SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

CLOPIWIN PLUS® 75/75 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains clopidogrel hydrogen sulphate (form II) equivalent of 75 mg clopidogrel base, and 75 mg acetylsalicylic acid (ASA) (aspirin).

Contains sugar (lactose 7,5 mg and mannitol 68,925 mg per tablet).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

CLOPIWIN PLUS 75/75 (Clopidogrel 75 mg/Acetylsalicylic acid 75 mg) tablets are yellow, oval, slightly biconvex, film-coated tablets engraved with “C75” on one side and “A75” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CLOPIWIN PLUS is indicated in adults for the reduction of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). CLOPIWIN PLUS is a fixed-dose combination product for continuation of therapy in:

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), clopidogrel 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, clopidogrel 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

Acute Coronary Syndrome:

CLOPIWIN PLUS should be given as a single daily dose (i.e. one CLOPIWIN PLUS tablet daily). CLOPIWIN PLUS is used following an initial loading dose of clopidogrel in combination with ASA.

It may be given with or without food.

- In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, but the maximum benefit was seen at 3 months.
- In patients with ST segment elevation acute myocardial infarction: 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. For patients older than 75 years of age therapy should be initiated without a loading dose of clopidogrel.

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.

4.3 Contraindications

Due to the presence of clopidogrel and acetylsalicylic acid in the medicine, CLOPIWIN PLUS is contraindicated in case of:

- Hypersensitivity to the active substances or to any of the excipients of CLOPIWIN PLUS (see section 6.1).
- Active or history of pathological bleeding such as recurrent peptic ulcer/haemorrhage/perforations or intracranial haemorrhage.

- Safety and efficacy in subjects below the age of 18 have not been established. ASA has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before aspirin is used in such patients.
- Safety and efficacy in pregnancy and lactation have not been established (see section 4.6).
- Severe hepatic impairment.
- Thrombocytopenia and platelet dysfunction.

In addition, due to the presence of ASA, CLOPIWIN PLUS is also contraindicated in:

- Patients with hypersensitivity (allergy) to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
- Patients with severe renal impairment.
- Patients with heart failure.
- Patients with a history of gastrointestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

Recent transient ischaemic attack or 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.

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 CLOPIWIN PLUS should be discontinued.

Fluid retention and oedema:

In view of the inherent potential of NSAIDs, including ASA, to cause fluid retention, heart failure may be precipitated in some compromised patients. Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with CLOPIWIN PLUS therapy.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding, ulceration and perforation (PUBs) which may be fatal.

Due to the presence of ASA caution is required:

- In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions.
- In patients with gout since low doses of ASA increase serum uric acid concentrations.
- There is an association between ASA and Reye's syndrome when ASA is given to children. Reye's syndrome is a very rare disease which can be fatal.
- Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking CLOPIWIN PLUS (see section 4.5). Patients should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking CLOPIWIN PLUS.
- CLOPIWIN PLUS must be administered under close medical supervision in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolysis (see section 4.8).
- Concomitant treatment with levothyroxine and salicylates, specifically at doses greater than 2,0 g/day, should be avoided (see section 4.5).

Bleeding and haematological disorders:

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

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).

The concomitant administration of CLOPIWIN PLUS with warfarin is not recommended since it may increase the intensity of bleeding (see section 4.5).

CLOPIWIN PLUS 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 other non-steroidal anti-inflammatory medicines including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers, or thrombolytics (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 invasive cardiac procedures or surgery**.**

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

The concomitant administration of CLOPIWIN PLUS with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.5).

CLOPIWIN PLUS prolongs bleeding time. CLOPIWIN PLUS should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intra-ocular).

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

Patients should be told that it may take longer than usual to stop bleeding when they take CLOPIWIN PLUS, and that they should report any unusual bleeding (site or duration) to their medical practitioner.

Patients should inform medical practitioners and dentists that they are taking CLOPIWIN PLUS before any surgery is scheduled and before any new medicine is taken.

Gastrointestinal:

CLOPIWIN PLUS should be used with caution in patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia), peptic ulcer, gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, as the condition may be exacerbated or may be due to gastric ulceration which may lead to gastric bleeding.

The risk of gastrointestinal bleeding, ulceration or perforation (PUBs) is higher with increasing doses of CLOPIWIN PLUS, in patients with a history of ulcers, and the elderly.
When gastrointestinal bleeding, perforation or ulceration occurs in patients receiving CLOPIWIN PLUS, treatment with CLOPIWIN PLUS should be stopped.
Gastrointestinal side effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, medical practitioners should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about signs and symptoms of GI side effects and what steps to take if they occur.

In patients concomitantly receiving nicorandil and NSAIDs including acetylsalicylic acid (ASA) and lysine acetylsalicylate (LAS), there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.5).

Skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. CLOPIWIN PLUS should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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. 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.

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).

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).

Cross-reactivity among thienopyridines:

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as 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 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:

CLOPIWIN PLUS must not be used in patients with severe hepatic impairment (see section 4.3).

