Sun

Week 1
Week 2 (for boxes of 14, 28 and 84 tablets)
Week 3 (for boxes of 28 and 84 tablets)
Week 4 (for boxes of 28 and 84 tablets)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER / 30, 50x1, 90 or 100 tablets

1. NAME OF THE MEDICINAL PRODUCT

Iscover 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Iscover 300 mg film-coated tablets
clopidogrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg of clopidogrel (as hydrogen sulphate).

3. LIST OF EXCIPIENTS

It also contains: hydrogenated castor oil and lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4x1 film-coated tablets
30x1 film-coated tablets
100x1 film-coated tablets
10x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. 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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/070/008 4x1 film-coated tablets in all aluminium unit-dose blisters
EU/1/98/070/009 30x1 film-coated tablets in all aluminium unit-dose blisters
EU/1/98/070/010 100x1 film-coated tablets in all aluminium unit-dose blisters
EU/1/98/070/012 10x1 film-coated tablets in all aluminium unit-dose blisters

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Iscover 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 4x1, 10x1, 30x1 or 100x1 tablets

1. NAME OF THE MEDICINAL PRODUCT

Iscover 300 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch:

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Iscover 75 mg film-coated tablets
clopidogrel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, including any side effects not listed in this leaflet, talk to your doctor or pharmacist. See section 4.

What is in this leaflet
1. What Iscover is and what it is used for
2. What you need to know before you take Iscover
3. How to take Iscover
4. Possible side effects
5 How to store Iscover
6. Contents of the pack and other information

1. What Iscover is and what it is used for

Iscover contains clopidogrel and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Iscover is taken by adults 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 Iscover 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 may 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.
- You have experienced symptoms of a stroke which go away within a short period of time (also known as transient ischemic attack) or an ischemic stroke mild in severity. You may also be given acetylsalicylic acid by your doctor starting within the first 24 hours.
- You have an irregular heartbeat, a condition called ‘atrial fibrillation’, and you cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Iscover and acetylsalicylic acid for this condition. Your doctor should have prescribed Iscover plus acetylsalicylic acid if you cannot take ‘oral anticoagulants’ and you do not have a risk of major bleeding.

2. What you need to know before you take Iscover

Do not take Iscover
- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of this medicine (listed in section 6).
- 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 Iscover.

Warnings and precautions
If any of the situations mentioned below apply to you, you should tell your doctor before taking Iscover:
- 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 (ischemic stroke) which occurred within the last seven days.
- if you have kidney or liver disease.
- if you have had an allergy or reaction to any medicine used to treat your disease.
- if you had a past medical history of non-traumatic brain hemorrhage.

While you are taking Iscover:
- 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 (also known as Thrombotic Thrombocytopenic Purpura or TTP) 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 section 4 ‘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 section 4 ‘Possible side effects’).
- Your doctor may order blood tests.

Children and adolescents
Do not give this medicine to children because it does not work.

Other medicines and Iscover
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
Some other medicines may influence the use of Iscover or vice versa.

You should specifically tell your doctor if you take
- medicines that may increase your risk of bleeding such as:
  - oral anticoagulants, medicines used to reduce blood clotting,
  - a non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammatory conditions of muscle or joints,
  - heparin or any other injectable medicine used to reduce blood clotting,
  - ticlopidine, or other antiplatelet agents,

  - a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
  - rifampicin (used to treat severe infections)
- omeprazole or esomeprazole, medicines to treat upset stomach,
- fluconazole or voriconazole, medicines to treat fungal infections,
- efavirenz, or other anti-retroviral medicines (used to treat HIV infections),
- carbamazepine, a medicine to treat some forms of epilepsy,
- moclobemide, medicine to treat depression,
- repaglinide, medicine to treat diabetes,
- paclitaxel, medicine to treat cancer,
- opioids: while you are treated with clopidogrel, you should inform your doctor before being prescribed any opioid (used to treat severe pain),
- rosuvastatin (used to lower your cholesterol level).

If you have experienced severe chest pain (unstable angina or heart attack), transient ischemic attack or ischemic stroke in mild severity, you may be prescribed Iscover 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.

Iscover with food and drink
Iscover may be taken with or without food.

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

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

You should not breast-feed while taking this medicine.
If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine.

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

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

Iscover contains lactose
If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

Iscover contains hydrogenated castor oil
This may cause stomach upset or diarrhoea.

3. How to take Iscover

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose, including for patients with a condition called ‘atrial fibrillation’ (an irregular heartbeat), is one 75 mg tablet of Iscover per day to be taken orally with or without food, and at the same time each day.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg or 600 mg of Iscover (1 or 2 tablets of 300 mg or 4 or 8 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of Iscover per day as described above.

