

AUSTRALIAN PRODUCT INFORMATION – CLOPIDOGREL® WINTHROP PLUS ASPIRIN (CLOPIDOGREL (AS HYDROGEN SULFATE)/ ASPIRIN) FILM COATED TABLET

1 NAME OF THE MEDICINE

Clopidogrel (as hydrogen sulfate) and aspirin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Clopidogrel Winthrop Plus Aspirin tablet contains clopidogrel 75 mg (as clopidogrel hydrogen sulfate) and aspirin 100 mg.

Excipient with known effect: lactose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Clopidogrel Winthrop Plus Aspirin tablets are light pink, oval, slightly biconvex, film-coated, engraved with “C75” on one side and “A100” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Clopidogrel Winthrop Plus Aspirin is a fixed-dose combination product.

Clopidogrel Winthrop Plus Aspirin is intended as continuation of therapy in patients with acute coronary syndrome already initiated with separate clopidogrel and aspirin products:

- Unstable angina or non-ST elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischaemia). Clopidogrel Winthrop Plus Aspirin is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).
- ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, Clopidogrel Winthrop Plus Aspirin 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 in medically treated patients eligible for thrombolytic therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Clopidogrel Winthrop Plus Aspirin is given as a single tablet (75mg/100mg) once a day taken with adequate water.

Acute Coronary Syndrome

Clopidogrel Winthrop Plus Aspirin is used following an initial loading dose of 300 mg clopidogrel in combination with aspirin in patients with acute coronary syndrome:

- Unstable angina or non-ST-elevation myocardial infarction:
 - Treatment should be initiated with a single 300 mg loading dose of clopidogrel plus aspirin (75 mg to 325 mg).
 - Long-term daily treatment should be continued with one Clopidogrel Winthrop Plus Aspirin tablet (75mg/100mg) once a day taken with adequate water.
- ST-segment elevation acute myocardial infarction:
 - Treatment should be initiated with or without a 300 mg loading dose of clopidogrel in combination with aspirin and with or without thrombolytics as soon as possible after symptoms start. There are no data on the use of a 300 mg loading dose in elderly patients (aged 75 years or more) with ST segment acute myocardial infarction, as no patients over 75 years old were included in the CLARITY study and no loading dose was used in the COMMIT study.
 - Daily treatment should continue with one Clopidogrel Winthrop Plus Aspirin tablet (75mg/100mg) once a day with adequate water. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting.

In patients who have had percutaneous coronary intervention with stent insertion, clopidogrel and aspirin should be continued for as long as is currently recommended in evidence-based guidelines for the type of stent and circumstances of implantation or for as long as otherwise indicated, taking into account the overall atherothrombotic risk profile of the patient.

Should doses of aspirin greater than 100 mg be required for daily maintenance therapy, clopidogrel and aspirin products should be administered separately.

Pharmacogenetics

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. A higher dose of clopidogrel (600 mg loading dose followed by 150 mg once daily) in poor metabolisers increases antiplatelet response (see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenetics). Consider the use of higher clopidogrel doses in patients who are poor CYP2C19 metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Renal Impairment

Experience is limited in patients with mild to moderate renal impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Clopidogrel Winthrop Plus Aspirin should not be used in patients with severe renal impairment (see Section 4.3 CONTRAINDICATIONS).

Hepatic Impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Clopidogrel Winthrop Plus Aspirin should not be used in patients with severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

Elderly

No dosage adjustment is necessary for elderly patients (see Section 5 PHARMACOLOGICAL PROPERTIES, SPECIAL POPULATIONS).

Children and Adolescents

Safety and efficacy in subjects below the age of 18 have not been established.

There is a possible association between aspirin and Reye's syndrome when aspirin is given to children. Reye's syndrome is a very rare disease which can be fatal.

4.3 CONTRAINDICATIONS

Due to the presence of both components of the product, Clopidogrel Winthrop Plus Aspirin is contraindicated in case of:

- Hypersensitivity to clopidogrel, salicylates or any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as haemophilia, intracranial haemorrhage or gastrointestinal bleeding.
- Peptic ulcer or erosive gastritis
- Breast-feeding (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in lactation).

In addition, due to the presence of aspirin, its use is also contraindicated in case of:

- Hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and in patients with the syndrome of asthma with rhinitis and/or 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).
- Severe renal impairment.

- Third trimester of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Clopidogrel and aspirin prolong bleeding time, and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions, as follows:

- If a patient is to undergo elective surgery and an anti-platelet effect is not desired, Clopidogrel Winthrop Plus Aspirin should be discontinued 7 days prior to surgery.
- If the patient is at high risk of ophthalmic bleeding due to intraocular lesions clopidogrel should be used with extra caution.
- Clopidogrel Winthrop Plus Aspirin prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Drugs that might induce such lesions (such as NSAIDs) are not recommended in patients taking Clopidogrel Winthrop Plus Aspirin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Clopidogrel Winthrop Plus Aspirin should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, as this may be due to gastric ulceration which may lead to gastric bleeding.
- Due to the increased risk of haemorrhage, triple antiplatelet therapy (clopidogrel + aspirin + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or TIA (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Gastrointestinal side effects, including stomach pain, heartburn, nausea, vomiting and gastrointestinal bleeding, may occur. Minor gastrointestinal symptoms, such as dyspepsia, are common and can occur anytime during therapy. Physicians should remain alert for signs of GI ulceration and bleeding, even in the absence of previous gastrointestinal symptoms (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).
- Patients should be told about the signs and symptoms of gastrointestinal side effects and what steps to take if they occur. Patients should be told that it may take longer than usual for bleeding to stop when they take Clopidogrel Winthrop Plus Aspirin, and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking Clopidogrel Winthrop Plus Aspirin before any surgery is scheduled and before any new drug is taken.
- In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding. Therefore, use of the combination of clopidogrel

and aspirin should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

- To prevent gastric irritation due to aspirin, Clopidogrel Winthrop Plus Aspirin should be taken with or after food.
- Due to the presence of aspirin, caution is required in patients with a history of asthma or allergic disorders (as they are at increased risk of hypersensitivity reactions) or with gout (as low doses of aspirin increase urate concentrations).
- In patients concomitantly receiving nicorandil and NSAIDs including aspirin, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Clopidogrel Winthrop Plus Aspirin 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).
- The hypoglycaemic effect of chlorpropamide may be enhanced by the concurrent administration of aspirin. Large doses of aspirin may have intrinsic hypoglycaemic activity when given to diabetic patients, but the effects on carbohydrate metabolism are complex and it may cause hyperglycaemia
- Alcohol - Due to the presence of aspirin:
 - alcohol may increase the risk of gastrointestinal injury when taken with aspirin. Therefore, alcohol should be used with caution in patients taking aspirin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
 - patients should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking clopidogrel plus aspirin.
- Concomitant treatment with levothyroxine and salicylates should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- Tinnitus is a premonitory sign of salicylism but may not be detected in patients with hearing loss
- This medicinal product also contains hydrogenated castor oil which may cause stomach upset and diarrhoea.
- Clopidogrel Winthrop Plus Aspirin is to be used under medical supervision only.
- Clopidogrel plus aspirin should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel plus aspirin (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Coronary Artery Bypass Surgery

When coronary artery bypass surgery is to be performed, clopidogrel and aspirin should be suspended at least 7 days before surgery to reduce the risk of bleeding (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

PHARMACOGENETICS

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is mainly due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.

In patients who are CYP2C19 poor metabolisers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function (see Section 5 PHARMACOLOGICAL PROPERTIES and Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenetics).

Use of drugs 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Although a higher dose regimen in poor metabolisers increases antiplatelet response (see Section 5 PHARMACOLOGICAL PROPERTIES, PHARMACOGENETICS), an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Consider alternative treatment strategies in patients identified as CYP2C19 poor metabolisers (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Pharmacogenetics).

