PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

CLOPIWIN® 75 mg Film-coated tablets

CLOPIWIN® 300 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOPIWIN 75 mg

Each CLOPIWIN 75 mg film-coated tablet contains Clopidogrel hydrogen sulphate (form II) equivalent to 75 mg of clopidogrel base.

Contains sugar (Each CLOPIWIN 75 mg film-coated tablet contains 3 mg lactose and 68,9 mg mannitol).

Each CLOPIWIN 75 mg film-coated tablet contains 3,3 mg of hydrogenated castor oil.

CLOPIWIN 300 mg

Each CLOPIWIN 300 mg film-coated tablet contains Clopidogrel hydrogen sulphate (form II) equivalent to 300 mg of clopidogrel base.

Contains sugar (Each CLOPIWIN 300 mg film-coated tablet contains 12 mg lactose and 275,7 mg mannitol).

Each CLOPIWIN 300 mg film-coated tablet contains 13,2 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

CLOPIWIN 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.

CLOPIWIN 300 mg (clopidogrel 300 mg) tablets are pink, oblong, film-coated tablets engraved with «300» on one side and «1332» on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CLOPIWIN is indicated in adults for the secondary 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), CLOPIWIN 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, CLOPIWIN 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.

4.2 Posology and method of administration

Posology

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

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

Acute Coronary Syndrome:

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

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

CLOPIWIN can be administered with or without food.

Elderly patients and patients with renal impairment:

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.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH CLOPIWIN 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 THROMBOCYTOPENICPURPURA.

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

4.3 Contraindications

- Hypersensitivity to the active substance or any component of CLOPIWIN (see section 6.1.)
- 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 section 4.6).
- CLOPIWIN is contraindicated in severe liver impairment.
- CLOPIWIN is contraindicated in thrombocytopenia and platelet dysfunction.
- Haemophilia, congenital or acquired, or history of acquired haemophilia related to clopidogrel.

4.4 Special warnings and precautions for use

Recent ischaemic stroke:

In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of Acetylsalicylic acid (ASA) 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, CLOPIWIN cannot be recommended in acute ischaemic stroke (less than 7 days).

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 section 4.8). Because of the increased risk of bleeding, the concomitant administration of warfarin with CLOPIWIN should be undertaken with caution.

CLOPIWIN 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 (ASA), non-steroidal anti-inflammatory medicines (NSAIDs) including COX-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), thrombolytics or CYP2C19 strong inducers (see section 4.5).

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.

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, CLOPIWIN 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.

CLOPIWIN prolongs bleeding time. CLOPIWIN 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 ASA and NSAIDs) should be used with caution in patients taking CLOPIWIN (see section 4.5).

Patients should be told that it may take longer than usual to stop bleeding when they take CLOPIWIN alone or in combination with ASA, and that they should report any unusual bleeding (site or duration) to their doctor. Patients should inform doctors and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicine is taken.

Thrombotic Thrombocytopenic Purpura (TTP):

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

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 section 4.3).

Cytochrome P450 2C19 (CYP2C19):

Pharmacogenetics: In patients who are CYP2C19 poor metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function (see section 5.2).

Use of medicines that induce the activity of CYP2C19 would be expected to result in increased medicine 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).

Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy (see section 5.2, Pharmacogenetics and section 4.2).

Cross-reactivity among thienopyridines:

Patients should be evaluated for history of hypersensitivity to another thienopyridine 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 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. CLOPIWIN 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.

Excipients:

CLOPIWIN contains lactose (see sections 2 and 6.1). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take CLOPIWIN.

CLOPIWIN contains hydrogenated castor oil (see sections 2 and 6.1) which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicines and other forms of interaction

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.

Acetylsalicylic acid (ASA): 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 section 4.4). However, clopidogrel and ASA (75-325 mg once daily) have been administered together for up to one year.

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 section 4.4).

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 section 4.4).

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:

Inducers of CYP2C19: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicines that induce the activity of this enzyme would be expected to result in increased medicine 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 medicine that inhibit the activity of this enzyme would be expected to result in reduced medicine levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole, esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, carbamazepine, and efavirenz.) should be discouraged (see section 4.4 and section 5.2,

Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with CLOPIWIN, 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.

Opioid agonists: Co-administration of opioid agonists has the potential to delay and reduce the absorption of an oral $P2Y_{12}$ antagonist such as 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 1.4-fold (AUC) without effect on C_{max}, after repeated administration of a 75 mg CLOPIWIN dose.

4.6 Fertility, pregnancy and lactation

Pregnancy

CLOPIWIN should not be used during pregnancy.

Breastfeeding

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 CLOPIWIN should not breastfeed their infants.

4.7 Effects on ability to drive or use machines

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

4.8 Undesirable 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:

Haemorrhagic disorders:

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 CLOPIWIN 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 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 (haemarthrosis), 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), acquired haemophilia A (see section 4.4), aplastic anaemia/pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia.

Immune system disorders:

Anaphylactoid reactions, serum sickness, cross-reactive drug hypersensitivity among thienopyridines (see section 4.4), insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)

Psychiatric disorders:

Confusion, hallucinations

Nervous system disorders:

Taste disturbances, ageusia

Cardiac disorders:

Kounis syndrome (vasospastic allergic angina)

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of CLOPIWIN is important. It allows continued monitoring of the benefit/risk balance of CLOPIWIN. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

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.

Further treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clopidogrel belongs to the medicine class A 8.2 Anticoagulants.

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

Clopidogrel is a specific and potent inhibitor of platelet aggregation.

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 irreversible binding, 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 – 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 medicines, not all patients will have adequate platelet inhibition.

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.

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, 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 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 non-functional. 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), inhibition of 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 section 5.2, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol (sugar)

Hydrogenated castor oil

Microcrystalline cellulose

Macrogol 6000

Low-substituted hydroxypropyl cellulose

Tablet coating:

Lactose monohydrate (milk sugar)

Hypromellose

Triacetin

Red iron oxide (E172)

Titanium dioxide (E171)

Carnauba wax.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

CLOPIWIN 75 mg: Store at or below 25 °C.

CLOPIWIN 300 mg: Store at or below 30 °C.

Protect from light.

Do not remove PVC/PVDC blisters from the carton until required.

6.5 Nature and contents of container

CLOPIWIN 75 mg: 28 or 30 tablets packed in PVC/PVDC or all aluminium blister strips in cardboard cartons.

CLOPIWIN 300 mg: Packs of 4, 30 or 100 tablets are supplied in aluminium blister strips. The packs consist of either 4 tablets per blister strip and one blister strip is packed into a cardboard carton, or 10 tablets per blister strip and 3 or 10 blister strips are packed into a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand, 1685

South Africa

8 REGISTRATION NUMBERS

CLOPIWIN 75 mg: 41/8.2/0051

CLOPIWIN 300 mg: 44/8.2/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

CLOPIWIN 75 mg: 9 December 2008

CLOPIWIN 300 mg: 5 December 2013

10 DATE OF REVISION OF THE TEXT

12 May 2022