If you have experienced symptoms of a stroke which go away within a short period of time (also known as transient ischemic attack) or an ischemic stroke mild in severity, your doctor may give you 300 mg of Iscover (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of Iscover per day as described above with acetylsalicylic acid for 3 weeks. Then the physician would prescribe either Iscover alone or acetylsalicylic acid alone. You should take Iscover for as long as your doctor continues to prescribe it.

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

If you forget to take Iscover
If you forget to take a dose of Iscover, 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 a forgotten tablet.

For the 7, 14, 28 and 84 tablets pack sizes, you can check the day on which you last took a tablet of Iscover by referring to the calendar printed on the blister.

If you stop taking Iscover
Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

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

4. Possible side effects

Like all medicines, this medicine 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 section 2 ‘Warnings and precautions’).
- 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 reported with Iscover 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 Iscover
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 section 2 ‘Warnings and precautions’).

Other side effects include:
Common side effects (may affect up to 1 in 10 people):
Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (may affect up to 1 in 100 people):
Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (may affect up to 1 in 1000 people):
Vertigo, enlarged breasts in males.

Very rare side effects (may affect up to 1 in 10,000 people):
Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting); swelling in the mouth; blisters of the skin; skin allergy; sore mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in taste or loss of taste of food.

Side effects with frequency not known (frequency cannot be estimated from the available data):
Hypersensitivity reactions with chest or abdominal pain, persistent low blood sugar symptoms.

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Iscover

Keep this medicine out of the sight and reach of children.

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

Refer to the storage conditions on the carton.
If Iscover is supplied in PVC/PVDC/aluminium blisters, store below 30°C.
If Iscover is supplied in all aluminium blisters, it does not require any special storage conditions.

Do not use this medicine if you notice any visible sign of deterioration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

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

The other ingredients are (see section 2 ‘Iscover contains lactose’ and ‘Iscover contains hydrogenated castor oil’):

- Tablet core: mannitol (E421), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose,

- Tablet coating: lactose monohydrate (milk sugar), hypromellose (E464), triacetin (E1518), red iron oxide (E172) and titanium dioxide (E171),
- Polishing agent: carnauba wax.

What Iscover looks like and contents of the pack

Iscover 75 mg film-coated tablets are round, biconvex, pink, engraved on one side with the number '75' and on the other side with the number '1171'. Iscover is supplied in cardboard cartons containing:

- 7, 14, 28, 30, 84, 90 and 100 tablets in PVC/PVDC/Aluminium blisters or in all aluminium blisters
- 50x1 tablets in PVC/PVDC/Aluminium blisters or in all aluminium unit-dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturers

Marketing Authorisation Holder:
Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

Manufacturers:
Sanofi Winthrop Industrie
1, rue de la Vierge, Ambarès & Lagrave, F-33565 Carbon Blanc cedex, France
or
Sanofi S.r.l.
Strada Statale 17, Km 22
67019 Scoppito (AQ) – Italy

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

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел: +359 (0)2 4942 480

Česká republika
Sanofi-, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel.: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800.536 389

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
Sanofi- Sp. z o.o.
Tel: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in <Month YYYY>.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/

Package leaflet: Information for the user

Iscover 300 mg film-coated tablets
clopidogrel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, including any side effects not listed in this leaflet, talk to your doctor or pharmacist. See section 4.

What is in this leaflet:
1. What Iscover is and what it is used for
2. What you need to know before you take Iscover
3. How to take Iscover
4. Possible side effects
5 How to store Iscover
6. Contents of the pack and other information

1. What Iscover is and what it is used for

Iscover contains clopidogrel and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Iscover is taken by adults 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 Iscover 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 may 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.
- You have experienced symptoms of a stroke which go away within a short period of time (also known as transient ischemic attack) or an ischemic stroke mild in severity. You may also be given acetylsalicylic acid by your doctor starting within the first 24 hours.
- You have an irregular heartbeat, a condition called ‘atrial fibrillation’, and you cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Iscover and acetylsalicylic acid for this condition. Your doctor should have prescribed Iscover plus acetylsalicylic acid if you cannot take ‘oral anticoagulants’ and you do not have a risk of major bleeding.

2. What you need to know before you take Iscover

Do not take Iscover:

- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of this medicine (listed in section 6).
- 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 Iscover.

Warnings and precautions
If any of the situations mentioned below apply to you, you should tell your doctor before taking Iscover:

- 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 (ischemic stroke) which occurred within the last seven days.
- if you have kidney or liver disease.
- if you have had an allergy or reaction to any medicine used to treat your disease.
- if you had a past medical history of non-traumatic brain hemorrhage.

