PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] ACT CLOPIDOGREL

Clopidogrel Tablets, USP

75 mg Clopidogrel (as clopidogrel bisulfate), Oral

Platelet Aggregation Inhibitor

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism	02/2023
7 WARNINGS AND PRECAUTIONS, Hematologic	02/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2
TABLE OF CONTENTS 2
PART I: HEALTH PROFESSIONAL INFORMATION 4
1 INDICATIONS 4
1.1 Pediatrics 4
1.2 Geriatrics 4
2 CONTRAINDICATIONS 4
4 DOSAGE AND ADMINISTRATION 5
4.2 Recommended Dose and Dosage Adjustment 5
4.4 Administration 5
4.5 Missed Dose 5
5 OVERDOSAGE 6
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 6
7 WARNINGS AND PRECAUTIONS 7
7.1 Special Populations 10
7.1.1 Pregnant Women 10
7.1.2 Breast-feeding 10
7.1.3 Pediatrics 10
8 ADVERSE REACTIONS 11
8.1 Adverse Reaction Overview 11
8.2 Clinical Trial Adverse Reactions 11
8.5 Post-Market Adverse Reactions 20
9 DRUG INTERACTIONS 22
9.1 Serious Drug Interactions 22
9.2 Drug Interactions Overview 22
9.4 Drug-Drug Interactions 23
9.5 Drug-Food Interactions 29
9.6 Drug-Herb Interactions 29
9.7 Drug-Laboratory Test Interactions 29
10 CLINICAL PHARMACOLOGY 30
10.1 Mechanism of Action 30
10.2 Pharmacodynamics 30
10.3 Pharmacokinetics 33
11 STORAGE, STABILITY AND DISPOSAL 37
12 SPECIAL HANDLING INSTRUCTIONS 37
PART II: SCIENTIFIC INFORMATION 38

13 PHARMACEUTICAL INFORMATION 38
14 CLINICAL TRIALS 39
14.1 Clinical Trials by Indication 39
14.3 Comparative Bioavailability Studies 53
15 MICROBIOLOGY 54
16 NON-CLINICAL TOXICOLOGY 54
17 SUPPORTING PRODUCT MONOGRAPHS 55
PATIENT MEDICATION INFORMATION 56

PART I:HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACT CLOPIDOGREL (clopidogrel bisulfate) is indicated:

- for the secondary prevention of atherothrombotic events (myocardial infarction, stroke and vascular death) in patients with atherosclerosis documented by stroke, myocardial infarction, or established peripheral arterial disease.

- in combination with acetylsalicylic acid (ASA), for the early and long-term secondary prevention of atherothrombotic events (myocardial infarction, ischemic stroke, cardiovascular death and/or refractory ischemia) in patients with acute coronary syndromes - without ST segment elevation (i.e., unstable angina or non-Q-wave myocardial infarction). These benefits of clopidogrel bisulfate have been shown only when these patients were concomitantly treated with ASA in addition to other standard therapies. These benefits were also seen in patients who were managed medically and those who were managed with percutaneous coronary intervention (with or without stent) or CABG (coronary artery bypass graft).

- For patients with ST-segment elevation acute myocardial infarction, clopidogrel bisulfate has been shown to reduce the rate of an endpoint of all-cause mortality and the rate of a combined endpoint of death, re-infarction or stroke.

1.1 Pediatrics

Pediatrics (< 18 years of age):

The safety and efficacy of ACT CLOPIDOGREL in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS).

1.2 Geriatrics

No differences in platelet aggregation or bleeding time were observed in the elderly (≥75 years) volunteers compared to young healthy subjects (see 10 CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

Clopidogrel bisulfate is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete

listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

- Patients with active bleeding such as peptic ulcer and intracranial hemorrhage (ICH).
- Patients with significant liver impairment or cholestatic jaundice.
- Patients who are using repaglinide (see 9 DRUG INTERACTIONS)

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

MI, Stroke or Established Peripheral Arterial Disease

The recommended dose of ACT CLOPIDOGREL is 75 mg once daily long term with or without food.

Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), ACT CLOPIDOGREL should be initiated with a 300 mg loading dose and continued long term at 75 mg once a day with ASA (80 mg-325 mg daily) (see 14 CLINICAL TRIALS).

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of ACT CLOPIDOGREL is 75 mg once daily, administered in combination with ASA, with or without thrombolytics. ACT CLOPIDOGREL may be initiated with or without a loading dose (300 mg was used in CLARITY; see 14 CLINICAL TRIALS).

No dosage adjustment is necessary for elderly patients or patients with renal impairment (see 10 CLINICAL PHARMACOLOGY).

Pharmacogenetics

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metaboliser healthy subjects increases antiplatelet response, an appropriate dose regimen for this patient population has not been established in clinical outcome trials (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

For oral use.

4.5 Missed Dose

If a dose of ACT CLOPIDOGREL is missed, it should be taken as soon as possible. However, if it is close to the time of the next dose, disregard the missed dose and return to the regular dosing schedule. Do not double doses.

5 OVERDOSAGE

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

A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and rats, and at 3000 mg/kg to baboons.

Treatment:

No antidote to the pharmacological activity of clopidogrel has been found. Platelet transfusion may be used to reverse the pharmacological effects of clopidogrel bisulfate when quick reversal is required.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablets, 75 mg	Tablet Core: Hydrogenated vegetable oil, low substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, polyethylene glycol, red iron oxide, Coating: Hypromellose, lactose, polyethylene glycol, red iron oxide and titanium dioxide

ACT CLOPIDOGREL tablets are available as pink, film-coated, round, biconvex tablets with “CP” on one side and “ ” on the other side.

ACT CLOPIDOGREL tablets are available in HDPE bottles of 500 tablets.

7 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery

No impairment of driving or psychometric performance was observed following clopidogrel administration.

Endocrine and Metabolism

Cytochrome P450 2C19 (CYP2C19)

Clopidogrel bisulfate is a pro-drug, which requires metabolism by the hepatic cytochrome CYP2C19 to form the active thiol metabolite. The function of this enzyme can be compromised, either through direct drug inhibition or dysfunctional genetic variants that lower enzyme activity, thus the effectiveness of clopidogrel bisulfate could diminish correspondingly.

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 avoided (see 9 DRUG INTERACTIONS).

Pharmacogenetics – CYP2C19 Poor Metabolisers

In patients who are CYP2C19 poor metabolisers, clopidogrel bisulfate 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 bisulfate at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolisers (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

Use with Proton Pump Inhibitors (PPI)

Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of clopidogrel bisulfate. Avoid use of strong or moderate CYP2C19 inhibitors with clopidogrel bisulfate. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity, or alternative treatment strategies. Pantoprazole, a weak CYP2C19 inhibitor, had less effect on the pharmacological activity of clopidogrel bisulfate than omeprazole (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).

Gastrointestinal

Active GI Lesions

Clopidogrel bisulfate prolongs bleeding time. Although clopidogrel bisulfate has shown a lower incidence of gastrointestinal bleeding compared to ASA in a large controlled clinical trial (CAPRIE), clopidogrel bisulfate should not be used in patients who have lesions with a propensity to bleed. In CURE, the incidence of major GI bleeding was 1.3% versus 0.7% (Clopidogrel bisulfate + ASA versus placebo + ASA, respectively).

In patients taking clopidogrel bisulfate, drugs that might induce GI lesions (such as acetylsalicylic acid and Non-Steroidal Anti-Inflammatory Drugs) should be used with caution.

Hematologic

Bleeding and hematological disorders

As with other antiplatelet agents, when considering prescribing clopidogrel bisulfate, physicians should inquire whether the patient has a history of bleeding. Clopidogrel bisulfate should be used with caution in patients who may be at risk of increased bleeding from recent trauma, surgery or other pathological condition(s), and in patients receiving treatment with acetylsalicylic acid, heparin, glycoprotein IIb/IIIa inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers.

Due to the increased risk of bleeding (including severe bleeding), triple antiplatelet therapy (Clopidogrel + aspirin + dipyridamole) for stroke secondary prevention should be avoided in patients with acute non-cardioembolic ischemic stroke or transient ischemic attack (TIA) (see 9 DRUG INTERACTIONS).

Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel bisulfate should be undertaken with caution (see 9 DRUG INTERACTIONS).

Due to the risk of bleeding and hematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever such suspected clinical symptoms arise during the course of treatment (see 8 ADVERSE REACTIONS).

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

In patients with recent TIA or stroke and who are at high risk of recurrent ischemic events, the combination of ASA and clopidogrel bisulfate has not been shown to be more effective than clopidogrel alone, but the combination has been shown to increase major bleeding (see 9 DRUG INTERACTIONS). Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

Platelet transfusion may be used to reverse the pharmacological effects of clopidogrel bisulfate when quick reversal is required.

Thrombotic thrombocytopenic purpura (TTP) has been reported rarely following the use of clopidogrel bisulfate, but it can occur anytime during the first year of exposure. Few cases have been reported after more than one year of exposure. TTP is a potentially fatal condition requiring prompt treatment with plasmapheresis. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological findings, renal dysfunction, and fever.