CYP2C19 Metabolism

Since clopidogrel is metabolised to its active metabolite partly 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. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole) should be discouraged (See Section 5 PHARMACOLOGICAL PROPERTIES, Pharmacogenetics and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole.

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Ischaemic Stroke

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

Haematological

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 (plasma exchange).

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have also been reported very rarely in patients taking clopidogrel (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Due to the risk of bleeding and haematological undesirable effects, 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. The concomitant administration of Clopidogrel Winthrop Plus Aspirin with warfarin is not recommended since it may increase the intensity of bleeding (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). With chronic administration, occult blood loss may lead to iron deficiency anaemia. As a dual anti-platelet agent, Clopidogrel Winthrop Plus Aspirin 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 other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers discouraged or thrombolytics. 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.

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopenia and neutropenia. Patients who have 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.

Use in hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel Winthrop Plus Aspirin should therefore be used with caution in this population. See also Section 4.3 CONTRAINDICATIONS for severe hepatic impairment.

Use in renal impairment

Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment. Therefore Clopidogrel Winthrop Plus Aspirin should be used with caution in this population. Patients should be observed closely for signs of salicylism. See also Section 4.3 CONTRAINDICATIONS for severe renal impairment.

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 aspirin. 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, hematological 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 aspirin and evaluate the patient immediately (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in the elderly

No data available

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Children and Adolescents.

Effects on laboratory tests

No data available

Alcohol

The effect of alcohol on the safety and efficacy of the combination of clopidogrel and aspirin has not been investigated in clinical trials. Concurrent ingestion of alcohol and aspirin may enhance occult blood loss and gastric irritation. In prolonged aspirin administration, occult blood loss may lead to iron deficiency anaemia. Aspirin inhibits ethanol dehydrogenase, a major enzyme in the first pass elimination of alcohol.

In vitro, the metabolism of clopidogrel has been shown to be altered in the presence of ethanol, such that clopidogrel is hydrolysed (inactivated) more slowly, and ethyl clopidogrel formed; the toxicity of ethyl clopidogrel has not been fully investigated. See Section 4.5

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Interaction with alcohol.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Aspirin

A pharmacodynamic interaction between clopidogrel and aspirin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to one year. See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - General

Clopidogrel Winthrop Plus Aspirin should not be administered simultaneously with other salicylate containing preparations, uricosuric agents or NSAIDs.

Drugs associated with bleeding risk:

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of drugs associated with bleeding risk should be undertaken with caution (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Oral Anticoagulants (including warfarin)

The concomitant administration of Clopidogrel Winthrop Plus Aspirin with oral anticoagulants, including warfarin, is not recommended since it may increase the intensity of bleeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Glycoprotein IIb/IIIa Inhibitors

Clopidogrel Winthrop Plus Aspirin should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). As a pharmacodynamic interaction between Clopidogrel Winthrop Plus Aspirin and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

Injectable Anticoagulants

A pharmacodynamic interaction between Clopidogrel Winthrop Plus Aspirin and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Anti-platelet Agents (such as eptifibatide, ticlopidine, tirofiban)

The effects of Clopidogrel Winthrop Plus Aspirin and other drugs which inhibit platelet aggregation may be additive, leading to an increased risk of bleeding.

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 aspirin. The safety of concomitant administration of Clopidogrel Winthrop Plus Aspirin with thrombolytic agents has not been formally established and should be undertaken with caution.

Nicorandil

In patients concomitantly receiving nicorandil and NSAIDs, including aspirin, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Methotrexate

Due to the presence of aspirin, methotrexate and Clopidogrel Winthrop Plus Aspirin should be used together with caution, as aspirin can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity. Salicylates can also displace methotrexate from albumin.

Acetazolamide

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

Non Steroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin may increase the risk of gastrointestinal side effects, including bleeding, when administered with NSAIDs. Aspirin displaces diclofenac from its binding sites, reducing diclofenac effectiveness.

Ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly and may limit the beneficial cardiovascular effects of aspirin in patients with increased cardiovascular risk.

In a clinical study conducted 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 Clopidogrel Winthrop Plus Aspirin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR 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.

Uricosuric Agents (e.g. probenecid)

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

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

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. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

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.

Drugs Metabolised by Cytochrome P450 2C9

At high concentrations in vitro, clopidogrel inhibits cytochrome P450 (2C9) and at lower concentrations inhibits CYP2B6 and CYP2C19. Accordingly, Clopidogrel Winthrop Plus Aspirin may interfere with the metabolism of bupropion, lansoprazole, omeprazole, pantoprazole, diazepam, phenytoin, tamoxifen, tolbutamide, warfarin, fluvastatin, and many NSAIDs, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is co-administered with Clopidogrel Winthrop Plus Aspirin.

Other Concomitant Therapy

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that induce 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly 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. The clinical relevance of this interaction is uncertain.

Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole) should be discouraged (see Section 5 PHARMACOLOGICAL PROPERTIES, Pharmacogenetics and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole.

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Proton Pump Inhibitors (PPI): In a crossover clinical study (N=72 healthy subjects), clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. Mean maximal platelet aggregation intensity % (MAI) was the primary pharmacodynamic endpoint of the clinical study and was used in the calculation of the mean inhibition of platelet aggregation % (IPA). Similar trends in results were seen across both the MAI% and IPA%. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation with 5 µM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together. The same results were observed when omeprazole 80mg was administered 12 hours apart.

In a crossover clinical study (N=66), healthy subjects were administered clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. Mean maximal platelet aggregation intensity % was the primary pharmacodynamic endpoint of the clinical study and was used in the calculation of the mean inhibition of platelet aggregation %. Similar trends in results were seen across both the MAI% and IPA%. The exposure to the active metabolite of clopidogrel was decreased by 20% (Day 1) and 14% (Day 5) when clopidogrel and pantoprazole were administered together. Mean inhibition of platelet aggregation was diminished by 15% (24 hours) and 11% (Day 5) when clopidogrel and pantoprazole were administered together. These results indicate that clopidogrel can be administered with pantoprazole.

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.

Care should be observed when coadministering aspirin and methotrexate, chlorpropamide, corticosteroids, sulfapyrazone, probenecid and spironolactone. The hypoglycaemic effect of chlorpropamide may be enhanced by the concurrent administration of aspirin

Hydrocortisone may increase the renal clearance of salicylate and when hydrocortisone is discontinued, serum salicylate levels may rise significantly. Aspirin may antagonise the diuretic effect of spironolactone. The rate and extent of aspirin absorption is increased by caffeine. The rate of excretion is increased by urinary alkalinisers. Aspirin at high doses reduces the uricosuric effects of probenecid and sulfapyrazone.

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

In a study comparing administration of warfarin with either clopidogrel (N=20) or placebo (N=23) the administration of clopidogrel 75 mg/day for 8 days did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy (at least 2 months). Coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis. However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9. It is unlikely that clopidogrel interferes with the metabolism of drugs such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

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

CYP2C8 substrate drugs:

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 drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

Rosuvastatin

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.

Combination use of ACE Inhibitors or Angiotensin Receptor Antagonists, Anti-inflammatory Drugs and Thiazide Diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including aspirin or COX-2 inhibitors) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function

(serum creatinine) should be monitored after initiation of concomitant therapy and periodically thereafter.

Interactions with Higher Dose Aspirin

Interactions with the following medicines with higher (anti-inflammatory) doses of aspirin have been reported: alendronate, ACE inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, systemic corticosteroids, diuretics, selective serotonin reuptake inhibitors (SSRIs), spironolactone, verapamil, hypoglycaemic agents and zafirlukast.

Other interactions with clopidogrel and aspirin

More than 30,000 patients entered into clinical trials with clopidogrel plus aspirin at maintenance doses lower than or equal to 325 mg, received a variety of concomitant medications, including diuretics, beta blockers, ACE inhibitors, calcium channel antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, hormone replacement therapy 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.

Interactions with alcohol

Alcohol may increase the risk of gastrointestinal injury when taken with aspirin. Therefore, alcohol should be used with caution in patients taking aspirin. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Alcohol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day.

