Professional Information for PLAOPLIC

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

PLAOPLIC 75 mg/75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (64 mg mannitol per tablet).

Excipients with known effects:

Contains sugar (2,8 mg lactose monohydrate per tablet).

Contains hydrogenated castor oil (3 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Yellow coloured, oval shaped, film-coated tablets debossed with “I” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PLAOPLIC is indicated in adults for the reduction of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). PLAOPLIC 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

PLAOPLIC should be given as a single daily dose (i.e. one PLAOPLIC tablet daily). PLAOPLIC 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.

Method of administration

Oral use.

4.3 Contraindications

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

- Hypersensitivity to the active substances or to any of the excipients of PLAOPLIC (see section 6.1).
- Active or history of pathological bleeding such as recurrent peptic ulcer/haemorrhage/perforations or intracranial haemorrhage.
- Children and adolescents below the age of 18 years (see section 4.4).
- Safety and efficacy in pregnancy and lactation have not been established (see section 4.6).
- Severe hepatic impairment (Child-Pugh C).
- Thrombocytopenia and platelet dysfunction.
- Haemophilia, congenital or acquired, or history of acquired haemophilia related to clopidogrel.

In addition, due to the presence of ASA, PLAOPLIC 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 (creatinine clearance < 30 mL/minute).
- 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).
- Combination with methotrexate at doses of 15 mg/week or more.

4.4 Special warnings and precautions for use

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH PLAOPLIC DURING POST-MARKETING EXPERIENCE. MOST CASES WERE REPORTED IN THE FIRST TWO WEEKS OF TREATMENT. MEDICAL PRACTITIONERS 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 treatment with PLAOPLIC must be discontinued (see section 4.3).

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 PLAOPLIC 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 and adolescents below 18 years with viral infections such as varicella (chickenpox) or influenza. Reye's syndrome is a less frequent disease which can be fatal. A medical practitioner should be consulted before PLAOPLIC is used in such patients (see section 4.3).
- Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking PLAOPLIC (see section 4.5). Patients should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking PLAOPLIC.
- PLAOPLIC 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

PLAOPLIC 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 PLAOPLIC with warfarin is not recommended since it may increase the intensity of bleeding (see section 4.5).

PLAOPLIC 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 drugs including COX-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers, or thrombolytics (see section 4.5). Due to the increased risk of haemorrhage, triple antiplatelet therapy (clopidogrel + ASA + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or transient ischaemic attack (TIA) (see sections 4.5 and 4.8).
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, PLAOPLIC should be discontinued 7 days prior to surgery.

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

PLAOPLIC prolongs bleeding time. PLAOPLIC 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 PLAOPLIC 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 PLAOPLIC, 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 PLAOPLIC before any surgery is scheduled and before any new medicine is taken.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as ASA, as contained in PLAOPLIC. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue PLAOPLIC and evaluate the patient immediately (see section 4.8).

Gastrointestinal (GI)

PLAOPLIC 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 PLAOPLIC, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding, perforation or ulceration occurs in patients receiving PLAOPLIC, treatment with PLAOPLIC 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 frequent 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. PLAOPLIC 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

PLAOPLIC 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, PLAOPLIC should be used with caution in this population.

Renal impairment

PLAOPLIC must not be used in patients with severe renal impairment (see section 4.3).
Therapeutic experience with PLAOPLIC is limited in patients with mild to moderate renal impairment. Therefore, PLAOPLIC should be used with caution in this population.

Excipients

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

PLAOPLIC 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 PLAOPLIC 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 (see section 4.4).

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 PLAOPLIC 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 medicines and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic medicines and heparins are co-administered with acetylsalicylic acid. However, the concomitant use of PLAOPLIC with thrombolytic medicines should be undertaken with caution.

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

Glycoprotein IIb/IIIa inhibitors: PLAOPLIC 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 drugs (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 PLAOPLIC (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 sections 4.4 and 5.2, Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with PLAOPLIC, consider using one with less CYP2C19 inhibitory activity.

Boosted antiretroviral therapy (ART): Human immunodeficiency virus (HIV) patients treated with boosted antiretroviral therapies (ART) are at high risk of vascular events.

Other medicines:

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 (phenobarbitone) 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 medicines have been reported with ASA:

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

Methotrexate: Due to the presence of ASA, PLAOPLIC should not be used in combination with methotrexate at doses higher than 15 mg/week, as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity (see section 4.3).

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 medicines 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 medicines.