Acquired hemophilia has been reported following use of clopidogrel, manifesting as a marked increase in bleeding or bruising. In cases of confirmed isolated activated partial thromboplastin time (aPTT) prolongation with or without bleeding, acquired hemophilia should be considered. Patients with a confirmed diagnosis of acquired hemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Hepatic/Biliary/Pancreatic

Experience is limited in patients with moderate hepatic impairment who may have bleeding diatheses. As with any patient exhibiting hepatic impairment, liver function should be carefully monitored and clopidogrel bisulfate should be used with caution.

In the CAPRIE study, there were 344 hepatically impaired patients (Alkaline phosphatase > 300 U/L, or ALT > 120 U/L, or AST > 75 U/L) and 168 received clopidogrel for a mean duration of 18 months. The adverse events were more common in this population, compared to the rest of the CAPRIE population, and more common in the clopidogrel (N=168) than in the ASA (N=176) group (any bleeding disorders, N=17 vs N=14; any rash, N=11 vs N=6; diarrhea, N=8 vs N=3, respectively).

Immune

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 8 ADVERSE REACTIONS). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or hematological reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or hematological 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.

Sensitivity to lactose

Clopidogrel bisulfate contains lactose. Patients with rare hereditary problems of galactose

intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see 2 CONTRAINDICATIONS).

Peri-Operative Considerations

If a patient is to undergo elective surgery, consideration should be given to discontinue clopidogrel bisulfate 5 to 7 days prior to surgery to allow for a reversal of its effect (see 10 CLINICAL PHARMACOLOGY and 14 CLINICAL TRIALS).

Renal

Therapeutic experience with clopidogrel is limited in patients with severe and moderate renal impairment. Therefore clopidogrel bisulfate should be used with caution in these patients.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women.

Reproduction studies have been performed in rats at doses ≤500 mg/kg per day and in rabbits at doses ≤300 mg/kg per day and have revealed no evidence of impaired fertility or harm to the fetus due to clopidogrel. Because animal reproduction studies are not always predictive of a human response, clopidogrel bisulfate should be used during pregnancy only if the potential benefits outweigh the potential risks to the fetus.

7.1.2 Breast-feeding

When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Studies in rats have also shown that clopidogrel and/or its metabolites are excreted in milk. It is not known whether this drug is excreted in human milk (see 16 NON-CLINICAL TOXICOLOGY, Teratogenicity and impairment of fertility). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to a nursing woman.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of clopidogrel bisulfate in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

In a randomized, placebo-controlled trial (CLARINET) involving 906 neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt, clopidogrel did not demonstrate a clinical benefit.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of clopidogrel has been evaluated in clinical trials in more than 44,000 patients including over 1,200 patients treated for ≥1 year and further assessed during post-marketing experience.

The most frequent adverse drug reactions (≥ 1%) with clopidogrel bisulfate (with or without associated ASA) in controlled clinical trials were hemorrhage and bleeding disorders including purpura, any rash, dyspepsia, abdominal pain and diarrhea (see "8.2 Clinical Trial Adverse Reactions").

The most serious adverse drug reactions from controlled clinical trials rarely reported (<1%) were bleeding and clotting disorders including gastrointestinal hemorrhage, hemorrhagic ulcer and hemothorax.

Blood disorders: agranulocytosis / granulocytopenia, aplastic anemia, neutropenia and thrombocytopenia.

Gastrointestinal system disorders: Duodenal, gastric or peptic ulcer, gastritis.

Skin disorders: Any rash and bullous eruption.

The overall incidence of study drug discontinuation because of adverse events was similar in both groups in CAPRIE (clopidogrel bisulfate 11.9% and ASA 11.9%). In CURE, study drug discontinuation occurred in 5.8% of patients with clopidogrel bisulfate plus ASA and 3.9% of patients with placebo plus ASA. In CLARITY, study drug discontinuation was greater in the placebo group (8.6%) compared with the clopidogrel group (6.9%). In COMMIT, the overall incidence of discontinuations was similar between the two treatment groups (2.4% in the clopidogrel group versus 2.2% in the placebo group).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Of the patients who participated in the CAPRIE, CURE and CLARITY double-blind international

clinical trials, approximately 50% were elderly patients (> 65 years) and 15% were ≥75 years. In COMMIT study, approximately 58% of the patients treated with clopidogrel bisulfate were ≥60 years, 26% of whom were ≥70 years.

CAPRIE:

With few exceptions (see Table 1) the overall tolerability of clopidogrel bisulfate was similar regardless of age, sex and race. However, in women there was a slightly higher incidence of bleeding disorders in the clopidogrel group (11.36% vs 9.88%).

Clinically Important Adverse Events

The clinically important adverse events observed in CAPRIE were the following.

Bleeding and clotting disorders: One case of Henoch-Schönlein purpura (acute visceral symptoms: vomiting, diarrhea, abdominal distension, hematuria, renal colic) was reported in a patient taking clopidogrel bisulfate. The patient recovered without sequellae within one month. The incidence of severe thrombocytopenia (<80 G/L) was 0.2% on clopidogrel and 0.1% on ASA; very rare cases of platelet count ≤ 30,000/mm^3 have been reported. The overall incidence of bleeding on clopidogrel and ASA was the same (9.3%). The incidence of severe cases was 1.4% and 1.6% in the clopidogrel and ASA groups respectively. The overall incidence of other bleeding disorders was higher in the clopidogrel group (7.3%) compared to ASA (6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs 0.4%).

Severe neutropenia (<0.450G/L) was observed in four patients (0.04%) on clopidogrel and two patients (0.02%) on ASA.

Two of the 9,599 patients who received clopidogrel and none of the 9,586 patients who received ASA had a neutrophil count of zero. Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel has a fever or demonstrates other sign of infection.

One case of aplastic anemia occurred on clopidogrel treatment.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel bisulfate was 27.1%, compared to 29.8% in those receiving ASA. The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for clopidogrel bisulfate and 4.0% for ASA.

Hepatic and biliary disorders: The overall incidence of hepatic and biliary disorders was similar in patients treated with clopidogrel (3.5%) compared to ASA (3.4%). The most frequent events were increased liver enzymes and bilirubinemia.

Skin disorders: The incidence of skin and appendage disorders in patients receiving clopidogrel bisulfate was 15.8% (0.7% serious); the corresponding rate in ASA patients was 13.1% (0.5% serious). There was no notable difference between treatment groups in the incidence of bullous eruptions (0.23% clopidogrel bisulfate versus 0.16% ASA). One case of a severe bullous eruption was reported in a patient taking clopidogrel bisulfate. The overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for clopidogrel bisulfate and 0.8% for ASA.

A summary of the clinically relevant adverse effects observed in CAPRIE are presented in Table 2 below. In CAPRIE, patients with a known intolerance to ASA were excluded from the study.

Table 2 – Summary of Adverse Events occurring in ≥ 1% of Clopidogrel Bisulfate patients in CAPRIE Trial

Adverse event	Clopidogrel Bisulfate n= 9599 (%)	ASA n= 9586 (%)
Body as a Whole		
Accidental / Inflicted Injury	7.9	7.3
Chest pain	8.3	8.3
Influenza-like symptoms	7.5	7
Fatigue	3.3	3.4
Pain	6.4	6.3
Cardiovascular		
Dependent Edema	1.2	1.3
Edema	1.0	1.2
Heart and rhythm disorder	4.3	5.0*
Hypertension	4.3	5.1
Peripheral edema	1.2	1.6
Central Nervous System		
Dizziness	6.2	6.7
Headache	7.6	7.2
Endocrine and Metabolism		
Hypercholesterolemia	4.0	4.4
Gastrointestinal		
Any Event	27.1	29.8
Abdominal pain	5.6	7.1*
Constipation	2.4	3.3*
Diarrhea	4.5*	3.4
- severe[(1)]	0.2	0.1
- leading to discontinuation[(1)]	0.4	0.3
Dyspepsia	5.2	6.1*
Flatulence	1.0	1.1
Nausea	3.4	3.8

Adverse event	Clopidogrel Bisulfate n= 9599 (%)	ASA n= 9586 (%)
Vomiting	1.3	1.4
Genitourinary		
Urinary tract infection	3.1	3.5
Hemorrhages or bleeding		
Epistaxis	2.9	2.5
Hematoma	1.6	1.5
Gastrointestinal hemorrhage	2.0	2.7*
- requiring hospitalization	0.7	1.1
Purpura (primarily bruising & ecchymosis)	5.3*	3.7
Musculoskeletal		
Arthralgia	6.3	6.2
Back pain	5.8	5.3
Psychiatric Disorder		
Depression	3.6	3.9
Skin		
Any Event	15.8	13.1
Pruritus	3.3*	1.6
Rash	4.2*	3.5
- severe (1)	0.1	0.1
- leading to discontinuation (1)	0.5	0.2
Respiratory		
Bronchitis	3.7	3.7
Coughing	3.1	2.7
Dyspnea	4.5	4.7
Rhinitis	4.2	4.2
Upper respiratory tract infection	8.7	8.3

*: Statistically significant difference between treatments ($p \leq 0.05$).

(1): Patients may be included in more than one category.