Aspirin had antispermatogenic effects by inhibiting prostaglandin formation in Long Evans rats at 250 mg/kg/day PO, but did not affect the fertility of male Wistar rats at 300 mg/kg/day IP. The clinical relevance of these observations is unknown.

For Aspirin in doses > 500 mg/day; there is some evidence that drugs which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Use in pregnancy

Pregnancy Category C

No clinical data on exposure to clopidogrel plus aspirin during pregnancy are available. Clopidogrel plus aspirin should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel in combination with aspirin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including clopidogrel plus aspirin at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

Due to the risk of oligohydramnios, if clopidogrel plus aspirin treatment is necessary from about 20 weeks gestation to the end of the second trimester, it should be managed under medical supervision and use limited to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid. Discontinue clopidogrel plus aspirin if oligohydramnios occurs and follow up according to clinical practice.

Due to the presence of aspirin clopidogrel plus aspirin is contraindicated during the third trimester of pregnancy (see Section 4.3 CONTRAINDICATIONS).

Clopidogrel and/or its metabolites are known to cross the placenta in pregnant rats and rabbits. However, teratology studies in rats and rabbits at doses up to 500 mg and 300 mg/kg/day PO, respectively, revealed no evidence of embryotoxicity or teratogenicity.

Reproduction toxicity data show that aspirin is teratogenic in several laboratory animals.

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the foetal ductus arteriosus, prolong labour and delay birth. Aspirin increases bleeding time both in the newborn infant and in the mother because of its anti-platelet effects.

Clopidogrel Winthrop Plus Aspirin should not be used in women during pregnancy unless the potential benefits outweigh the risks.

Use in lactation

Breast-feeding is contraindicated during treatment with Clopidogrel Winthrop Plus Aspirin (see Section 4.3 CONTRAINDICATIONS). Studies in rats have shown that clopidogrel and/or its metabolites are excreted in breast milk. Salicylates are excreted in breast milk. Chronic high doses of aspirin can cause adverse effects in the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clopidogrel

Clinical Studies Experience

Clopidogrel has been evaluated for safety in more than 44,000 patients, including over 30,000 patients treated with clopidogrel plus aspirin, and over 12,000 patients treated for 1 year or more. The clinically relevant adverse events observed in CURE, CLARITY, COMMIT, CHARISMA, ACTIVE-A and ACTIVE-W are discussed below.

CURE, CLARITY AND COMMIT

Haemorrhagic Disorders

In CURE, there was a significant difference between the two treatment groups for non life-threatening major bleeds (1.6% clopidogrel + aspirin vs. 1.0% placebo + aspirin), primarily gastrointestinal and at arterial puncture sites, and minor bleeds (5.1% clopidogrel + aspirin vs. 2.4% placebo + aspirin). The major bleeding event rate for clopidogrel + aspirin was dose-dependent on aspirin (<100 mg: 2.6%; 100-200 mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo + aspirin (<100 mg: 2.0%; 100-200 mg: 2.3%; >200 mg: 4.0%).

The administration of clopidogrel + aspirin as compared to placebo + aspirin, was not associated with an increase in life-threatening or fatal bleeds (event rates 2.2% vs. 1.8% and 0.2% vs. 0.2%, respectively). The incidence of intra-cranial bleeding was 0.1% in both groups.

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel + aspirin vs. 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + aspirin group (17.4%) versus the placebo + aspirin group (12.9%), with the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in haemoglobin > 5 g/dL) being similar between groups (1.3% versus 1.1% in the clopidogrel + aspirin and the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel + aspirin and in the placebo + aspirin groups, respectively) and intracranial haemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of non-cerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups, as shown in Table 1.

Table 1 - Number of patients with bleeding events in COMMIT

| Type of bleeding | Clopidogrel + aspirin (n = 22,961) | Placebo + aspirin (n = 22,891) | p-value |
|---|--|--------------------------------------|---------|
| Major * non-cerebral or cerebral bleeding | 134 (0.6%) | 125 (0.5%) | 0.59 |
| Major non-cerebral | 82 (0.4%) | 73 (0.3%) | 0.48 |
| Fatal | 36 (0.2%) | 37 (0.2%) | 0.90 |
| Haemorrhagic stroke | 55 (0.2%) | 56 (0.2%) | 0.91 |
| Fatal | 39 (0.2%) | 41 (0.2%) | 0.81 |
| Other non-cerebral bleeding (non major) | 831 (3.6%) | 721 (3.1%) | 0.005 |
| Any non-cerebral bleeding | 896 (3.9%) | 777 (3.4%) | 0.004 |

*Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion

Haematological Disorders

In CURE and CLARITY, the numbers of patients with thrombocytopenia or neutropenia were similar in both groups.

Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other signs of infection.

Gastrointestinal

In CURE, there was no significant difference in the incidence of non-haemorrhagic gastrointestinal effects in the clopidogrel or placebo groups.

In CLARITY, the incidence of gastrointestinal adverse events was 6.9% for clopidogrel treated patients, compared to 7.2% in placebo treated patients.

In COMMIT, 2 patients reported gastrointestinal adverse events in the clopidogrel treated group, compared to one in the placebo treated group.

Rash

In CURE, rash occurred in more patients in the clopidogrel group. In CLARITY, 0.7% of patients in the clopidogrel group reported a rash, compared to 0.5% in the placebo group.

Treatment Discontinuation

In CURE, the overall incidence of discontinuation due to adverse events was greater in the clopidogrel group than in the placebo group (366 [5.8%] and 247 [3.9%] patients, respectively), with the main differences being in events in the platelet, bleeding and clotting disorders (1.1% versus 0.7%) and skin disorders (0.7% versus 0.3%). The increase in the rate of study drug discontinuation due to non-haemorrhagic adverse events was primarily due to

the increase in rash seen in the clopidogrel group. There was no apparent difference between the 2 treatment groups in the rates of discontinuations due to other adverse events.

In CLARITY, the overall incidence of discontinuation due to adverse events was greater in the placebo group compared with the clopidogrel group (6.9% for clopidogrel treated patients compared to 8.6% for placebo treated patients).

In COMMIT, the overall incidence of discontinuation due to adverse events was similar in each treatment group (2.4% for clopidogrel treated patients compared to 2.2% for placebo treated patients).

ACTIVE Studies

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that treatment with VKA was more effective than the combination of clopidogrel and aspirin. The rate of major bleeding episodes was higher in the clopidogrel + aspirin group than in the VKA group: 101 (3.03%) subjects compared with 93 (2.76%).

The ACTIVE-A study demonstrated when preventing atherothrombotic and thromboembolic events including stroke, the rate of major bleeding was greater in the clopidogrel + aspirin group 251 (6.7%) than in the placebo + aspirin group 162 (4.3%).

CAPRIE & CHARISMA

The following safety data is extracted from clinical studies for different indications of clopidogrel.

Haemorrhagic Disorders

In CAPRIE a study conducted in 19,185 patients with established atherosclerosis or history of atherothrombosis as manifested by myocardial infarction, ischaemic stroke or peripheral arterial disease, who randomised to clopidogrel 75 mg/day or aspirin 325 mg/day, and followed for 1 to 3 years, the overall incidence of any bleeding in patients treated with either clopidogrel or aspirin was similar (9.3%). The incidence of severe bleeds was 1.4% in the clopidogrel group and 1.6% in the aspirin group.

The overall incidence of other bleeding disorders was higher in the clopidogrel group (7.3%) compared to aspirin (6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs. 0.4%). The most frequent events reported were purpura/bruising and epistaxis. Other less frequently reported events were haematoma, haematuria and eye bleeding (mainly conjunctival).

Gastrointestinal haemorrhage was significantly less frequent with clopidogrel (1.99%) compared to aspirin (2.66%). The incidence of intracranial haemorrhage was 0.35% for clopidogrel compared to 0.49% for aspirin.