While you are taking Iscover:

- 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 (also known as Thrombotic Thrombocytopenic Purpura or TTP) 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 section 4 ‘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 section 4 ‘Possible side effects’).
- Your doctor may order blood tests.

Children and adolescents
Do not give this medicine to children because it does not work.

Other medicines and Iscover:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
Some other medicines may influence the use of Iscover or vice versa.

You should specifically tell your doctor if you take

- medicines that may increase your risk of bleeding such as:
  - oral anticoagulants, medicines used to reduce blood clotting,
  - a non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammatory conditions of muscle or joints,
  - heparin or any other injectable medicine used to reduce blood clotting,

  - ticlopidine, or other antiplatelet agents,
  - a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
  - rifampicin (used to treat severe infections)
- omeprazole or esomeprazole, medicines to treat upset stomach,
- fluconazole or voriconazole, medicines to treat fungal infections,
- efavirenz, or other anti-retroviral medicines (used to treat HIV infections),
- carbamazepine, a medicine to treat some forms of epilepsy,
- moclobemide, medicine to treat depression,
- repaglinide, medicine to treat diabetes,
- paclitaxel, medicine to treat cancer,
- opioids: while you are treated with clopidogrel, you should inform your doctor before being prescribed any opioid (used to treat severe pain),
- rosuvastatin (used to lower your cholesterol level).

If you have experienced severe chest pain (unstable angina or heart attack), transient ischemic attack or ischemic stroke in mild severity, you may be prescribed Iscover 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.

Iscover with food and drink
Iscover may be taken with or without food.

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

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

You should not breast-feed while taking this medicine.
If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine. Ask your doctor or pharmacist for advice before taking any medicine.

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

Iscover contains lactose
If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

Iscover contains hydrogenated castor oil
This may cause stomach upset or diarrhoea.

3. How to take Iscover

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose, including for patients with a condition called ‘atrial fibrillation’ (an irregular heartbeat), is one 75 mg tablet of Iscover per day to be taken orally with or without food, and at the same time each day.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg or 600 mg of Iscover (1 or 2 tablets of 300 mg or 4 or 8 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of Iscover per day as described above.

If you have experienced symptoms of a stroke which go away within a short period of time (also known as transient ischemic attack) or an ischemic stroke mild in severity, your doctor may give you 300 mg of Iscover (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of Iscover per day as described above with acetylsalicylic acid for 3 weeks. Then the physician would prescribe either Iscover alone or acetylsalicylic acid alone.

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

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

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

4. Possible side effects

Like all medicines, this medicine 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 section 2 ‘Warnings and precautions’).
- 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 reported with Iscover 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 Iscover
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 section 2 ‘Warnings and precautions’).

Other side effects include:
Common side effects (may affect up to 1 in 10 people):
Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (may affect up to 1 in 100 people):
Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (may affect up to 1 in 1000 people):
Vertigo, enlarged breasts in males.

Very rare side effects (may affect up to 1 in 10,000 people):
Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions (for example, overall sensation of heat with

sudden general discomfort until fainting); swelling in the mouth; blisters of the skin; skin allergy; sore mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in taste or loss of taste of food.

Side effects with frequency not known (frequency cannot be estimated from the available data): Hypersensitivity reactions with chest or abdominal pain, persistent low blood sugar symptoms.

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Iscover

Keep this medicine out of the sight and reach of children.

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

This medicinal product does not require any special storage conditions.

Do not use this medicine if you notice any visible sign of deterioration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

What Iscover contains
The active substance is clopidogrel. Each tablet contains 300 mg of clopidogrel (as hydrogen sulphate).

The other ingredients are (see section 2 ‘Iscover contains lactose’ and ‘Iscover contains hydrogenated castor oil’):

- Tablet core: mannitol (E421), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose
- Tablet coating: lactose monohydrate (milk sugar), hypromellose (E464), triacetin (E1518), red iron oxide (E172) and titanium dioxide (E171),
- Polishing agent: carnauba wax.

What Iscover looks like and contents of the pack

Iscover 300 mg film-coated tablets are oblong, pink, engraved on one side with the number ‘300’ and on the other side with the number ‘1332’. Iscover is supplied in cardboard cartons containing 4x1, 10x1, 30x1 and 100x1 tablets in all aluminium unit-dose blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

Manufacturer:
Sanofi Winthrop Industrie
1, rue de la Vierge, Ambarès & Lagrave, F-33565 Carbon Blanc cedex, France

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

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Česká republika
Sanofi s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel.: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Polska
Sanofi Sp. z o.o.
Tel: +48 22 280 00 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Portugal
Sanofi - Produtos Farmacêuticos, Lda
Tel: +351 21 35 89 400

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800.536 389

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in <Month YYYY>.

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