No clinically relevant events other than those observed in CAPRIE have been reported with a frequency ≥ 2.5% during the CURE, CLARITY and COMMIT controlled studies.

The number of patients discontinuing due to adverse reactions in CAPRIE are shown in Table 3.

Table 3 - Patients Discontinued because of Adverse Experiences in CAPRIE (number and percentage of patients)

Adverse Experience	Study drug permanently discontinued	
	Clopidogrel Bisulfate n=9599 (%)	ASA n=9586 (%)
Rash	0.9	0.41*
Diarrhea	0.42	0.27
Indigestion / nausea / vomiting	1.9	2.41*
Any bleeding disorder	1.2	1.37
Intracranial hemorrhage	0.21	0.33
Gastrointestinal hemorrhage	0.52	0.93*
Abnormal liver function	0.23	0.29

* statistically significant, $p<0.05$

CURE:

In CURE, clopidogrel bisulfate was given with ASA and was not associated with a significant increase in life-threatening or fatal bleeds compared to placebo given with ASA; the incidences of non-life threatening major bleeding and minor bleeding were significantly larger in the clopidogrel bisulfate + ASA group. The incidence of intracranial hemorrhage was 0.1% in both groups. The principal sites for major bleeding were primarily gastrointestinal and at arterial puncture sites. In patients receiving both clopidogrel bisulfate and ASA in CURE, the incidence of bleeding is described in Table 4 below:

Table 4 – Incidence of Bleeding Complications (% patients) – CURE Trial

Event	CLOPIDOGREL Bisulfate + ASA* (N=6259)	PLACEBO + ASA* (N=6303)	p-value
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	
Hemorrhagic strokes	0.1	0.1	
Requiring inotropes	0.5	0.5	
Requiring transfusions (≥ 4 units)	1.2	1	
Other major bleeding	1.6	1	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Major bleeding†	3.7‡	2.7§	0.001
Minor bleeding¶	5.1	2.4	<0.001
Total with bleeding complications	8.5	5	<0.001

* Other standard therapies were used as appropriate. All patients received ASA 75-325 mg daily (mean=160 mg)

† Life threatening and other major bleeding necessitating transfusion of ≥ 2 units of blood.

‡ Major bleeding event rate for clopidogrel bisulfate + ASA was dose-dependent on ASA: < 100 mg = 2.6%; 100-200 mg = 3.5%; > 200 mg = 4.9%.

§ Major bleeding event rate for placebo + ASA was dose-dependent on ASA: < 100 mg = 2.0%; 100-200 mg = 2.3%; > 200 mg = 4.0%.

¶ Led to interruption of study medication.

The number of patients with bleeding that met the criteria for major bleeding established by the Thrombolysis in Myocardial Infarction (TIMI) trial was 68 (1.09%) in the clopidogrel group and 73 (1.16%) in the placebo group (relative risk, 0.94; p=0.70). The number with bleeding that met the criteria for life-threatening or severe bleeding established by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUST) trial was 78 in the clopidogrel group and 70 in the placebo group (relative risk, 1.12; p=0.48). Some patients had more than one bleeding episode.

Ninety-two percent (92%) of the patients in the CURE study received unfractionated or low

molecular weight heparin, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% clopidogrel bisulfate + ASA; 5.3% placebo + ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel bisulfate + ASA, 6.3% for placebo + ASA, which was not significantly different.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received clopidogrel bisulfate in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to clopidogrel bisulfate. In general, the incidence of these events was similar to that in patients receiving ASA (in CAPRIE) or placebo + ASA (in CURE).

Body as a whole: Allergic reaction and necrosis ischemic.

Cardiovascular disorders: Edema generalized.

Gastrointestinal system disorders: Gastric ulcer perforated, gastritis hemorrhagic and upper GI ulcer hemorrhagic.

Liver and biliary system disorders: Bilirubinemia, hepatitis infectious and liver fatty.

Platelet, bleeding and clotting disorders: Hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary embolism, pulmonary hemorrhage, purpura allergic.

Red blood cell disorders: Anemia aplastic, anemia hypochromic.

Reproductive disorders, female: Menorrhagia.

Respiratory system disorders: Hemothorax.

Skin and appendage disorders: Bullous eruption, rash erythematous, rash maculopapular, urticaria.

Urinary system disorders: Abnormal renal function, acute renal failure.

White cell and reticuloendothelial system disorders: Agranulocytosis, granulocytopenia, leukemia.

Other clinically relevant adverse drug reactions pooled from CAPRIE and CURE studies, or observed in other studies, with an incidence > 0.1% as well as serious and relevant adverse drug

reactions with an incidence < 0.1% are presented below:

Central and peripheral nervous system disorders:

Uncommon: Dizziness, paresthesia

Rare: Vertigo

Gastrointestinal system disorder:

Common: Abdominal pain, diarrhea, dyspepsia

Uncommon: Constipation, duodenal ulcer, flatulence, gastric ulcer, gastritis, nausea, vomiting

Platelet bleeding and clotting disorders:

Uncommon: Bleeding time increased, platelets decreased

Very rare: Thrombotic thrombocytopenic purpura (TTP)

Skin and appendages disorders:

Uncommon: Rash, pruritus

White cell and RES disorders:

Uncommon: leucopenia, neutrophils decreased, eosinophilia

CLARITY:

In CLARITY, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin > 5 g/dL) was similar between groups (1.3% versus 1.1% in the clopidogrel bisulfate + ASA and in the placebo + ASA 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 bisulfate + ASA and in the placebo + ASA groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

COMMIT:

The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 5 below:

Table 5 – Number (%) of Patients with Bleeding Events in COMMIT

Type of bleeding	Clopidogrel bisulfate (+ ASA) (N = 22961)	Placebo (+ ASA) (N = 22891)	P-value
Major* noncerebral or cerebral bleeding**	134 (0.6%)	125 (0.5%)	0.59
Major noncerebral	82 (0.4%)	73(0.3%)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.90
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.81
Other noncerebral bleeding (non-major)	831 (3.6%)	721 (3.1%)	0.005
Any noncerebral 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

** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for clopidogrel bisulfate + ASA by age were <60 years = 0.3%, ≥ 60 to <70 years = 0.7%, ≥ 70 years 0.8%. Event rates for placebo + ASA by age were: <60 years = 0.4%, ≥ 60 to <70 years = 0.6%, ≥ 70 years 0.7%.

8.5 Post-Market Adverse Reactions

The following additional adverse reactions were reported in marketed use, however a causal relationship with clopidogrel has not been clearly established.

Frequencies for the following adverse reactions are not known (cannot be estimated from available data).

Blood and lymphatic system disorders:

Agranulocytosis, acquired hemophilia A, aplastic anemia/pancytopenia; cases of bleeding with fatal outcome (especially gastrointestinal, intracranial and retroperitoneal hemorrhage); serious cases of bleeding, mainly eye (conjunctival, ocular, retinal), musculo-skeletal, respiratory tract and skin bleeding, epistaxis, hematuria and hemorrhage of operative wound, hematoma; acquired hemophilia, thrombotic thrombocytopenic purpura (TTP). Some cases of TTP resulted in fatal outcomes (see 7 WARNINGS AND PRECAUTIONS).

Cardiovascular disorders:

- Hypotension, often related to bleeding or allergic reaction.
- Kounis syndrome (vasospastic allergic angina or allergic myocardial infarction) in the context of a hypersensitivity or anaphylactoid/anaphylactic or reaction due to clopidogrel

Gastro-intestinal disorders:

Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis.

General disorders and administration site conditions:

Fever.

Hepato-biliary disorders:

Hepatitis, abnormal liver function test, acute liver failure.

Immune System disorders:

Anaphylactoid reactions, serum sickness.

Cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see 7 WARNINGS AND PRECAUTIONS).

Insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with human leukocyte antigen (HLA) DRA4 subtype (more frequent in the Japanese population).

Musculo-skeletal, connective tissue and bone disorders:

Arthralgia, arthritis, myalgia.

Nervous System disorders:

Taste disturbances, ageusia.

Psychiatric disorders:

Confusion, hallucinations.

Renal and urinary disorders:

Glomerulopathy, elevated blood creatinine.

Respiratory, thoracic and mediastinal disorders:

Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia.

Skin and subcutaneous tissue disorders:

Acute generalised exanthematous pustulosis [AGEP]), angioedema, bullous dermatitis (erythema multiforme), drug-induced hypersensitivity syndrome, drug rash with eosinophilia

and systemic symptoms (DRESS), eczema, lichen planus, maculopapular, erythematous or exfoliative rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

Vascular disorders:

Vasculitis.

Reproductive systems and breast disorders:

Gynecomastia.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• **Concomitant treatment with repaglinide (see 9.4 Drug-Drug Interactions)**

9.2 Drug Interactions Overview

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 7 WARNINGS AND PRECAUTIONS)

CYP2C19 Mediated Interactions

Clopidogrel bisulfate is metabolized to its active metabolite mostly by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in altered plasma concentrations of the active metabolite of clopidogrel bisulfate and a change in platelet inhibition. See Table 6 for drugs that inhibit CYP2C19 activity.