In CHARISMA, a study conducted in patients with coronary artery disease, cerebrovascular disease or peripheral arterial disease as well as patients with a combination of atherothrombotic risk factors only, all receiving a background therapy with low dose aspirin (75-162 mg), there was an excess in moderate and severe bleeding, as adjudicated to the GUSTO definitions, in the clopidogrel group (see Table 2). This represented a number needed to treat, to harm, of 84 in 23 months of follow-up.

Table 2 - Number of patients with bleeding events in CHARISMA

| Type of bleeding (GUSTO) | Number (%) with event | | Difference Clopidogrel – Placebo (%) (95% CI) |
|--------------------------|-----------------------------------|-------------------------------|---|
| | Clopidogrel + aspirin (N=7802) | Placebo + aspirin (N=7801) | |
| Any | 2827 (36.2) | 1616 (20.7) | 15.52 (14.12, 16.91) |
| Severe/moderate | 290 (3.7) | 197 (2.5) | 1.19 (0.65, 1.74) |

Haematological Disorders

In CAPRIE, Clopidogrel was not associated with an increase in the incidence of thrombocytopenia compared to aspirin. Very rare cases of platelet count $<30 \times 10^9/L$ have been reported.

Severe neutropenia ($<0.45 \times 10^9/L$) was observed in four patients (0.04%) that received clopidogrel and in two patients that received aspirin. Two of the 9599 patients who received clopidogrel and none of the patients who received aspirin had a neutrophil count of zero. One of the clopidogrel treated patients was receiving cytostatic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel.

One case of aplastic anaemia occurred on clopidogrel treatment.

The incidence of severe thrombocytopenia ($<80 G/L$) was 0.2% on clopidogrel and 0.1% on aspirin; very rare cases of platelet count $\leq 30 G/L$ have been reported.

Gastrointestinal

In CAPRIE, overall the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel was significantly lower than in those receiving aspirin. The incidence of peptic, gastric, or duodenal ulcers was 0.68% for clopidogrel and 1.15% for aspirin. Cases of diarrhoea were reported at a higher frequency in the clopidogrel group (4.46%) compared to the aspirin group (3.36%).

Rash

In CAPRIE, there were significantly more patients with rash in the clopidogrel group (4.2%) compared to the aspirin group (3.5%).

Treatment Discontinuation

In the clopidogrel and aspirin treatment groups of the CAPRIE study, discontinuation due to adverse events occurred in approximately 13% of patients after 2 years of treatment.

Adverse events occurring in $\geq 2.5\%$ of patients on clopidogrel in the CAPRIE and CURE controlled clinical trials are shown in Table 3 regardless of relationship to clopidogrel.

Table 3 - Adverse events occurring in $\geq 2.5\%$ of patients receiving clopidogrel in CAPRIE and CURE

| BODY SYSTEM/EVENT | CAPRIE | | CURE | |
|---|------------------------------------|---------------------|------------------------------------|-------------------------------|
| | % Incidence (% discontinuation) | | % Incidence (% discontinuation) | |
| | Clopidogrel n = 9599 | Aspirin n = 9586 | Clopidogrel + aspirin n = 6259 | Placebo + aspirin n = 6303 |
| Body as a Whole - general disorders | | | | |
| Chest pain | 8.3 (0.2) | 8.3 (0.3) | 2.7 (0.02) | 2.8 (0.0) |
| Accidental/inflicted injury | 7.9 (0.1) | 7.3 (0.1) | 1.1 (0.06) | 1.2 (0.03) |
| Influenza like symptoms | 7.5 (<0.1) | 7.0 (<0.1) | 1.1 (0.0) | 1.1 (0.0) |
| Pain | 6.4 (0.1) | 6.3 (0.1) | 1.3 (0.02) | 1.4 (0.0) |
| Fatigue | 3.3 (0.1) | 3.4 (0.1) | 1.5* (0.02) | 1.0 (0.0) |
| Cardiovascular disorders - general | | | | |
| Hypertension | 4.3 (<0.1) | 5.1* (<0.1) | 0.9 (0.0) | 0.9 (0.0) |
| Central and peripheral nervous system disorders | | | | |
| Headache | 7.6 (0.3) | 7.2 (0.2) | 3.1 (0.08) | 3.2 (0.10) |
| Dizziness | 6.2 (0.2) | 6.7 (0.3) | 2.4 (0.08) | 2.0 (0.02) |
| Gastrointestinal | | | | |
| Abdominal pain | 5.6 (0.7) | 7.1* (1.0) | 2.3 (0.26) | 2.8 (0.27) |
| Dyspepsia | 5.2 (0.6) | 6.1* (0.7) | 2.0 (0.08) | 1.9 (0.02) |
| Diarrhoea | 4.5* (0.4) | 3.4 (0.3) | 2.1 (0.11) | 2.2 (0.13) |
| Nausea | 3.4 (0.5) | 3.8 (0.4) | 1.9 (0.18) | 2.3 (0.08) |
| Metabolic and nutritional disorders | | | | |
| Hypercholesterolaemia | 4.0 (0) | 4.4 (<0.1) | 0.1 (0.0) | 0.2 (0.0) |
| Musculoskeletal system disorders | | | | |
| Arthralgia | 6.3 (0.1) | 6.2 (0.1) | 0.9 (0.0) | 0.9 (0.0) |
| Back pain | 5.8 (0.1) | 5.3 (<0.1) | 1.0 (0.03) | 1.2 (0.0) |
| Myo-, endo-, pericardial and valve disorders | | | | |
| Angina pectoris | 10.1 (0.6) | 10.7 (0.4) | 0.1 (0.0) | 0.1 (0.0) |
| Coronary artery disorder | 6.2 (0.3) | 5.6 (0.3) | 0.03 (0.0) | 0.06 (0.0) |
| Platelet, bleeding and clotting disorders | | | | |
| Purpura | 5.3* (0.3) | 3.7 (0.1) | 0.3 (0.0) | 0.1 (0.0) |
| Epistaxis | 2.9 (0.2) | 2.5 (0.1) | 0.2 (0.08) | 0.1 (0.02) |
| Psychiatric disorders | | | | |
| Depression | 3.6 (0.1) | 3.9 (0.2) | 0.7 (0.02) | 0.7 (0.0) |

| BODY SYSTEM/EVENT | CAPRIE | | CURE | |
|-----------------------------------|------------------------------------|---------------------|------------------------------------|-------------------------------|
| | % Incidence (% discontinuation) | | % Incidence (% discontinuation) | |
| | Clopidogrel n = 9599 | Aspirin n = 9586 | Clopidogrel + aspirin n = 6259 | Placebo + aspirin n = 6303 |
| Resistance mechanism disorders | | | | |
| Infection | 4.7 (<0.1) | 4.2 (0.1) | 1.3 (0.0) | 1.2 (0.0) |
| Respiratory system disorders | | | | |
| Upper respiratory tract infection | 8.7 (<0.1) | 8.3 (<0.1) | 1.1 (0.0) | 1.0 (0.0) |
| Dyspnoea | 4.5 (0.1) | 4.2 (0.1) | 1.9 (0.0) | 1.9 (0.02) |
| Rhinitis | 4.2 (0.1) | 4.2 (<0.1) | 0.2 (0.0) | 0.1 (0.0) |
| Bronchitis | 3.7 (0.1) | 3.7 (0) | 1.1 (0.0) | 1.5 (0.0) |
| Coughing | 3.1 (<0.1) | 2.7 (<0.1) | 1.3 (0.0) | 1.2 (0.0) |
| Skin and appendage disorders | | | | |
| Rash | 4.2* (0.5) | 3.5 (0.2) | 1.3 (0.29) | 1.1 (0.14) |
| Pruritis | 3.3* (0.3) | 1.6 (0.1) | 0.5 (0.11) | 0.5 (0.05) |
| Urinary system disorders | | | | |
| Urinary tract infection | 3.1 (0) | 3.5 (0.1) | 1.5 (0.0) | 1.4 (0.0) |
| Vascular (extracardiac) disorders | | | | |
| Claudication intermittent | 3.8 (0.2) | 3.8 (0.2) | 0.1 (0.02) | 0.1 (0.0) |
| Peripheral ischaemia | 3.2 (0.2) | 3.4 (0.2) | 0.4 (0.03) | 0.3 (0.0) |
| Cerebrovascular disorder | 2.6 (0.3) | 2.9 (0.3) | 0.3 (0.03) | 0.4 (0.03) |

* indicates statistical significance ($p \leq 0.05$)

Incidence of discontinuation, regardless of relationship to therapy is shown in parentheses.

