SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

PLAVIX® 75 mg Film-coated tablets

COMPOSITION:

Each film-coated tablet contains:

Clopidogrel hydrogen sulphate (form II) equivalent to 75 mg of clopidogrel base.

Inactive excipients: Mannitol (sugar), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose in the tablet core, and lactose (milk sugar), hypromellose, triacetin, red iron oxide (E172), titanium dioxide (E171), and carnauba wax in the tablet coating.

Contains sugar and lactose monohydrate.

CATEGORY AND CLASS:

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Clopidogrel is a specific and potent inhibitor of platelet aggregation.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce

inhibition of platelet aggregation. However, an active metabolite responsible for the activity of the drug has not been isolated.

Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover (approximately 7 days).

Dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel.

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

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.

Metabolism

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. In vitro, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

Elimination

Following an oral dose of 14C-labelled clopidogrel in man, approximately 50 % was excreted in the urine and approximately 46 % in the faeces in the 120-hour interval after dosing. 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 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 white (85 %) and Asian (99 %) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, 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 poor CYP2C19 metaboliser genotypes are approximately 2 % for whites, 4 % for blacks and 14 % for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

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. At steady state, platelet aggregation inhibition (5 µM ADP) was decreased in poor metabolisers with mean IPA of 37 % compared to 58 % in the extensive metabolisers and 60 % in the intermediate metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.
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.

There is some evidence that patients who are either intermediate or poor metabolisers may have a higher rate of cardiovascular events (death, myocardial infarction, stroke or stent thrombosis) compared to extensive metabolisers.

Special populations

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

Elderly:

In elderly (≥ 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renal impairment:

After repeated administration of 75 mg clopidogrel/day in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) ADP-induced platelet aggregation was lower (25 %) than that observed in healthy subjects, however, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg clopidogrel per day.

Ethnicity:

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

INDICATIONS:

PLAVIX is indicated for the reduction of atherothrombotic events as follows:

Recent Myocardial Infarction (MI), Recent Stroke, or Established Peripheral Arterial Disease:

Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease.

Acute Coronary Syndrome:

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction [MI]) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG (coronary artery bypass graft), PLAVIX in combination with ASA has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischaemia.

For patients with ST-segment elevation acute myocardial infarction, PLAVIX in combination with ASA has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or any component of PLAVIX.
- Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.
- Safety and efficacy in subjects below the age of 18 have not been established.
- Safety and efficacy in pregnancy and lactation have not been established (see HUMAN REPRODUCTION).
- PLAVIX is contraindicated in severe liver impairment.
- PLAVIX is contraindicated in thrombocytopenia and platelet dysfunction.

- Haemophilia, congenital or acquired, or history of acquired haemophilia related to clopidogrel.

WARNINGS and SPECIAL PRECAUTIONS:

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH PLAVIX DURING POST-MARKETING EXPERIENCE. MOST CASES WERE REPORTED IN THE FIRST TWO WEEKS OF TREATMENT. PRESCRIBERS SHOULD ALSO WARN PATIENTS ABOUT THE SIGNS AND SYMPTOMS OF THROMBOTIC THROMBOCYTOPENIC PURPURA.

Recent ischemic stroke:

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

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

Clopidogrel produces irreversible inhibition of platelet aggregation for the life of the platelet, which is 7-10 days.

If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 7 days prior to surgery.

Spinal and epidural anaesthesia should not be administered to a patient taking clopidogrel or for 7 days thereafter. No lumber puncture should be done during these 7 days due to risk of haematoma formation following lumber puncture or spinal and epidural anaesthesia.

Bleeding and haematological disorders:

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever such suspected clinical symptoms arise during the course of treatment (see SIDE EFFECTS).

PLAVIX should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions associated with bleeding diathesis and in patients receiving treatment with acetylsalicylic acid, non-steroidal anti-inflammatory medicines including COX-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs) or thrombolytics. Patients should be continuously followed carefully for any signs of bleeding including occult bleeding, especially but not limited to during the first weeks of treatment and/or after cardiac procedures or surgery.