Anticoagulant drugs

In view of the possible increased risk of bleeding, anticoagulant drugs should be used with caution as tolerance and safety of simultaneous administration with clopidogrel bisulfate has not been established. **Risk factors should be assessed for individual patients before using clopidogrel bisulfate**.

Other concomitant therapy

CYP2C8 substrate drugs

Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers (see Table 7, below). In vitro studies have shown the increase in repaglinide exposure is due to strong inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Concomitant use of clopidogrel with repaglinide is contraindicated (see 2 CONTRAINDICATIONS).

Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and other drugs primarily cleared by CYP2C8 metabolism (e.g. paclitaxel) should be undertaken with caution.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 – Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
ASA	CT	Potentiated effect of ASA on collagen-induced platelet aggregation.	ASA (2 x 500 mg once) did not modify clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Potential increased risk of gastrointestinal bleeding with concomitant administration of ASA. Clopidogrel bisulfate (75 mg) and ASA (75-325 mg) have been administered together for up to 1 year. As a pharmacodynamic interaction between clopidogrel and ASA is possible, concomitant use should be undertaken with caution. In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of ASA and clopidogrel bisulfate has not been shown to be more effective than clopidogrel bisulfate alone, but the combination has been shown to increase major bleeding.
ASA and dipyridamole	CT	Increased major bleeding	The use of triple antiplatelet therapy with clopidogrel, ASA and dipyridamole for the secondary prevention of stroke in patients with acute non-cardioembolic stroke or TIA resulted in an increase in major bleeding. The use of clopidogrel in combination with ASA and dipyridamole should be avoided (see 7 WARNINGS AND PRECAUTIONS, Hematologic)

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
Glycoprotein IIb/IIIa inhibitors	T		As a pharmacodynamic interaction is possible, concomitant use should be undertaken with caution.
Inducers of CYP2C19 (e.g. rifampin)	T	Increased drug levels of the active metabolite of clopidogrel	Since clopidogrel is metabolized 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. Rifampin 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 avoided** (see 7 WARNINGS AND PRECAUTIONS).

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
Inhibitors of CYP2C19 (e.g. Proton Pump inhibitor omeprazole, pantoprazole)	CT	Reduced drug levels of the active metabolite of clopidogrel clopidogrel 300/75mg + 80 mg omeprazole: Day 1: Active metabolite: ↓46% Cmax, ↓45% AUC; ↓39% Platelet inhibition; Day 5: Active metabolite: ↓42% Cmax; ↓40% AUC; ↓21% Platelet inhibition clopidogrel 300/75mg 80 mg pantoprazole: Day 1: Active metabolite: ↓24% Cmax; ↓20% AUC; ↓15% Platelet inhibition; Day 5: Active metabolite: ↓28% Cmax; ↓14% AUC; ↓11% Platelet inhibition	Since clopidogrel is metabolized to its active metabolite mostly 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. The use of strong or moderate CYP2C19 inhibitors should be discouraged in patients taking clopidogrel. If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole. Inhibitors of CYP2C19 include but are not limited to omeprazole, esomeprazole, lansoprazole, cimetidine, ticlopidine, fluvoxamine, fluoxetine, moclobemide, felbamate, chloramphenicol, ketoconazole.

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
Injectable Anticoagulants (e.g. heparin)	CT	No effect	Clopidogrel at steady state did not modify effect of heparin on coagulation in healthy volunteers. Co-administration of heparin had no effect on platelet aggregation inhibition induced by clopidogrel bisulfate. As a pharmacodynamic interaction between clopidogrel and heparin is possible, concomitant use should be undertaken with caution.
NSAIDs	T	↑ occult gastrointestinal blood loss (with naproxen co-administration)	Potential increased risk of gastrointestinal bleeding with concomitant administration of NSAIDS. NSAIDS and clopidogrel should be co-administered with caution.
Opioids (e.g. morphine)	CT	In a published study, co-administration of 5 mg intravenous morphine with 600 mg loading dose of clopidogrel in healthy adults decreased the AUC and C_{max} of clopidogrel's thiol metabolites by 34%.	**As with other oral P2Y12 inhibitors, co-administration of opioid agonists delays and reduces the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites.** 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.**
Oral Anticoagulants (e.g. warfarin)	T		Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution (See 7 Warnings and Precautions).

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
Repaglinide (a substrate of CYP2C8)	CT	A single dose of 0.25 mg repaglinide, administered 1 hr following a loading dose of 300 mg clopidogrel, and then 1 hr after a dose of 75 mg clopidogrel at steady-state, resulted in ↑ in repaglinide AUC of 5.1-fold and 3.9-fold, respectively.	Concomitant administration of clopidogrel and repaglinide is contraindicated (see 2 CONTRAINDICATIONS).
Rosuvastatin	CT	Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (C_{max}) after administration of a 300 mg clopidogrel dose. Eight days after initiation of clopidogrel administration (300 mg loading dose followed by 75 mg daily for 7 days) rosuvastatin exposure was increased by 1.4-fold (AUC) without effect on C_{max}.	The dose of rosuvastatin should not exceed 20 mg daily when used concomitantly with clopidogrel
Selective Serotonin Reuptake Inhibitors (SSRIs)	C	Affect platelet activation and increase the risk of bleeding. Also see above, effect on CYP2C19.	The concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
Thrombolytics	C		The safety of the concomitant administration of clopidogrel, rt-PA and heparin was assessed in patients with recent myocardial infarction. Based on historical data, the incidence of clinically significant bleeding was similar to that observed when rt-PA and heparin are co-administered with acetylsalicylic acid.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

No clinically significant pharmacodynamics interactions were observed when clopidogrel was co-administered with antacids, atenolol, cimetidine, digoxin, estrogens, nifedipine, phenobarbital and theophylline.

Antacids did not modify the extent of clopidogrel absorption.

9.5 Drug-Food Interactions

There is no interaction of clopidogrel bisulfate with food since administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

None known.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The role of platelets in the pathophysiology of atherosclerotic disease and atherothrombotic events has been established. Long-term prophylactic use of antiplatelet drugs has shown consistent benefit in the prevention of ischemic stroke, myocardial infarction, unstable angina, peripheral arterial disease, need for vascular bypass or angioplasty, and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis. Clopidogrel bisulfate is a specific inhibitor of adenosine-diphosphate (ADP)-induced platelet aggregation.

10.2 Pharmacodynamics

Clopidogrel is a potent inhibitor of platelet aggregation, active *in vivo* against a large spectrum of inducers. Due to this antiaggregating effect, clopidogrel has a powerful antithrombotic activity in various models of thrombosis and prolongs bleeding time; it also inhibits the development of myointimal hyperplasia after injury of the vascular endothelium by preventing platelet adhesion.

The pharmacological profile of clopidogrel can be summarized as follows:

- *Antiaggregating effect*: after administration to various animal species, clopidogrel inhibits platelet aggregation induced by ADP and other agonists which release ADP from platelet storage. Clopidogrel is not active "*in vitro*". The failure to identify an active metabolite in plasma and the long lasting effect on platelets indicate that after hepatic metabolization, the active entity formed (probably a labile and highly reactive derivative) interacts rapidly with platelets and induces an irreversible modification at the level of ADP receptor.

- *Hemostasis*: a dose dependent prolongation of bleeding time was observed after clopidogrel treatment. This effect is related to the antiaggregating activity, as clopidogrel has no anticoagulant or fibrinolytic activity.

- *Thrombosis*: clopidogrel inhibits thrombus formation in a large variety of models. This is consistent with the capacity of clopidogrel to reduce aggregation induced by various agonists. The onset of the antithrombotic effect of clopidogrel and its potency closely correlate with those described for its antiaggregating activity.

- *Atherogenesis*: Clopidogrel reduces the development of intimal hyperplasia after injury of the endothelium. This effect is mainly due to the inhibition of platelet adhesion and of the release of platelet-derived growth factors at the site of vascular injury.

Studies to determine the general pharmacological properties of clopidogrel were carried out on

major systems including: the central nervous system (mouse, rat); autonomic nervous system (dog); cardiovascular system (rat, dog); respiratory system (dog, guinea pig); gastrointestinal system (mouse, rat); and urinary system (rat). The anti-inflammatory activity (rat) was also tested.

Minor side effects appeared only at high dose levels (≥ 62.5 mg/kg). (See Table 7 below). The high ratio between these doses and the antiaggregating doses active against thrombosis (ED50 ~ 1 to 5 mg/kg), indicates a wide margin of safety for clopidogrel.

Table 7 – Summary of the main general pharmacodynamic effects of clopidogrel

SYSTEM	SPECIES	DOSE (mg/kg)	EFFECTS
Nervous	Mouse	oral 250	Slight analgesic effect of peripheral origin (20-30%[a])
	Mouse	oral 62.5-250	Slight potentiation of barbiturate-induced narcosis (15-40%[a])
	Rat	oral 125-250	Slight EEG changes (similar to those induced by a nootropic agent)
Cardiovascular	Dog	ID[c] 125-250	Decrease in cardiac output (-15 to 25%[b])
Respiratory	Dog	ID[c] 62.5-250	Slight increase in respiratory frequency (5-7 cycles/min.[b])
	Guinea pig	ID[c] 250	Moderate and transient antagonistic effect on serotonin-induced bronchospasm
Gastro-intestinal	Rat	oral 200	Decrease (-36%[a]) in gastric emptying

a : Modification versus mean value of control group
b : Modification versus values before administration
c: ID = intraduodenal route

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

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

Clopidogrel does not inhibit phosphodiesterase activity. Acetylsalicylic acid (ASA) inhibits the cyclooxygenase enzyme pathway preventing the production of prostaglandin and thus, the synthesis of thromboxane A2 which induces platelet aggregation. Clopidogrel acts on the ADP receptor and ASA acts on a separate receptor thereby inhibiting different pathways of platelet activation and aggregation. Therefore, there is potential for synergy between the two agents.