Clinically relevant adverse reactions not listed above pooled from CAPRIE, CURE, CLARITY and COMMIT studies with an incidence of $\geq 0.1\%$ as well as all serious and clinically relevant adverse reactions are listed below according to the World Health Organisation classification.

Their frequency is defined using the following conventions:

common: $\geq 1/100$ (1%) and $< 1/10$ (10%)

uncommon: $\geq 1/1000$ (0.1%) and $< 1/100$ (1%)

rare: $\geq 1/10000$ (0.01%) and $< 1/1000$ (0.1%)

Central and peripheral nervous system disorders

uncommon: Headache, dizziness, paraesthesia,

rare: Vertigo

Gastrointestinal system disorders

common: Dyspepsia, abdominal pain, diarrhea

uncommon: Nausea, gastritis, flatulence, constipation, vomiting, gastric, peptic or duodenal ulcer

Platelet, bleeding and clotting disorders

uncommon: Bleeding time increased, decreased platelets

Skin and appendages disorders

uncommon: Rash, pruritus

White cell and RES disorders

uncommon: Leucopenia, decreased neutrophils, eosinophilia

Post-Marketing Experience

In addition to clinical study experience with clopidogrel either alone or in combination with aspirin, the following is a list of adverse reactions reported with clopidogrel or aspirin.

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

The following have been reported spontaneously from worldwide post-marketing experience with clopidogrel:

| | | |
|------|--------------------|--|
| Note | <i>very common</i> | $\geq 1/10$ ($\geq 10\%$) |
| | <i>common</i> | $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$) |
| | <i>uncommon</i> | $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1.0\%$) |
| | <i>rare</i> | $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$) |
| | <i>very rare</i> | $< 1/10,000$ ($< 0.01\%$) |
| | <i>Not known</i> | cannot be estimated from available data |

Musculoskeletal, connective and bone

very rare: Arthralgia, arthritis, myalgia

Immune system disorders

very rare: Anaphylactoid reactions, serum sickness

unknown: Cross-reactive hypersensitivity among thienopyridine (such as ticlopidine, prasugrel) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Not known: Insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)

Vascular disorders

very rare: Vasculitis, hypotension

Blood and lymphatic system disorders

very rare: Serious cases of bleeding, mainly skin, musculo-skeletal (haemarthrosis, haematoma), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), epistaxis, haematuria and haemorrhage of operative wound. Fatal haemorrhage, especially intracranial, gastrointestinal and retroperitoneal haemorrhage.

Cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with aspirin or clopidogrel with aspirin and heparin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Very rare cases of thrombotic thrombocytopenic purpura (TTP) have been reported.

Aplastic anaemia, neutropenia, pancytopenia, bicytopenia, agranulocytosis, granulocytopenia, anaemia, bone marrow failure.

Very rare cases of acquired haemophilia A have been reported.

uncommon: Eosinophilia, leucopenia, decreased neutrophils, decreased platelets, increased bleeding time

Cardiac disorders:

Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction.

Skin and subcutaneous tissue disorders

very rare: Maculopapular, erythematous or exfoliative rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP)), drug-induced hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), eczema, lichen planus.

Psychiatric

very rare: Confusion, hallucinations

Nervous system disorders

very rare: Taste disturbances

Not known: Ageusia

Hepatobiliary disorders

very rare: Hepatitis, acute liver failure

Gastrointestinal disorders

very rare: Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

Respiratory, thoracic and mediastinal disorders

very rare: Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Renal and urinary disorders

very rare: Glomerulopathy, renal failure

Reproductive systems and breast disorders

very rare: Gynaecomastia

Investigations

very rare: Blood creatinine increase, abnormal liver function tests

General disorders and administration site conditions

very rare: Fever, syncope

Aspirin

In addition to some of the adverse reactions listed above, aspirin is associated with the following adverse effects.

Aspirin produces a prolongation of the bleeding time and may produce epigastric distress, nausea and vomiting, gastric or duodenal ulcers and erosive gastritis which may lead to serious gastrointestinal bleeding. These side effects are more likely to occur when higher doses are administered, although they may also occur when low doses are used.

Oesophagitis, oesophageal ulceration, perforation. Erosive gastritis, erosive duodenitis, gastro-duodenal ulcer/perforations, upper gastro-intestinal symptoms such as gastralgia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, colitis and intestinal perforation. These reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patient with or without warning symptoms or a previous history or serious GI events.

Iron deficiency anaemia may develop as a result of occult gastrointestinal bleeding when aspirin is used for long periods of time.

Aspirin may cause intracranial haemorrhage that may be fatal, especially in the elderly.

Aspirin may cause haemolysis, thrombocytopenia or haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Cases of pancytopenia, bicytopenia,

aplastic anaemia, bone marrow failure, agranulocytosis, neutropenia and leukopenia have also been reported.

Vasculitis, including Henoch-Schönlein purpura has been reported.

Aspirin may cause tinnitus, dizziness, vertigo or hearing loss.

Aspirin sensitivity is most commonly manifested by asthma, vasomotor rhinitis, urticaria, angioneurotic oedema and allergic dermatological reactions, hypoglycaemia, gout. As well as anaphylactic shock, aggravation of allergic symptoms of food allergy.

Aspirin may cause an elevation of hepatic enzymes, liver injury, mainly hepatocellular, chronic hepatitis.

Low doses of aspirin have been reported to cause retention of uric acid, whereas high dosage may increase excretion.

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

Aspirin may cause fixed eruption.

Oedema has been reported with higher (anti-inflammatory) doses of aspirin.

Respiratory, thoracic and mediastinal disorder; non-cardiogenic pulmonary oedema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid.

Hypersensitivity to aspirin may cause cardiac disorders (Kounis Syndrome) and acute pancreatitis.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In animals, clopidogrel at single oral doses ≥ 1500 mg/kg caused necrotic-haemorrhagic gastritis, oesophagitis and enteritis in mice, rats and baboons. Necrotic tubulopathy and tubulo-interstitial nephritis were also noted in mice.

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

Aspirin overdosage is manifested by the following symptoms:

Moderate overdose: tinnitus, hearing loss, dizziness, headaches, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

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

In case of severe aspirin overdose, the following actions should be undertaken: admission to hospital is necessary, control of acid-base balance, possibility of haemodialysis or peritoneal dialysis if necessary.

Apart from general measures, treatment of aspirin overdose consists chiefly of measures to accelerate the excretion (forced alkaline diuresis) and to restore the acid-base and electrolyte balance. Infusions of sodium bicarbonate and potassium chloride solutions may be given.

Overdose with salicylates, particularly in young children, can result in severe hypoglycaemia and potentially fatal poisoning.

Non-cardiogenic pulmonary oedema can occur with acute and chronic acetylsalicylic acid overdose (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Clopidogrel

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Platelets have an established role in the pathophysiology of atherosclerotic disease and thrombotic events. Long term use of anti-platelet drugs has shown consistent benefit in the prevention of ischaemic stroke, myocardial infarction and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet ADP receptors, P2Y₁₂, thus inhibiting platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover (approximately 7 days).

Statistically significant and 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 7 days after treatment was discontinued.

Aspirin

Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and the production of thromboxane A₂, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

Clinical trials

The safety and efficacy of clopidogrel and aspirin has been evaluated in patients in three double-blind studies: the CURE, CLARITY, and COMMIT studies, which compared clopidogrel to placebo, both given in combination with aspirin and other standard therapy.