PLAVIX prolongs bleeding time. PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intra-ocular). Medicines that might induce gastrointestinal lesions (such as acetylsalicylic acid and non-steroidal anti-inflammatory agents) should be used with caution in patients taking PLAVIX (see INTERACTIONS).

Patients should be told that it may take longer than usual to stop bleeding when they take PLAVIX, and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicine is taken.

Because of the increased risk of bleeding, the concomitant administration of warfarin with PLAVIX should be undertaken with caution.

In view of the possible increased risk of bleeding, the concomitant administration of PLAVIX with ASA, heparin, or thrombolytics should be undertaken with caution (see INTERACTIONS).

Thrombotic Thrombocytopenic Purpura (TTP):

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of PLAVIX, sometimes after a short exposure (see WARNINGS). 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 plasmapharesis (plasma exchange).

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 (see CONTRAINDICATIONS).

Cytochrome P450 2C19 (CYP2C19):

Pharmacogenetics:

Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. (see Pharmacogenetics and DOSAGE AND DIRECTIONS FOR USE).

Cross-reactivity among thienopyridines:

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since cross-reactivity among theinopyridines has been reported (see SIDE EFFECTS). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema or haematological reactions such as thrombocytopenia and neutropenia. 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 cross-reactivity is advised.

Hepatic impairment:

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

Renal impairment:

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

Effects on ability to drive and use machines:

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

Lactose Intolerance:

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

PLAVIX contains hydrogenated castor oil which may cause stomach upset or diarrhoea.

INTERACTIONS:

Acetylsalicylic acid: Acetylsalicylic acid (ASA) did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of acetylsalicylic acid twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. Clopidogrel potentiated the effect of acetylsalicylic acid on collagen-induced platelet aggregation. As a pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, concomitant use should be undertaken with caution (see Special Precautions).
However, clopidogrel and ASA (75-325 mg once daily) have been administered together for up to one year.

Medicines associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicines associated with bleeding risk should be undertaken with caution.

Injectable anticoagulants: 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. As a pharmacodynamic interaction between clopidogrel and heparin is possible, concomitant use should be undertaken with caution.

Thrombolytics: The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when

thrombolytic agents and heparins are co-administered with acetylsalicylic acid. However, the concomitant use of clopidogrel with thrombolytic agents should be undertaken with caution.

Oral anticoagulants: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution (see Special Precautions).

Glycoprotein IIb/IIIa inhibitors: As a pharmacodynamic interaction between clopidogrel and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs): 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 and clopidogrel should be co-administered with caution (see Special Precautions).

Selective Serotonin Reuptake Inhibitors (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: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicine that inhibit the activity of this enzyme would be expected to result in reduced medicine levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole and esomeprazole) should be discouraged (see Special Precautions and Pharmacokinetics,

Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with PLAVIX, consider using one with less CYP2C19 inhibitory activity.

No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. 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 studies with human liver microsomes indicated that clopidogrel could inhibit the activity of one of the Cytochrome P450 (CYP) enzymes (CYP 2C9). This could lead to increased plasma levels of medicines such as phenytoin, tolbutamide, torsemide, tamoxifen, fluvastatin and NSAID's which are metabolised by CYP 2C9. Data indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

CYP2C8 substrate medicines: Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and medicines primarily cleared by CYP2C8 metabolism (e.g. repaglinide, paclitaxel) should be undertaken with caution.

In addition to the above specific interaction studies, patients entered into large clinical studies received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents, anti-epileptic agents and hormone replacement therapy, without evidence of clinically significant adverse interactions.

HUMAN REPRODUCTION:

Pregnancy:

PLAVIX should not be used during pregnancy.

Breastfeeding mothers:

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether clopidogrel is excreted in human breast milk. Mothers treated with PLAVIX should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

Recent Myocardial Infarction (MI), Recent Stroke, or Established Peripheral Arterial Disease:

The recommended daily dose of PLAVIX is 75 mg once daily.

Acute Coronary Syndrome:

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg–325 mg once daily) should be initiated and continued in combination with PLAVIX.

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of PLAVIX is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. PLAVIX may be initiated with or without a loading dose.

PLAVIX can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease.