Clopidogrel acts by modifying irreversibly the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan (approximately 7 – 10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Single administration is not sufficient to reach a desired therapeutic effect. 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 inhibition of ADP-induced platelet aggregation from the first day. Steady state was reached between Day 3 and Day 7. At steady state, with a dose of 75 mg per day, the average inhibition level observed was between 40% and 60%. The aggregation level and bleeding time gradually returned to baseline values within 5-7 days after treatment was discontinued. The precise correlation between inhibition of platelet aggregation, prolongation of bleeding time and prevention of atherothrombotic events has not been established. The effect of a loading dose has been clinically evaluated in the CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events). The benefits of clopidogrel with concomitant ASA were apparent within 24 hours after randomization in the CURE trial.

10.3 Pharmacokinetics

The main pharmacokinetic parameters for clopidogrel are presented in the table below.

	Cmax	**$t_{½}$ (h)**	**AUC $_{0-\infty}$**
Single Dose mean	2.2 – 2.5 ng/mL	6 h	2.7 ng.·h/L

The pharmacokinetics of clopidogrel after single oral administration was studied in the rat and monkey. The oral absorption of clopidogrel in rats was complete while in monkeys it was estimated to be about 80%. The plasma concentration of clopidogrel was higher in female than in male rats. In the 20-400 mg/kg clopidogrel dose range, the rat plasma concentrations of clopidogrel increased proportionally with the dose administered, while in monkeys it increased more than proportionally with the dose. Following administration of ^{14}C-labeled clopidogrel in rats, the excretion of radioactivity was mainly by feces (through the bile) while in monkeys radioactivity was roughly equally excreted in urine and feces. Distribution of ^{14}C-labeled clopidogrel was studied in rats and radioactivity was found mainly in excretory organs and the pancreas. The transfer of radioactivity across the blood brain barrier was low. During gestation, low levels of radioactivity were found in the embryo or foetuses and placenta. There were three primary metabolic pathways of clopidogrel in rats and monkeys: (i) hydrolysis of the ester group by carboxylesterases, (ii) sulfoxidation and (iii) oxidation of the tetrahydropyridine.

Absorption

After single and repeated oral doses of 75 mg/day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/mL after a single 75-mg oral dose) occurred approximately 45 minutes after dosing.

Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Distribution:

Clopidogrel and the main circulating (inactive) metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is non saturable *in vitro* up to a concentration of 100 µg/mL.

Metabolism:

Clopidogrel is extensively metabolized by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2- oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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

Elimination

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of the radiolabel with a half-life of 11 days.

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. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include, but are not

limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese.

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). Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see Table 8). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Table 8 – Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metaboliser Status (healthy subjects)

	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 (%)*	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), * 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 bisulfate-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 was decreased with differences in inhibition of platelet aggregation (IPA) of 6% for intermediate metabolisers and 21% for poor metabolisers, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes has been evaluated in several retrospective analyses. In TRITON-TIMI 38 (n=1477) and 3 of the cohort studies (total n = 3516), carriers of a reduced function CYP2C19 allele (intermediate or poor metaboliser) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis

compared to extensive metabolizers. In another retrospective analysis (CHARISMA, n = 2428) and one cohort study (n=2208), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

Special Populations and Conditions

- **Pediatrics**

  No information available.

- **Geriatrics**

  In elderly (≥ 75 years) volunteers compared to young healthy subjects, there were no differences in platelet aggregation and bleeding time (See 4 DOSAGE AND ADMINISTRATION). No dosage adjustment is needed for the elderly.

- **Sex**

  In a small study comparing men and women (N=10 males and 10 females), less inhibition of ADP-induced platelet aggregation was observed in women. In the CAPRIE study (Clopidogrel versus ASA in Patients at Risk of Ischemic Events; for details see below), the incidence of clinical outcome events was similar in men and women.

- **Ethnic Origin**

  The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see 10 CLINICAL PHARMACOLOGY). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

- **Hepatic Insufficiency**

  After repeated doses of clopidogrel 75 mg/day for 10 days in patients with Class A or B hepatic cirrhosis (mild to moderate hepatic impairment), slightly higher main active circulating metabolite of clopidogrel was observed compared to healthy subjects. However, inhibition of ADP-induced platelet aggregation and mean bleeding time prolongation was similar in the two groups.

- **Renal Insufficiency**

  After repeat doses of 75 mg per day in subjects with moderate and severe renal impairment (creatinine clearance from 30-60 mL/min and from 5-15 mL/min, respectively), a 25% inhibition of ADP-induced platelet aggregation was observed. Although this effect was lower than that typically observed in healthy subjects, the

prolongation in bleeding time was similar to healthy volunteers.

Since no differences in C_{max} for both clopidogrel and the main circulating metabolite were observed, a compensatory phenomenon i.e. biliary excretion, which has been observed in animals, may explain the lower values of AUC observed in subjects with severe chronic renal failure (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

ACT CLOPIDOGREL tablets should be stored at room temperature (15-30^{0}C). Protect from moisture and light.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

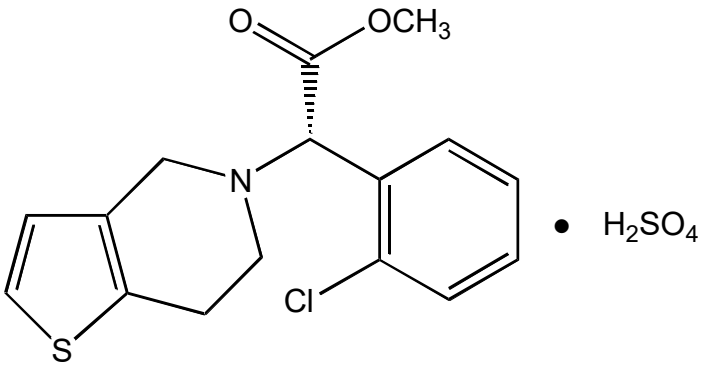
Drug Substance

Proper name: Clopidogrel bisulfate

Chemical name: Methyl (+)-(S)-α-(o-chlorophenyl)-6,7-dihydrothieno [3,2-c] pyridine-5(4H)-acetate, sulphate (1:1)

Molecular formula and molecular mass: $C_{16}H_{16}Cl\ NO_2S \bullet H_2SO_4$; 419.9 g/mol

Structural formula:



Physicochemical properties:

Description: Clopidogrel bisulfate is a white to cream powder.

Solubility: Clopidogrel bisulfate is soluble in water and methanol.

Optical Rotation: 55.08° (c = 1.890% in methanol)

pKa: 2.27 and 4.1

pH: 2.02 (1% solution in water)

UV Absorption Maxima: 203 nm (recorded in 0.001% w/v methanol)

Melting Range: 183-205°C (capillary method)

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The safety and efficacy of clopidogrel bisulfate in preventing atherothrombotic events has been evaluated in five large double-blind trials involving more than 88,000 patients: the CAPRIE study (Clopidogrel vs. ASA in Patients at Risk of Ischemic Events), a comparison of clopidogrel bisulfate to ASA, the CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction) and the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing clopidogrel to placebo, both given in combination with aspirin and other standard therapy.

MYOCARDIAL INFARCTION (MI), STROKE OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

CAPRIE

The CAPRIE trial was a 19,185 patient, 304 centres, international, randomized, double-blind, parallel-group study comparing clopidogrel bisulfate (75 mg daily) to ASA (325 mg daily). Patients ranged in age from 21 to 94 years (mean 62 years). The study was composed of 72.4% men and 27.6% women and included patients with established atherosclerosis or history of atherothrombosis as manifested by myocardial infarction, ischemic stroke or peripheral arterial disease. Patients received randomized treatment for up to 3 years (mean treatment period 1.6 years) and were followed to 3 years or study termination, irrespective of whether study drug had been discontinued (mean follow-up 1.9 years).

Table 9 – Summary of patient demographics for CAPRIE in patients at risk of ischemic events

Study #	Study design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex
CAPRIE	international, randomized, double-blind, parallel-group study comparing clopidogrel bisulfate to ASA	Dosage: Clopidogrel bisulfate (75 mg daily) or ASA (325 mg daily); Administration: oral; Duration: up to 3 years	n=19,185 Clopidogrel bisulfate: n=9599 ASA: n=9586	62 years (21-94 years)	72.4% male 27.6% female

The primary outcome of the trial was a composite outcome which included new ischemic stroke (fatal or non-fatal), new myocardial infarction (fatal or non-fatal), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

As shown in the Table 10, clopidogrel bisulfate was associated with a statistically significant reduction in the primary composite outcome (absolute risk reduction 0.86% and relative risk reduction 8.7%, p=0.045) and a lower incidence of IS and MI. The event curves continued to diverge over the 3-year follow-up period.