The CURE study included 12,562 patients with acute coronary syndrome (unstable angina or non-ST-elevation myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, n = 6244) or placebo (n = 6287), both given in combination with aspirin (75-325 mg once daily) and other standard therapies (oral anti-coagulants and long term NSAIDs were not permitted). Patients were treated for up to one year.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p = 0.00009) for the clopidogrel-treated group. The benefits of clopidogrel were seen within a few hours and maintained throughout the course of the study (up to 12 months). The primary outcome was reduced to a similar extent within the first 30 days (relative risk reduction of 22 %), from 30 days to one year (relative risk reduction of 19%), and for the entire one year study (relative risk reduction of 20%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1035 (16.5%) in the clopidogrel-treated group and 1187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p = 0.0005) for the clopidogrel-treated group, a benefit which was consistent for each component, indicating that clopidogrel reduced a range of atherothrombotic events.

In the course of the study, patients who underwent cardiac revascularisation (surgical or percutaneous coronary intervention with or without coronary stent implantation), received similar benefit from clopidogrel + aspirin (including standard therapies) as those who did not have a cardiac revascularisation.

The results obtained in populations with different characteristics (e.g. unstable angina or non-ST-elevation MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering drugs, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of aspirin (75-325 mg once daily).

In patients with ST-segment elevation acute myocardial infarction, safety and efficacy of clopidogrel have been evaluated in two randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The randomised, double-blind, placebo-controlled CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomised to receive either clopidogrel (300 mg loading dose, followed by 75 mg/day; n = 1752) or placebo (n = 1739), together with aspirin (150 to 325 mg loading dose followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

The primary endpoint was the occurrence of the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the predischARGE angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge, if prior to Day 8.

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% were 65 years or over. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta-blockers, 54.7% ACE inhibitors and 63% statins.

The number of patients who reached the primary endpoint was 262 (15.0%) in the clopidogrel-treated group and 377 (21.7%) in the placebo group, representing an absolute reduction of 6.7% and a 36% reduction in the odds of the endpoint in favour of treatment with clopidogrel (95% CI: 0.53, 0.76; p<0.001), as shown in [Table 4](#), mainly related to a reduction in occluded infarct-related arteries.

The benefit of clopidogrel on the primary endpoint was consistent across all prespecified subgroups, including patients' age, gender, infarct location and type of fibrinolytic or heparin used.

Table 4 - Event rates for the primary composite endpoint in the CLARITY study

| | Clopidogrel + aspirin N = 1753 | Placebo + aspirin N = 1739 | OR | 95% CI |
|---|---|---|-----------|---------------|
| Number (%) of patients reporting the composite endpoint | 262 (15.0%) | 377 (21.7%) | 0.64 | 0.53, 0.76 |
| Occluded IRA | | | | |
| N (subjects undergoing angiography) | 1640 | 1634 | | |
| n (%) patients reporting endpoint | 192 (11.7%) | 301 (18.4%) | 0.59 | 0.48, 0.72 |

| | Clopidogrel + aspirin N = 1753 | Placebo + aspirin N = 1739 | OR | 95% CI |
|-----------------------------------|---|---|-----------|---------------|
| Death | | | | |
| n (%) patients reporting endpoint | 45 (2.6%) | 38 (2.2%) | 1.18 | 0.76, 1.83 |
| Recurrent MI | | | | |
| n (%) patients reporting endpoint | 44 (2.5%) | 62 (3.6%) | 0.69 | 0.47, 1.02 |

The total number of patients with a component event (occluded IRA, death or recurrent MI) is greater than the number of patients with a composite event because some patients had more than a single type of component event.

The randomised, double-blind, placebo-controlled, 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected myocardial infarction with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients were randomised to receive clopidogrel (75 mg/day) or placebo, in combination with aspirin (162 mg/day), for 28 days or until hospital discharge, whichever came first.

The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The patient population included 27.8% women, 58.4% 60 years or over (26% 70 years or over) and 54.5% patients who received fibrinolytics, 68% who received ACE-inhibitors and 10.9% who received non-trial beta-blockers (as well as half of the patients who received metoprolol as study medication).

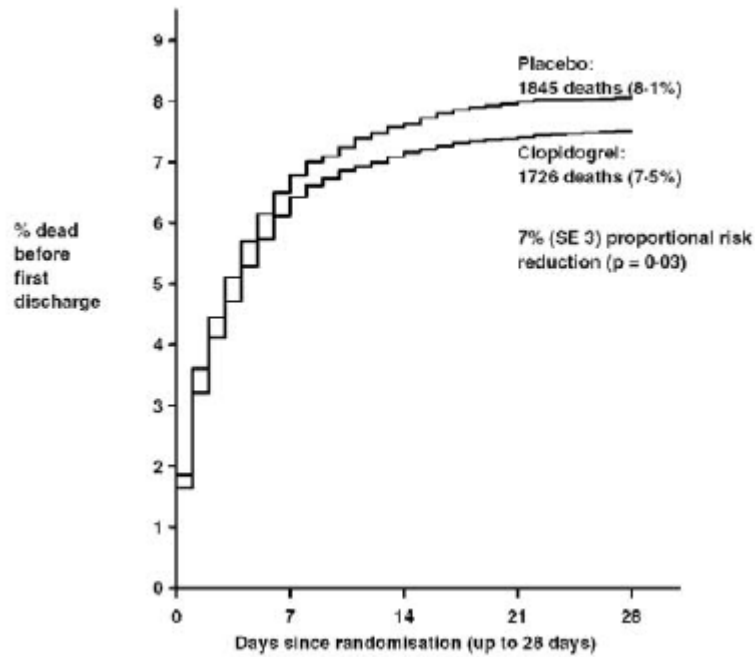
As shown in Table 5, Figure 1 and Figure 2 below, clopidogrel significantly reduced the relative risk of death from any cause by 7% ($p = 0.029$) and the relative risk of the combination of re-infarction, stroke or death by 9% ($p = 0.002$), representing an absolute risk reduction of 5 and 9 patients per 1000 treated (0.5 and 0.9%), respectively.

Table 5 - Outcome events in the COMMIT analysis

| Event | Clopidogrel +aspirin n = 22961 | Placebo +aspirin n = 22891 | Odds ratio (95% CI) | p-value |
|---------------------|---|---|--------------------------------|----------------|
| Composite endpoint: | | | | |
| Death, MI or Stroke | 2121 (9.2%) | 2310 (10.1%) | 0.91 (0.86, 0.97) | 0.002 |
| Death | 1726 (7.5%) | 1845 (8.1%) | 0.93 (0.87, 0.99) | 0.029 |
| Non-fatal MI | 270 (1.2%) | 330 (1.4%) | 0.81 (0.69, 0.95) | 0.011 |
| Non-fatal Stroke | 127 (0.6%) | 142 (0.6%) | 0.89 (0.70, 1.13) | 0.33 |

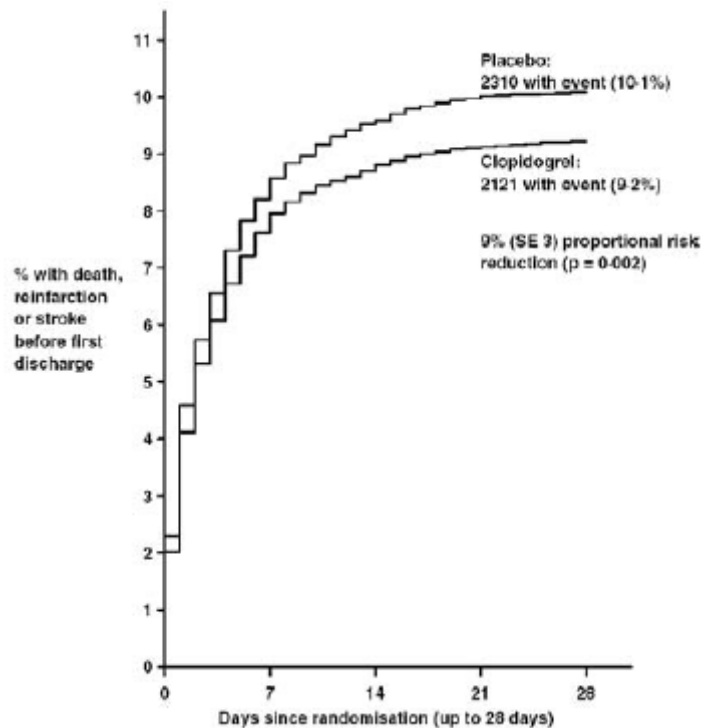
Note: 9 patients (2 clopidogrel and 7 placebo) suffered from both a non-fatal stroke and a non-fatal MI, hence the apparent disparity between composite endpoint and the sum of death, non-fatal MI and non-fatal stroke. Values for non-fatal MI and non-fatal stroke exclude patients who died of any cause.

