

1. NAME OF THE MEDICINAL PRODUCT

Kogrel 75 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg clopidogrel.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Kogrel 75 mg film-coated tablets are pink colored, round shaped, engraved with 'SZ' 75 on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated for the prevention of atherothrombotic events in:

- Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- Adult patients suffering from acute coronary syndrome:
 - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
 - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

For further information, please refer to section 5.1.

4.2 Posology and method of administration

Adults and elderly

Clopidogrel should be given as a single daily dose of 75 mg with or without food.

In patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): Clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg - 325 mg daily). Since higher doses of ASA were associated with higher bleeding risk, it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.
- ST segment elevation acute myocardial infarction: Clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting.

If a dose is missed:

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

Paediatric population

Clopidogrel should not be used in children because of efficacy concerns.

Renal impairment

Therapeutic experience is limited in patients with renal impairment (see section 4.4).

Hepatic impairment

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

Method of administration

For oral use.

The medicinal product may be given with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8).

As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors, or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors or selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers, or other medicinal products associated with bleeding risk such as pentoxifylline (see section 4.5).

Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

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

Thrombotic Thrombocytopenic Purpura (TTP)

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

Acquired haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia

should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Recent ischaemic stroke

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

There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics

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

Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.

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

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

CYP2C8 substrates

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

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8).

Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as 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 signs of hypersensitivity in patients with a known allergy to thienopyridines

is advised.

Renal impairment

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients (see section 4.2).

Hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk

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

Oral anticoagulants

The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, co-administration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis.

Glycoprotein IIb/IIIa inhibitors

Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

Acetylsalicylic acid (ASA)

ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

Heparin

In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

Thrombolytics

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8).

NSAIDs

In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

SSRIs

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

Other concomitant therapy

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.4).

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g. proton pump inhibitors) should be discouraged.

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

Proton Pump Inhibitors (PPI)

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

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

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

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

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

Boosted anti-retroviral therapy (ART)

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

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

Other medicinal products

A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal

products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from a clinical study indicates that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

CYP2C8 substrate medicinal products

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

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

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

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

4.6 Pregnancy and lactation

Pregnancy

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

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

Breast-feeding

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with clopidogrel.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

List of adverse reactions

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are

presented in the list below. Their frequency is defined using the following conventions: common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/1000$), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders

Uncommon: Thrombocytopenia, leucopenia, eosinophilia
Rare: Neutropenia, including severe neutropenia
Very rare, not known:* Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia

Immune system disorders

Very rare, not known:* Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*, insulin autoimmune syndrome which may cause severe hypoglycemia particularly in patients with the HLA DRA4 subtype (more commonly occurring in the Japanese population)*

Psychiatric disorders

Very rare, not known:* Hallucinations, confusion

Nervous system disorders

Uncommon: Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness
Very rare, not known:* Taste disturbances, ageusia

Eye disorders

Uncommon: Eye bleeding (conjunctival, ocular, retinal)

Ear and labyrinth disorders

Rare: Vertigo

Cardiac disorders

Very rare, not known:* Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*

Vascular disorders

Common: Haematoma
Very rare, not known:* Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension

Respiratory, thoracic and mediastinal disorders

Common: Epistaxis
Very rare, not known:* Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders

Common: Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia
Uncommon: Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence
Rare: Retroperitoneal haemorrhage
Very rare, not known:* Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis

Hepatobiliary disorders

Very rare, not known:* Acute liver failure, hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders

Common: Bruising

Uncommon: Rash, pruritus, skin bleeding (purpura)

Very rare, not known:* Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus

Musculoskeletal and connective tissue disorders

Very rare, not known:* Musculoskeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia

Renal and urinary disorders

Uncommon: Haematuria

Very rare, not known:* Glomerulonephritis, blood creatinine increased

Reproductive systems and breast disorders

Rare: Gynaecomastia

General disorders and administration site conditions

Common: Bleeding at puncture site

Very rare, not known:* Fever

Investigations

Uncommon: Bleeding time prolonged, neutrophil count decreased, platelet count decreased

* Information related to clopidogrel with frequency “not known”.

4.9 Overdose

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excl. heparin.

ATC Code: BO1AC/04.

Mechanism of action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation.

The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet 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 their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

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

Pharmacodynamic effects

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Clopidogrel and the main circulating (inactive) metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Biotransformation

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite.

Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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

The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19.

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* platelet aggregation assays, differ according to CYP2C19 genotype.

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

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

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

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

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials.

Special populations

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

Renal impairment

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

Hepatic impairment

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

Race

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Mannitol
Cellulose Microcrystalline
Hydroxypropyl Cellulose
Hydrogenated Vegetable Oil

Coating:

Opadry Pink 03B54942
Purified Water

Overprinting:
Opacode S-1-17823 Black

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

Alu-Alu blisters in cardboard cartons.
14 tablets, 28 tablets or 30 tablets per carton.

Not all pack size may be marketed.

6.6 Special precautions for disposal

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

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
3A-2 & 3A-3, Level 3A, Menara KEN TTDI,
No. 37, Jalan Burhanuddin Helmi, Taman Tun Dr Ismail,
60000 Kuala Lumpur, Malaysia

8. DATE OF REVISION OF THE TEXT

Aug 2026