Pharmacogenetics:

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

SIDE EFFECTS:

Bleeding is the most common reaction reported both in clinical studies where frequencies varied from common to very common, as well as in post-marketing experience.

Clinical studies adverse events:

In the CAPRIE study, for patients treated with clopidogrel, the overall incidence of any bleeding was 9,3 %. The incidence of severe cases was 1,4 % and gastrointestinal bleeding occurred at a rate of 2,0 %, and required hospitalisation in 0,7 %.

In the CURE study, the incidence of major and minor bleeding in the clopidogrel + ASA group was 3,7 % and 5,1 %, respectively. The principal sites for major bleeding included gastrointestinal and at arterial puncture sites.

In an acute coronary syndrome study where clopidogrel was administered concomitantly with ASA, the major bleeding event rate for clopidogrel + ASA was dose-dependent on ASA (< 100 mg: 2,6 %; 100–200 mg: 3,5 %; > 200 mg: 4,9 %).

There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4,4 % clopidogrel + ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9,6 % for clopidogrel + ASA.

Adverse reactions have been ranked under heading of system-organ class and frequency using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000).

Blood and the lymphatic system disorders:

Uncommon: thrombocytopenia (sometimes severe), increased bleeding time, leucopenia, eosinophilia, neutropenia (sometimes severe)

Very rare: aplastic anaemia

These events related to myelotoxicity should be considered when a patient receiving PLAVIX demonstrates fever or other signs of infection.

Nervous system disorders:

Uncommon: intracranial bleeding, headache, dizziness, paraesthesia

Eye disorders:

Uncommon: eye bleeding (mainly conjunctival)

Ear and labyrinth disorders:

Rare: vertigo

Vascular disorders:

Common: haematoma

Respiratory, thoracic and mediastinal disorders:

Common: epistaxis

Gastrointestinal system disorders:

Common: dyspepsia, abdominal pain, diarrhoea

Uncommon: nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer

Skin and subcutaneous tissue disorders:

Common: bruising

Uncommon: rash, pruritus, purpura

Renal and urinary disorders:

Uncommon: haematuria

General disorders and administrative site conditions: *Common*: bleeding at the puncture site

Post marketing experience

Adverse reactions have been ranked under heading of system-organ class.

Blood and the lymphatic system disorders:

Serious cases of bleeding, mainly skin, musculoskeletal, eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), epistaxis, haematuria and

haemorrhage of operative wound; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage).

Thrombotic thrombocytopenic purpura (TTP) (see Special Precautions), aplastic anaemia/pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia, acquired haemophilia A.

Cardiac disorders:

Kounis syndrome (vasospastic allergic angina)

Immune system disorders:

Anaphylactoid reactions, serum sickness, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see WARNINGS and SPECIAL PRECAUTIONS).

Psychiatric disorders:

Confusion, hallucinations

Nervous system disorders:

Taste disturbances, ageusia

Vascular disorders:

Vasculitis, hypotension

Respiratory, thoracic and mediastinal disorders:

Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders:

Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

Hepato-biliary disorders:

Acute liver failure, hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders:

Maculopapular, erythematous or exfoliative rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP)), drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, lichen planus

Musculoskeletal, connective tissue and bone disorders:

Arthralgia, arthritis, myalgia

Renal and urinary disorders:

Glomerulonephritis, blood creatinine increased

Reproductive systems and breast disorders:

Gynaecomastia

General disorders and administration site conditions:

Fever

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

Further treatment is symptomatic and supportive.

IDENTIFICATION:

PLAVIX 75 mg (Clopidogrel 75 mg) tablets are pink, round, slightly biconvex, film-coated tablets engraved with «75» on one side and «1171» on the other side.

PRESENTATION:

28 or 30 tablets packed in PVC/PVDC or all aluminium blister strips in cardboard cartons.

STORAGE INSTRUCTIONS:

Store below 25 °C. Protect from light. Do not remove blisters from the carton until required.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

36/8.2/0408

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand, 1685

South Africa

DATE OF PUBLICATION OF PROFESSIONAL INFORMATION:

11 October 2013

Revision date: 16 August 2018