Figure 1 - Cumulative event rates for death in the COMMIT study*



* All treated patients received aspirin.

Figure 2 - Cumulative event rates for the combined endpoint re-infarction, stroke or death in the COMMIT study*



* All treated patients received aspirin

The benefit associated with clopidogrel on the combined endpoint was consistent across age, gender and with or without fibrinolytics and was observed as early as 24 hours.

The bioequivalence of Clopidogrel Winthrop Plus Aspirin to reference clopidogrel and aspirin tablets has been demonstrated in three open-label, randomised, single-dose, 2-sequence, 2-period, 2-treatment crossover studies. One study was performed with Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg (BDR4659) and two with Clopidogrel Winthrop Plus Aspirin 75 mg/100 mg (BDR5000 and BEQ10600). Study BEQ10600 (Clopidogrel Winthrop Plus Aspirin 75 mg/100 mg) evaluated bioequivalence in 121 young healthy subjects based on clopidogrel and its inactive carboxylic acid metabolite (Table 6), and aspirin and salicylic acid (Table 7). Studies BDR4659 (Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg) and BDR5000 (Clopidogrel Winthrop Plus Aspirin 75 mg/100 mg) evaluated bioequivalence in 40 young healthy subjects based on clopidogrel inactive carboxylic acid metabolite, and aspirin and salicylic acid.

Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to the clopidogrel 75 mg tablets in terms of clopidogrel C_{max} and AUC, and/or carboxylic acid metabolite. For aspirin, Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to aspirin 75 mg and 100 mg, respectively, in terms of aspirin AUC, and salicylic acid C_{max} and AUC. The 90% CIs for these parameters were entirely within the bioequivalence interval [0.80 1.25].

In terms of C_{max} , aspirin was not bioequivalent in the 3 studies, with the C_{max} being 1.3 to 1.6 fold higher for Clopidogrel Winthrop Plus Aspirin than for the aspirin tablets. However, considering the large number of aspirin formulations on the market and the clinical studies evaluating the benefit/risk of clopidogrel in combination with aspirin (see above), a slight difference in aspirin C_{max} is not considered to be clinically significant.

Table 6 - Mean (coefficient of variation %) exposure of clopidogrel and its inactive carboxylic acid metabolite after a single oral dose of Clopidogrel Winthrop Plus Aspirin 75mg/75mg or 75mg/100mg and Plavix 75mg

| Compound | PK parameter | Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg | | | Clopidogrel Winthrop Plus Aspirin 75 mg/100 mg | | | | | |
|----------------------------|-------------------|---|-----------|------------|--|------------------------|------------|-----------------------------------|-------------------------|------------|
| | | BDR4659 | | | BDR5000 | | | BEQ10600 | | |
| | | Clopidogrel Winthrop Plus Aspirin | Plavix | 90%CI | Clopidogrel Winthrop Plus Aspirin | Plavix | 90%CI | Clopidogrel Winthrop Plus Aspirin | Plavix | 90%CI |
| Clopidogrel | C_{max} (ng/mL) | Not assessed | | | Not assessed | | | 2.49 (306) | 2.23 (255) | 0.94; 1.23 |
| | AUC (ng.h/mL) | Not assessed | | | Not assessed | | | 2.74 (210) ^a | 2.72 (189) ^a | 0.92; 1.15 |
| Carboxylic acid metabolite | C_{max} (ng/mL) | 3319 (26) | 3105 (27) | 0.99; 1.17 | 3042 (25) | 2810 (26) | 0.98; 1.20 | 3640 (30) | 3590 (30) | 0.96; 1.06 |
| | AUC (ng.h/mL) | 9215 (29) | 8947 (27) | 0.98; 1.07 | 8059 (19) | 8004 (26) ^a | 0.98; 1.07 | 9830 (25) | 9860 (27) | 0.98; 1.02 |

^an=39; ^bn=110, ^cn=1116

Table 7 - Mean (coefficient of variation %) exposure of aspirin and salicylic acid after a single oral dose of Clopidogrel Winthrop Plus Aspirin 75mg/75mg or 75mg/100mg and aspirin 75mg or 100mg

| Compound | PK parameter | Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg | | | Clopidogrel Winthrop Plus Aspirin 75 mg/100 mg | | | | | |
|----------------|---------------|---|-----------------------|------------|--|------------------------|------------|-----------------------------------|------------------------|------------|
| | | BDR4659 | | | BDR5000 | | | BEQ10600 | | |
| | | Clopidogrel Winthrop Plus Aspirin | Aspirin | 90%CI | Clopidogrel Winthrop Plus Aspirin | Aspirin | 90%CI | Clopidogrel Winthrop Plus Aspirin | Aspirin | 90%CI |
| Aspirin | Cmax (ng/mL) | 1207 (25) | 738 (26) | 1.51; 1.78 | 1492 (26) | 964 (23) | 1.41; 1.69 | 1580 (31) | 1230 (35) | 1.22; 1.39 |
| | AUC (ng.h/mL) | 936 (17) | 826 (22) ^a | 1.10; 1.20 | 1131 (16) ^a | 1007 (21) ^b | 1.08; 1.19 | 1440 (24) ^c | 1300 (22) ^d | 1.07; 1.13 |
| Salicylic acid | Cmax (ng/mL) | 3533 (16) | 3094 (17) | 1.10; 1.20 | 4878 (14) | 4189 (16) | 1.12; 1.22 | 5390 (22) | 5030 (21) | 1.04; 1.10 |
| | AUC (ng.h/mL) | 12217 (21) ^a | 11778 (19) | 1.00; 1.06 | 17791 (32) ^a | 17225 (30) | 1.01; 1.05 | 21700 (29) ^c | 20900 (28) | 1.02; 1.04 |

^an=39; ^bn=37; ^cn=116; ^dn=111

5.2 PHARMACOKINETIC PROPERTIES

Clopidogrel

Absorption

Clopidogrel: after single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Clopidogrel mean peak plasma levels (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 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 and Elimination

Clopidogrel is a prodrug which is extensively hydrolysed in the liver by HCE1 (human carboxylesterase1). In vitro and in vivo, clopidogrel is metabolised according to two main metabolic pathways:

- One mediated by esterases and leading to hydrolysis into its carboxylic acid derivative, which is inactive and is the main circulating metabolite (about 85% of the circulating compound in plasma). Mean peak plasma levels of this metabolite (approx. 3600 ng/ml after single 75 mg oral dose) occurred approximately 45 minutes after dosing. In vitro in the presence of ethyl alcohol, the rate of clopidogrel

hydrolysis was decreased, and some of the clopidogrel was converted to ethyl clopidogrel.

- One mediated by multiple cytochromes P450 in the gastrointestinal tract and liver leading to the active metabolite(s) of clopidogrel, a thiol derivative, which is generated through formation of 2 oxo clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes including CYP3A4, CYP3A5, CYP1A2, CYP2C9, CYP2E1 and CYP2B6. The active thio CYP I metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. Clinical studies have indicated that individuals with loss of function variants of CYP2C9 and CYP2C19 are more likely to have lower concentrations of the active metabolite and higher residual platelet activity; clopidogrel is therefore less likely to be efficacious in these poor metabolisers.