Table 10 - Summary of the numbers of events of the primary outcome (composite and individual components) of the CAPRIE Study (intent-to-treat analysis)

Outcome Events of the Primary Analysis				
Patients	**Clopidogrel bisulfate N=9599**	**ASA N=9586**	**p**	**Relative Risk Reduction (95% CI)**
Primary Composite Outcome	939 (9.78%)	1020 (10.64%)	0.045	8.7% (0.2, 16.4)
MI (fatal or not)	275 (2.86%)	333 (3.47%)		
Other vascular death	226 (2.35%)	226 (2.36%)		
IS (fatal or not)	438 (4.56%)	461 (4.81%)		

IS = ischemic stroke; MI = myocardial infarction

ACUTE CORONARY SYNDROME

CURE

The CURE study included 12,562 patients with an acute coronary syndrome, defined as unstable angina or non Q-wave myocardial infarction without significant ST segment elevation and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia.

Patients were required to have either ECG changes compatible with new ischemia (without significant ST segment elevation) or elevated cardiac enzymes or Troponin I or T to at least twice the upper limit of normal. Patients with contraindication to antithrombotic or antiplatelet therapy, at high risk for bleeding, severe heart failure, on oral anticoagulants, and those with recent revascularization or those having received IV glycoprotein IIb/IIIa inhibitors in the previous 3 days were excluded. During the trial, patients were allowed to receive other standard cardiovascular therapies such as heparin, glycoprotein IIb/IIIa inhibitors, lipid-lowering drugs, calcium channel blockers, nitrates, beta blockers, ACE-inhibitors, percutaneous coronary intervention (with or without stent) or CABG, as needed.

Patients were randomized to clopidogrel bisulfate (300 mg loading dose followed by 75 mg/day) plus ASA (75-325 mg once daily; median 150 mg, mean 160 mg), or placebo plus ASA (75-325 mg once daily; median 150 mg, mean 160 mg). Patients were treated for 3 to 12 months (median 10.8 months; mean 9 months; 4806 patients were followed for entire 12 months). The

baseline characteristics, medical history, electrocardiographic changes, and drug therapy were similar for both treatment groups.

Table 11 – Summary of patient demographics for CURE trial in patients with acute coronary syndrome

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
CURE	international, randomized, double-blind, parallel-group study comparing clopidogrel bisulfate + ASA to placebo + ASA	Dosage: Clopidogrel bisulfate (loading dose – 300 mg then 75 mg daily) or placebo in addition to ASA (75-325 mg daily); Administration: oral; Duration: 3-12 months	n=12,562 Clopidogrel bisulfate: n=6259; ASA: n=6303	64.2 years (52.9-75.5)	62% male 38% female

The number of patients experiencing the primary outcome, a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI) and stroke was 582 (9.30%) in the clopidogrel bisulfate -treated group and 719 (11.41%) in the placebo-treated group; an absolute risk reduction of 2.11%, and a relative risk reduction of 20% (p=0.00009) for the clopidogrel bisulfate-treated group (see Table 12).

The number of patients experiencing the co-primary outcome (CV death, non-fatal MI, stroke or refractory ischemia) was 1035 (16.54%) in the clopidogrel bisulfate–treated group and 1187 (18.83%) in the placebo-treated group; an absolute risk reduction of 2.29% and a relative risk reduction of 14% (p=0.0005) for the clopidogrel bisulfate-treated group.

Events for each component of the composite outcome (CV death, non-fatal myocardial infarction, stroke, refractory ischemia) occurred less frequently with clopidogrel bisulfate than in the placebo group but the differences did not reach statistical significance except for non-fatal MI. The results are summarized in Table 12.

Table 12 – Incidence of the main study outcomes in the CURE study.

Outcome	Clopidogrel bisulfate + ASA* (N=6259)	Placebo+ASA* (N=6303)	Absolute Risk Reduction %	Relative Risk (95 % CI)
Primary outcome (Cardiovascular death, non-fatal MI, Stroke)	582 (9.30%)	719 (11.41%)	2.11%	0.80 (0.72, 0.90) p=0.00009
Co-primary outcome (Cardiovascular death, non-fatal MI, Stroke, Refractory Ischemia)	1035 (16.54%)	1187 (18.83%)	2.29%	0.86 (0.79, 0.94) p=0.00052
All Individual Outcome Events:†				
CV death	318 (5.08%)	345 (5.47%)	0.39%	0.93 (0.79, 1.08)
non-fatal MI**	324 (5.18%)	419 (6.65%)	1.47%	0.77 (0.67, 0.89)
Q-wave	116 (1.9%)	193 (3.1%)	1.20%	0.60 (0.48, 0.76)
Non-Q-wave	216 (3.5%)	242 (3.8%)	0.30%	0.89 (0.74, 1.07)
Stroke	75 (1.20%)	87 (1.38%)	0.18%	0.86 (0.63, 1.18)
Refractory ischemia‡	544 (8.69%)	587 (9.31%)	0.62%	0.93 (0.82, 1.04)
During initial hospitalization	85 (1.4%)	126 (2.0%)	0.60%	0.68 (0.52, 0.90)
After discharge	459 (7.6%)	461 (7.6%)	0%	0.99 (0.87, 1.13)

* Other standard therapies were used as appropriate. All patients received acetylsalicylic acid (ASA) 75-325 mg daily (mean=160 mg)

** Some patients had both a Q-wave and a non-Q-wave MI.

† The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

‡ Only the first ischemic event was counted for each patient.

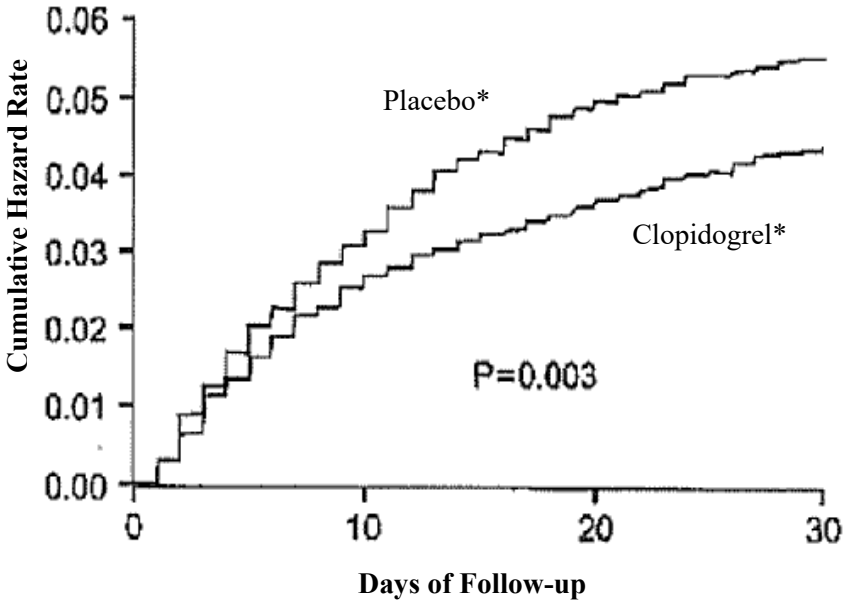
CV death: excludes clear non-CV deaths;

MI: two of three usual criteria (chest pain, ECG or enzyme/cardiac marker changes);

Stroke: neurological deficit ≥24 hours (CT/MRI encouraged)
Refractory ischemia (in-hospital): recurrent chest pain lasting more than 5 minutes with new ischemic ECG changes while patient on optimal medical therapy and leading to additional interventions ranging from thrombolytic therapy to coronary revascularization.
Refractory ischemia (after discharge): rehospitalization lasting at least 24 hours for unstable angina with ischemic ECG changes.

The event curves for CV death, non-fatal MI and stroke separated within the first 24 hours after initiation of therapy (Figure 1) and continued to diverge throughout the study follow-up (up to 12 months) (Figure 2). The rate of the first primary outcome was significantly lower in the clopidogrel group both within the first 30 days after randomization (relative risk, 0.79; 95 percent confidence interval, 0.67 to 0.92) and between days 30 and the end of the study (relative risk, 0.82; 95 percent confidence interval, 0.70 to 0.95).

Figure 1: Cumulative Hazard Rates for First Primary Outcome (death from cardiovascular causes, non-fatal myocardial infarction, or stroke) During the First 30 days after Randomization in the CURE Study.