Alcohol: Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking PLAOPLIC (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 medicines including diuretics, beta blockers, ACE inhibitors, calcium antagonists, cholesterol lowering medicines, coronary vasodilators, antidiabetic medicines (including insulin), antiepileptic medicines and glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicine interaction information described above, interaction studies with PLAOPLIC and some medicines frequently 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 medicine in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Regular use of NSAIDs, as in ASA, during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed, and its duration increased. The use of NSAIDs around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

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 PLAOPLIC should not breastfeed their infants (see section 4.3).

Fertility

There are no fertility data with PLAOPLIC.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Bleeding is the most frequent reaction reported.

Blood and lymphatic system disorders:

Less frequent: thrombocytopenia (sometimes severe), increased bleeding time, leucopenia, eosinophilia, neutropenia (sometimes severe), decreased platelets, aplastic anaemia, thrombotic thrombocytopenic purpura (TTP) (see section 4.4), pancytopenia, granulocytopenia, anaemia, agranulocytosis, acquired haemophilia A

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

Immune system disorders:

Less frequent: serum sickness, anaphylactoid reactions

Psychiatric disorders:

Less frequent: confusion, hallucinations

Nervous system disorders:

Less frequent: intracranial haemorrhage (may be fatal, especially in the elderly), headache, dizziness, paraesthesia, taste disturbances, ageusia

Eye disorders:

Less frequent: eye bleeding (conjunctival, ocular, retinal)

Ear and labyrinth disorders:

Less frequent: vertigo

Vascular disorders:

Frequent: haematoma

Less frequent: hypotension, serious haemorrhage, haemorrhage of operative wound

Respiratory, thoracic and mediastinal disorders:

Frequent: epistaxis

Less frequent: respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal system disorders:

Frequent: dyspepsia, abdominal pain, diarrhoea, gastrointestinal haemorrhage

Less frequent: nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer, stomatitis, gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, upper gastrointestinal disorders such as esophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis, colitis (including ulcerative or lymphocytic colitis)

Hepato-biliary disorders:

Less frequent: acute liver failure, hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders:

Frequent: bruising

Less frequent: rash, pruritus, purpura, bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome (DiHS), erythematous or exfoliative rash, urticaria, eczema, lichen planus

Musculoskeletal, connective tissue and bone disorders:

Less frequent: musculoskeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia

Renal and urinary disorders:

Less frequent: haematuria, glomerulonephritis, increased blood creatinine

Reproductive systems and breast disorders:

Less frequent: gynaecomastia

General disorders and administrative site conditions:

Frequent: bleeding at the puncture site

Less frequent: fever

Post marketing

Clopidogrel

Immune system disorders:

- 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)

Cardiac disorders:

- Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel

Vascular disorders:

- vasculitis

Skin and subcutaneous tissue disorders:

- maculopapular

Acetylsalicylic acid (ASA)

Blood and lymphatic system disorders:

- haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, bicytopenia, bone marrow failure

Immune system disorders:

- anaphylactic shock, aggravation of allergic symptoms of food allergy

Metabolism and nutrition disorders:

- hypoglycaemia, gout (see section 4.4)

Ear and labyrinth disorders:

- hearing loss or tinnitus

Cardiac disorders:

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

Vascular disorders:

- 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:

- gastro-duodenal ulcer/perforations, upper gastrointestinal symptoms such as gastralgia (see

section 4.4), peptic ulcers, small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, intestinal perforation. 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.

- melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease
- acute pancreatitis in the context of a hypersensitivity reaction due to ASA.

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

- fixed eruption
- drug rash with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

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 PLAOPLIC is important. It allows continued monitoring of the benefit/risk balance of PLAOPLIC. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no information concerning overdosage with the fixed-dose combination as contained in

PLAOPLIC.

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. 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

Category and 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 pro-drug, 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 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.

Biotransformation

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

CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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 PLAOPLIC is hydrolysed 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 foetal tissues.

Biotransformation and elimination

The ASA in PLAOPLIC is rapidly hydrolysed in plasma to salicylic acid, with a half-life of 0,3 – 0,4 hours for ASA doses from 75 – 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 PLAOPLIC 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

Core:

Hydrogenated colloidal silica [E551]

Hydrogenated castor oil [E1503]

Low-substituted hydroxypropyl cellulose

Mannitol [E421]

Microcrystalline cellulose [E460]

Polyethylene glycol

Stearic acid [E570]

Yellow iron oxide [E172].

Coating:

Opadry II yellow (containing hypromellose, lactose monohydrate, titanium dioxide [E171], triacetin and yellow iron oxide [E172]).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep in the original container until required for use.

6.5 Nature and contents of container

OPA/aluminium/desiccant PE blister strip containing 10 tablets, packed in an outer carton.

Pack sizes: 10 or 30 tablets.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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10. DATE OF REVISION OF THE TEXT