Caution is advised in patients with mild and moderate hepatic impairment.

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore CLOPIWIN PLUS should be used with caution in this population.

Renal impairment:

CLOPIWIN PLUS must not be used in patients with severe renal impairment (see section 4.3).

Therapeutic experience with CLOPIWIN PLUS is limited in patients with mild to moderate renal impairment. Therefore CLOPIWIN PLUS should be used with caution in this population.

Excipients:

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

CLOPIWIN PLUS also contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicines and other forms of interaction

There are no studies on the concomitant use of clopidogrel and acetylsalicylic acid with other medicines. The information below was obtained with clopidogrel or ASA alone. Safety of CLOPIWIN PLUS and the concomitant use with the medicines mentioned below have not been established.

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.

Nicorandil: In patients concomitantly receiving nicorandil and NSAIDs including acetylsalicylic acid (ASA) and lysine acetylsalicylate (LAS), there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.4).

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 CLOPIWIN PLUS 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 CLOPIWIN PLUS with thrombolytic agents should be undertaken with caution.

Oral anticoagulants: Because of the increased risk of bleeding, the concomitant administration of warfarin with CLOPIWIN PLUS is not recommended (see section 4.4).

Glycoprotein IIb/IIIa inhibitors: CLOPIWIN PLUS should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and who receive concomitant glycoprotein IIb/IIIa inhibitors.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs): In healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs, including Cox-2 inhibitors, is not recommended with CLOPIWIN PLUS (see section 4.4).

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly (see section 5.1). However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

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 with clopidogrel:

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 and a reduction in clinical efficacy. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole and esomeprazole) should be discouraged (see section 4.4 and section 5.2, Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with CLOPIWIN PLUS, consider using one with less CYP2C19 inhibitory activity.

Other medicinal products: 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 (CYP2C9). This could potentially lead to increased plasma levels of medicines such as phenytoin, tolbutamide, torsemide, tamoxifen, fluvastatin and NSAIDs which are metabolised by CYP2C9. Data indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

CYP2C8 substrate medicines: 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 medicines primarily cleared by CYP2C8 metabolism (e.g. repaglinide, paclitaxel) should be undertaken with caution.
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 clopidogrel dose.

Other concomitant therapy with ASA:
Interactions with the following medicinal products have been reported with ASA:

Uricosurics: Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Methotrexate: Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with CLOPIWIN PLUS as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Metamizole: Metamizole may reduce the effect of ASA on platelet aggregation when taken concomitantly. Therefore, this combination should be used with caution in patients taking low-dose ASA for cardioprotection.

NSAIDs: Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids: Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Acetazolamide: Caution is recommended when co-administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.

Varicella vaccine: It is recommended that patients not be given salicylates for an interval of six weeks after receiving the varicella vaccine. Cases of Reye's syndrome have occurred following the use of salicylates during varicella infections (see section 4.4).

Levothyroxine: Salicylates, specifically at doses greater than 2,0 g/day, may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

Valproic acid: The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.

Tenofovir: Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Other interactions with ASA: Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycaemic agents.

Alcohol: Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking CLOPIWIN PLUS (see section 4.4).

Other interactions with clopidogrel and ASA:

More than 30 000 patients who entered into clinical trials with clopidogrel plus ASA, at maintenance doses lower than or equal to 325 mg received a variety of concomitant medications including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicine interaction information described above, interaction studies with CLOPIWIN PLUS and some medicines commonly administered in patients with atherothrombotic disease have not been performed.

Opioid agonists: Co-administration of opioid agonists has the potential to delay and reduce the absorption of an oral P2Y12 inhibitor 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

CLOPIWIN PLUS should not be used during pregnancy (see section 4.3).

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. ASA is known to be excreted in human breast milk. Mothers treated with CLOPIWIN PLUS should not breastfeed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

CLOPIWIN PLUS 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.

In the CAPRIE study, for patients treated with clopidogrel, the overall incidence of any bleeding was 9,3 %. For clopidogrel, 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 lymphatic system disorders:

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

Very rare: aplastic anaemia

These events related to myelotoxicity should be considered when a patient receiving CLOPIWIN PLUS demonstrates fever or other sign 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

Bleeding is the most common reaction reported in the post-marketing experience with clopidogrel or ASA.

1. Clopidogrel

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), acquired haemophilia A
- cases of serious haemorrhage have been reported in patients taking CLOPIWIN PLUS with or without heparin
- thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia/pancytopenia, agranulocytosis, severe thrombocytopenia, 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:

- anaphylactoid reactions, serum sickness
- cross-reactive medicine hypersensitivity among thienopyridines, such as ticlopidine or prasugrel (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

Vascular disorders:

- vasculitis, hypotension

Respiratory, thoracic and mediastinal disorders:

- bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders:

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

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 (DiHS), drug rash with eosinophilia and systemic symptoms (DRESS), eczema; lichen planus

Musculoskeletal, connective tissue and bone disorders:

- arthritis, arthralgia, myalgia

Renal and urinary disorders:

- glomerulonephritis, increased blood creatinine

Reproductive systems and breast disorders:

- gynaecomastia

General disorders and administration site conditions:

- Fever

2. Acetylsalicylic acid (ASA):

Blood and lymphatic system disorders:

- thrombocytopenia, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, pancytopenia, bicytopenia, aplastic anaemia, bone marrow failure, agranulocytosis, neutropenia, leukopenia

Immune system disorders:

- anaphylactic shock, aggravation of allergic symptoms of food allergy

Cardiac disorders:

- Kounis syndrome in the context of a hypersensitivity reaction due to ASA

Nervous system disorders:

- intracranial haemorrhage (may be fatal, especially in the elderly)

Metabolism and nutrition disorders:

- hypoglycaemia, gout

Ear and labyrinth disorders:

- hearing loss or tinnitus

Vascular disorders:

- hypertension, cardiac failure, vasculitis including Henoch-Schönlein purpura

Respiratory, thoracic and mediastinal disorders:

- non-cardiogenic pulmonary oedema with chronic use and in the context of a hypersensitivity reaction due to ASA

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature.

- gastro-duodenal ulcer/perforations, upper gastrointestinal symptoms such as gastralgia, peptic ulcers, small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis, colitis. These reactions may or may not be associated with haemorrhage, and may occur at any dose of ASA and in patients with or without warning symptoms or a previous history of serious gastrointestinal events.

- nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis
- acute pancreatitis in the context of a hypersensitivity reaction due to ASA

Hepato-biliary disorders:

- elevation of hepatic enzymes, liver injury, mainly hepatocellular, chronic hepatitis

Skin and subcutaneous tissue disorders:

- bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis; fixed eruption

Renal and urinary disorders:

- renal failure, acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)

General disorders and administration site conditions:

- oedema

Reporting of suspected adverse reactions

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

4.9 Overdose

There is no information concerning overdosage with the fixed-dose combination, CLOPIWIN PLUS.

Signs and symptoms:

Clopidogrel:

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications.

Acetylsalicylic acid (ASA):

Overdosage is manifested by the following symptoms:

Moderate overdose: ringing in the ears, sensation of reduced hearing, headaches, vertigo and gastrointestinal symptoms (nausea, vomiting and gastric pain).

Severe overdose: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycaemia.

Non-cardiogenic pulmonary oedema can occur with acute and chronic acetylsalicylic acid overdose (see section 4.8).

Management:

Clopidogrel:

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.

Acetylsalicylic acid (ASA):

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

CLOPIWIN PLUS (clopidogrel and acetylsalicylic acid) belongs to the medicine class A 8.2 Anticoagulants.

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excl. Heparin, ATC Code: B01AC30.

Clopidogrel:

Clopidogrel is a specific and potent inhibitor of platelet aggregation.

Clopidogrel is a promedicine, 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 P2Y12 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 the 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 medicines, not all patients will have adequate platelet inhibition.

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

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.

Acetylsalicylic acid (ASA):

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

5.2 Pharmacokinetic properties:

Clopidogrel:

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. 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.

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* 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 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.

Acetylsalicylic acid (ASA):

***Absorption*:**

Following absorption, the ASA in CLOPIWIN PLUS is hydrolised to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1,5 - 3 hours after dosing.

***Distribution*:**

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (< 100 µg/ml), approximately 90 % of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and fetal tissues.

***Metabolism and Elimination*:**

The ASA in CLOPIWIN PLUS is rapidly hydrolised in plasma to salicylic acid, with a half-life of 0,3 - 0,4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in CLOPIWIN PLUS has a plasma half-life of approximately 2 hours.

Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10 - 20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher.

Renal excretion of unchanged medicine depends upon urinary pH. As urinary pH rises above 6,5, the renal clearance of free salicylate increases from < 5 % to > 80 %. Following therapeutic doses, approximately 10 % is found excreted in the urine as salicylic acid, 75 % as salicyluric acid, 10 % phenolic- and 5 % acyl-glucuronides of salicylic acid.

Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, macrogol, microcrystalline cellulose, low-substituted hydroxypropylcellulose, maize starch, hydrogenated castor oil, stearic acid, anhydrous silica,lactose, hypromellose, triacetin, yellow iron oxide, titanium dioxide and carnauba wax.

Contains sugar: lactose and mannitol. Each tablet contains 7,0 mg lactose and 68,925 mg mannitol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove blisters from the carton until required.

6.5 Nature and contents of container

CLOPIWIN PLUS 75/75 film-coated tablets are packed into aluminium blister strips placed in cardboard cartons. Each strip contains either 7 or 10 tablets.

Pack sizes: 14 (2 strips of 7), 28 (4 strips of 7), or 84 (12 strips of 7) or 30 (3 strips of 10), 50 (5 strips of 10), 90 (9 strips of 10) or 100 (10 strips of 10).

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

8 REGISTRATION NUMBER

CLOPIWIN PLUS 75/75: 44/8.2/0657

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 November 2014

10 DATE OF REVISION OF THE TEXT

13 April 2022