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

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 metabolite was 8 hours after single and repeated administration.

Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (≥ 75 years) as compared to young healthy volunteers. However, these higher plasma levels were not associated with differences in platelet aggregation and bleeding time.

Plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 mL/min) and healthy subjects, after repeated doses of 75 mg/day. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day.

Aspirin

Absorption

Following absorption, the aspirin in Clopidogrel Winthrop Plus Aspirin is hydrolysed to salicylic acid, with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of aspirin are essentially undetectable 1.5 to 4 hours after dosing. Administration of aspirin with meals did not significantly modify its bioavailability.

Distribution

Based on available data, aspirin 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 $\mu\text{g/mL}$), 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.

Metabolism and Elimination

The aspirin in Clopidogrel Winthrop Plus Aspirin is rapidly hydrolysed by HCE2 (human carboxylesterase 2) in the intestine and the liver to salicylic acid, with a half-life of 0.3 to 0.4 hours for aspirin doses from 75 to 100 mg. This salicylic acid has a plasma half-life of approximately 2 hours. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide and a number of minor metabolites. 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 aspirin doses (10 to 20 g), the plasma half-life may be increased to over 20 hours. At high aspirin 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 drug 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.

Clopidogrel/Aspirin Bioequivalence

Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to the clopidogrel 75 mg tablets in terms of clopidogrel C_{max} and AUC, and/or carboxylic acid metabolite. For aspirin, Clopidogrel Winthrop Plus Aspirin 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to aspirin 75 mg and 100 mg, respectively, in terms of aspirin AUC, and salicylic acid C_{max} and AUC. In terms of C_{max} , aspirin was not bioequivalent with the C_{max} being 1.3 to 1.6 fold higher for Clopidogrel Winthrop Plus Aspirin than for the aspirin tablets. However, a slight difference in aspirin C_{max} is not considered to be clinically significant (See Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

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 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). As shown in Table 8, 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 µM 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Table 8 - Active metabolite pharmacokinetics and antiplatelet responses by CYP2C19 metaboliser status

| | Dose | Ultrarapid (n=10) | Extensive (n=10) | Intermediate (n=10) | Poor (n=10) |
|----------------------|----------------|----------------------|---------------------|------------------------|----------------|
| AUClast (ng.h/mL) | 300 mg (Day 1) | 33 (11) | 39 (24) | 31 (14) | 14 (6) |
| | 600 mg (Day 1) | 56 (22) | 70 (46) | 56 (27) | 23 (7) |
| | 75 mg (Day 5) | 11 (5) | 12 (6) | 9.9 (4) | 3.2 (1) |
| | 150 mg (Day 5) | 18 (8) | 19 (8) | 16 (7) | 7 (2) |
| IPA (%) ^a | 300 mg (24 h) | 40 (21) | 39 (28) | 37 (21) | 24 (26) |
| | 600 mg (24 h) | 51 (28) | 49 (23) | 56 (22) | 32 (25) |
| | 75 mg (Day 5) | 56 (13) | 58 (19) | 60 (18) | 37 (23) |
| | 150 mg (Day 5) | 68 (18) | 73 (9) | 74 (14) | 61 (14) |

Values are mean (SD)

^a Inhibition of platelet aggregation with 5µM ADP; larger value indicates greater platelet inhibition

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 µM 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. There have, however, been a number of retrospective analyses to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY TIMI 28 (n=227), TRITON TIMI 38 (n=1477) and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

Special Populations

Geriatric Patients

Plasma concentrations of the main circulating metabolite of clopidogrel are significantly higher in the elderly (≥ 75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients

Clopidogrel Winthrop Plus Aspirin is contraindicated in severe renal impairment. After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75 mg of clopidogrel per day. Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment. Therefore Clopidogrel Winthrop Plus Aspirin should be used with caution in this population (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with Hepatic Impairment

Clopidogrel Winthrop Plus Aspirin is contraindicated in severe hepatic impairment. Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel Winthrop Plus Aspirin should therefore be used with caution in this population (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

CYP2C9 and CYP2C19 Poor Metabolisers

Clinical studies have indicated that individuals with loss of function variants of CYP2C9 and CYP2C19 are more likely to have lower concentrations of the active metabolite and higher residual platelet activity; clopidogrel is therefore less likely to be efficacious in these poor metabolisers.

Gender

No significant difference was observed in the plasma levels of the main circulating metabolite of clopidogrel between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Ethnicity

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Section 5 PHARMACOLOGICAL PROPERTIES, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Clopidogrel was not genotoxic in four in vitro tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts and metaphase chromosome analysis of human lymphocytes) and in one in vivo test (micronucleus test by the oral route in mice).

Aspirin was not genotoxic in bacterial reverse mutation assays or in a recessive lethal mutation assay in *Drosophila*. However, there are conflicting results on the clastogenicity of aspirin in mammalian cells.

Carcinogenicity

There was no evidence of carcinogenic effects when clopidogrel was given in the diet for 78 weeks to mice and 104 weeks to rats at doses up to 77 mg/kg per day (representing an exposure approx. 18 times the anticipated patient exposure, based on plasma AUC for the main circulating metabolite in elderly subjects).

Carcinogenicity studies have not been conducted with aspirin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Clopidogrel Winthrop Plus Aspirin tablets are film coated and each tablet contains mannitol, carnauba wax, macrogol 6000, microcrystalline cellulose, hydrogenated castor oil, hypromellose, maize starch, stearic acid, colloidal anhydrous silica and OPADRY II complete film coating system 32K24375 Pink (ARTG PI No: 12607).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

Clopidogrel Winthrop Plus Aspirin tablets are registered in PA/Al/PVC/Al blister packs containing 30 tablets.

Clopidogrel Winthrop Plus Aspirin is a registered trademark of sanofi-aventis.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Clopidogrel

Clopidogrel hydrogen sulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It is freely soluble in methanol, sparingly soluble in methylene chloride and is practically insoluble in ethyl ether. It has a specific optical rotation of about + 56°.

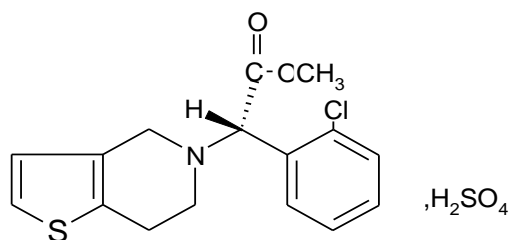
Aspirin

Aspirin is a white crystalline powder or colourless crystals, odourless or almost odourless, slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether. It melts at about 135°C.

Chemical structure

Clopidogrel

Clopidogrel hydrogen sulfate has the following chemical structure:



Molecular Formula: $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$

Molecular Weight: 419.9

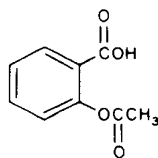
Chemical Name: methyl (+)-(S)- α -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate sulfate (1:1).

CAS number:

120202-66-6 (Clopidogrel hydrogen sulfate), 113 665-84-2 (Clopidogrel base).

Aspirin

Aspirin has the following chemical structure:



Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.2

Chemical Name: 2-acetoxybenzoic acid.

CAS number:

50-78-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription only medicine).

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

Toll Free Number (medical information): 1800 818 806

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

24 September 2009

10 DATE OF REVISION

03 February 2023

SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|------------------|---|
| 4.4 | Addition of drug reaction with eosinophilia systemic symptoms (DRESS). Revisions to precautions for triple anti-platelet therapy and pregnancy |
| 4.5, 4.6 and 5.1 | Editorial changes. |
| 4.6 | Addition of oligohydramnios/neonatal impairment |
| 4.8 | Revision of AE relating to drug reaction with eosinophilia systemic symptoms (DRESS). |