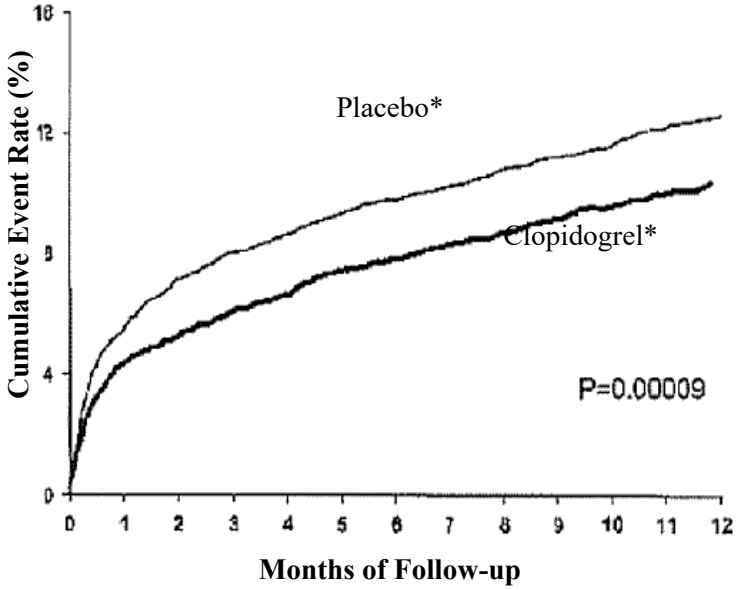


No. AT RISK

Placebo	6303	6108	5998	5957
Clopidogrel	6259	6103	6035	5984

* Other standard therapies were used as appropriate. All patients received ASA 75 - 325 mg daily (mean = 160 mg).

Figure 2: Cardiovascular Death, Myocardial Infarction or Stroke During 12 months follow-up in the CURE Study



No. AT RISK

Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

* Other standard therapies were used as appropriate. All patients received ASA 75 - 325 mg daily (mean = 160 mg).

The risk reduction of the secondary prospectively chosen outcomes (in-hospital severe ischemia without urgent intervention, need for revascularization and heart failure) were lower in the clopidogrel bisulfate group than in the placebo group and the differences observed were statistically significant.

Table 13 – Secondary In-Hospital Outcomes in the CURE Study

	Clopidogrel bisulfate +ASA* (N=6259)	**Placebo+ASA* (N=6303)**	**Absolute Risk Reduction %**	**Relative Risk (95% CI)**
Severe ischemia	176 (2.81%)	237 (3.76%)	1.0%	0.74 (0.61, 0.90)
Revascularization procedure	1302 (20.8%)	1431 (22.7%)	1.9%	0.92 (0.69, 0.98)
Heart failure	229 (3.7%)	280 (4.4%)	0.7%	0.82 (0.69, 0.98)

Severe ischemia: chest pain lasting more than 5 minutes with new ischemic ECG changes while patient on optimal medical therapy and leading to additional interventions ranging from thrombolytic therapy to coronary revascularization but no urgent intervention performed.
* Other standard therapies were used as appropriate. All patients received ASA 75-325 mg daily (mean=160 mg; median 150 mg)

In general, the results obtained in populations with different characteristics, including patients with low to high risk and on other acute and long-term cardiovascular therapies were consistent with the results of the primary analyses irrespective of other treatments or interventions.

CLARITY

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

The randomized, 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 randomized to receive clopidogrel bisulfate (300 mg loading dose, followed by 75 mg/day) or placebo. Patients also received ASA (150 to 325 mg as a 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.

Table 14 – Summary of patient demographics for CLARITY trial in STEMI patients

Study #	StudyDesign	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
CLARITY-TIMI 28	International, randomized, double-blind, placebo-controlled study comparing clopidogrel bisulfate + ASA to placebo + ASA	Dosage: Clopidogrel bisulfate (loading dose-300 mg then 75 mg daily) or placebo in addition to ASA (150-325 mg on first day, and 75-162 mg daily thereafter to be taken simultaneously with the study drug) Administration: oral Duration: Up to and including day of angiography or Day 8 or by hospital discharge, whichever comes first	n = 3491 Clopidogrel bisulfate: n=1752 ASA: n=1739	57.4 years (18-79 years)	80.3% males 19.7% females

STEMI = ST-elevation myocardial infarction

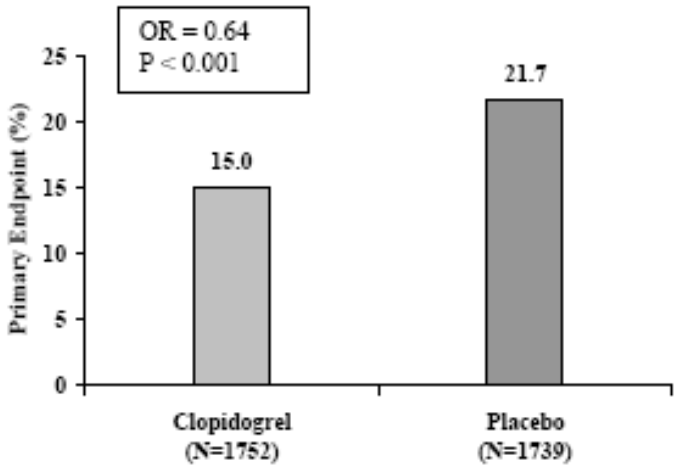
The primary endpoint was the occurrence of the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the predischarge angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography. For patients who did not undergo angiography,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

Secondary efficacy assessments were based on the following endpoints analyzed in a hierarchical order [established for interpretation of the 3 secondary endpoints: an early electrocardiographic endpoint (degree of ST segment resolution at 180 minutes after first dose of study drug); a late angiographic endpoint (occluded IRA on predischarge angiogram); and a clinical endpoint [composite outcome of death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularization) by the time of start of angiography or Day 8 or hospital discharge, whichever came first].

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% patients ≥ 65 years. 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 bisulfate-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 primary endpoint in favor of treatment with clopidogrel bisulfate (95% CI: 0.53, 0.76; p<0.001), as shown in Figure 3 below:

Figure 3: Event Rates for the Primary Composite Endpoint in the CLARITY Study



Based on odds of an occluded infarct-related artery (TFG 0/1), death or MI by angiography for clopidogrel versus placebo (OR: 0.64 [0.53 to 0.76]; p<0.001)

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

Table 15 – Components of the primary endpoint: occluded IRA on the predischarge angiogram, or death or recurrent MI by the time of start of predischarge angiography, or Day 8 or hospital discharge, whichever came first (ITT population) in the CLARITY Study

	Clopidogrel 300/75 mg[a]	Placebo[a]	Odds Ratio (95% CI)	p value
Occluded IRA				
N	1640	1634	0.59	<0.001
n (%) of patients reporting endpoint	192 (11.7%)	301 (18.4%)	(0.48, 0.72)	
Death				
N	1752	1739	1.17	0.492
n (%) of patients reporting endpoint	45 (2.6%)	38 (2.2%)	(0.75, 1.82)	
Recurrent MI				
N	1752	1739	0.70	0.077
n (%) of patients reporting endpoint	44 (2.5%)	62 (3.6%)	(0.47, 1.04)	

[a] With background ASA and initial fibrinolytic therapy.

The secondary endpoints are listed in the table below:

Table 16– Secondary efficacy endpoint analyses (ITT population) in the CLARITY Study

Secondary Efficacy Endpoint	**Clopidogrel 300/75 mg [a]**	**Placebo [a]**	**p-value**	**Mean Difference**	**95% CI**
Adjusted mean ST segment resolution of an ECG at 180 minutes after the first dose of study drug	N = 1068 53.0	N = 1021 55.1	0.223[b]	-2.11	-5.50, 1.28
Secondary Efficacy Endpoint	**Clopidogrel 300/75 mg**	**Placebo**	**p-value**	**Odds Ratio**	**95% CI**
Number (%) of patients with occluded IRA on predischarge angiogram	N = 1640 192 (11.7%)	N = 1634 301 (18.4%)	<0.001 [b]	0.59	0.48, 0.72
Number (%) of patients with death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularization) by the time	N = 1752 145 (8.3%)	N = 1739 162 (9.3%)	0.274[b]	0.88	0.69, 1.11

of the start of predischarge angiography [c]					

[a]: With background ASA and initial fibrinolytic therapy
[b]: p-value to be interpreted following the hierarchical procedure described in the CLARITY Study
[c]: For patients who did not undergo angiography, Day 8 or hospital discharge, whichever came first, was used.

COMMIT

The randomized, 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 randomized to receive clopidogrel bisulfate (75 mg/day) or placebo, in combination with ASA (162 mg/day), for 28 days or until hospital discharge whichever came first.

Table 17 – Summary of patient demographics for COMMIT trial in STEMI patients

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
CCS-2 / COMMIT	International, randomized, double-blind, placebo-controlled study comparing clopidogrel + ASA to placebo + ASA, 2 by 2 factorial design	Dosage: Clopidogrel bisulfate (75 mg daily) or placebo in addition to ASA (162 mg daily to be taken simultaneously with the study drug) Administration: oral Duration: Maximum 4 weeks (in hospital)	n = 45 852 Clopidogrel bisulfate: n = 22961 ASA: n = 22891	61.3 years (15-100)	72.2% male 27.8% female

STEMI = ST-elevation myocardial infarction

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% patients ≥60 years (26% patients ≥ 70 years) and 54.5% patients who received fibrinolytics. As shown in Table 18 and Figures 4 and 5 below, with clopidogrel bisulfate the relative risk of death from any cause was reduced by a statistically significant 7% (p = 0.029) as was the relative risk of the combination of re-infarction, stroke or death (9%, p = 0.002).

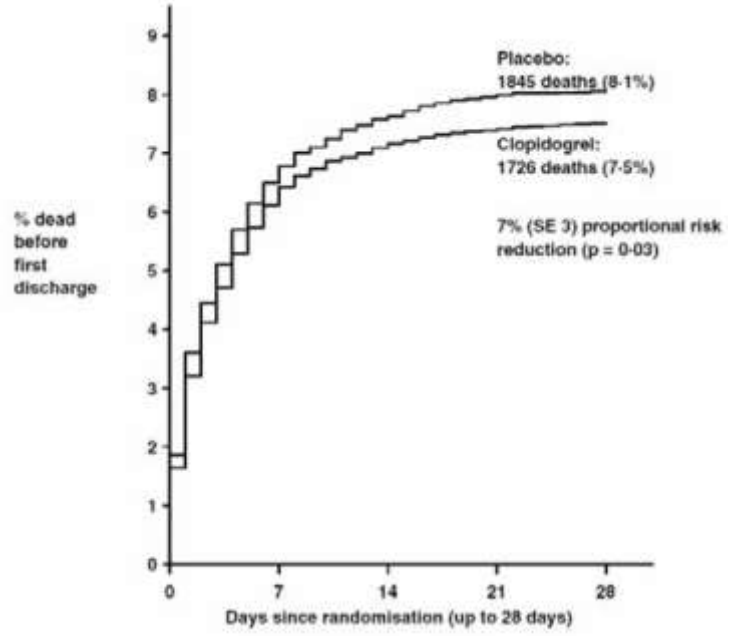
Table 18 – Outcome Events in the COMMIT Analysis

Events	Clopidogrel bisulfate (+ASA) (N=22961)	Placebo (+ASA) (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

* The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI

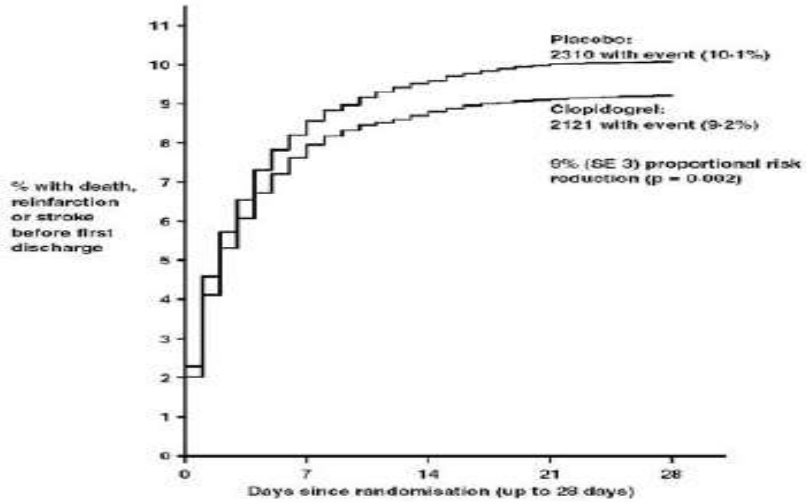
** Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 4: Cumulative Event Rates for Death in the COMMIT Study*



*All treated patients received ASA

Figure 5: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study*

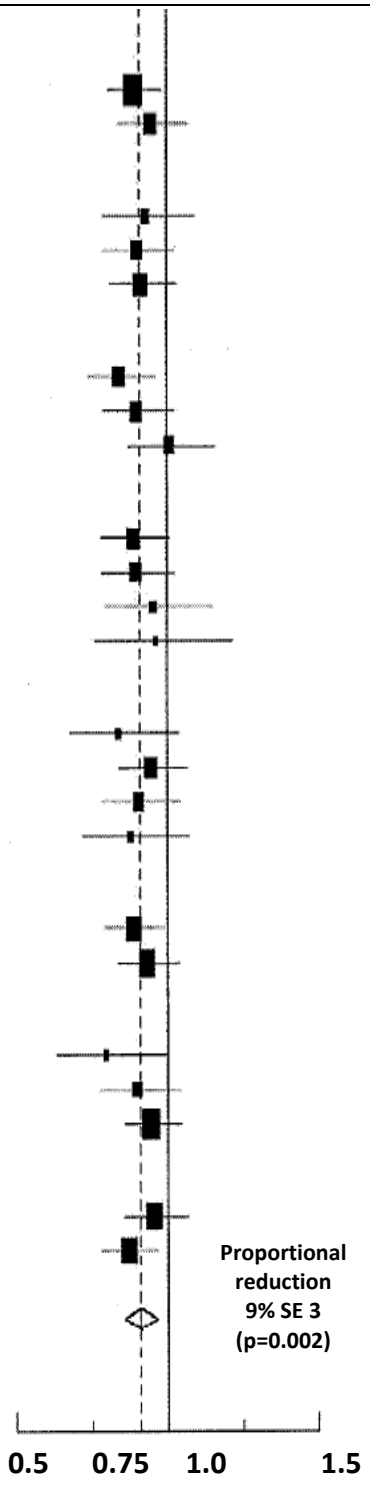


* All treated patients received ASA

The benefit associated with clopidogrel bisulfate on the combined endpoint was consistent across age, gender and with or without fibrinolytics as shown in Figure 6, and was observed as early as 24 hours.

Figure 6: Proportional Effects of Adding Clopidogrel bisulfate to ASA on the Combined Primary Endpoint across Baseline and Concomitant Medication Subgroups for the COMMIT Study

Baseline Categorisation	Events (%)		Odds ratio & C.I.	Heterogeneity or trend test
	Clopidogrel (22 961)	Placebo (22 891)	Clopidogrel better : Placebo better	χ^2 (p-value)
Sex:				
Male	1274 (7.7%)	1416 (8.6%)		1.0 (0.3)
Female	847 (13.3%)	894 (14.0%)		
Age at entry (years):				
<60	485 (5.0%)	512 (5.4%)		0.0 (0.9)
60-69	745 (10.1%)	835 (11.2%)		
70+	891 (14.9%)	963 (16.2%)		
Hours since onset:				
<6	709 (9.2%)	830 (10.8%)		5.7 (0.02)
6 to <13	738 (9.8%)	808 (10.8%)		
13 to 24	674 (8.8%)	672 (8.8%)		
SBP (mmHg):				
<120	797 (10.4%)	892 (11.6%)		1.0 (0.3)
120-139	693 (8.6%)	770 (9.5%)		
140-159	388 (8.5%)	389 (8.9%)		
160+	243 (9.2%)	249 (9.6%)		
Heart rate (bpm):				
<70	268 (5.3%)	315 (6.2%)		0.0 (1.0)
70-89	898 (8.1%)	952 (8.5%)		
90-109	632 (12.3%)	683 (13.5%)		
110+	323 (19.9%)	360 (22.2%)		
Fibrinolytic agent given:				
Yes	1003 (8.8%)	1122 (9.9%)		0.7 (0.4)
No	1118 (9.7%)	1188 (10.3%)		
Prognostic index (3 equal groups):				
Good	228 (3.0%)	282 (3.7%)		3.1 (0.08)
Average	574 (7.9%)	636 (8.3%)		
Poor	1319 (17.3%)	1392 (18.2%)		
Metoprolol allocation:				
Yes	1063 (9.3%)	1110 (9.7%)		2.4 (0.1)
No	1058 (9.2%)	1200 (10.5%)		
Total	**2121 (9.2%)**	**2310 (10.1%)**		



Global Heterogeneity Test: χ^2_{15} = 16.4; p=0.4

99% or 95% confidence interval

14.3 Comparative Bioavailability Studies

A blinded, single-dose, randomized, 2-way, cross-over bioavailability study of ACT CLOPIDOGREL tablets, 75 mg (Teva Canada Ltd.) and Plavix™ tablets, 75 mg (Sanofi-Synthelabo Canada Inc. / Bristol-Myers Squibb Canada Inc.) was conducted in 29 healthy adult subjects (20 females and 9 males) under fasting conditions. The summary of the comparative bioavailability data from the 29 subjects that were included in the statistical analysis are presented in the following table.

Clopidogrel (1 x 75 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90 % Confidence Interval**
AUC_T (pg·h/mL)	1007.67 1128.78 (48.91)	958.56 1159.09 (63.11)	105.1	94.4 - 117.1
AUC_I (pg·h/mL)	1022.20 1134.47 (47.10)	969.83 1155.65 (61.03)	105.40	94.6 - 117.4
C_{MAX} (pg/mL)	698.45 838.34 (58.48)	635.74 859.57 (85.11)	109.9	93.6 - 129.0
T_{MAX} [3] (h)	0.696 (27.87)	0.821 (47.95)		
$T_{½}$ [3] (h)	4.23 (34.71)	4.73 (41.65)		

[1] ACT CLOPIDOGREL (clopidogrel bisulfate) tablets, 75 mg (Teva Canada Ltd.).
[2] Plavix™ (clopidogrel bisulfate) tablets, 75 mg (Sanofi-Synthelabo Canada Inc. / Bristol-Myers Squibb Canada Inc.).
[3] Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Preclinical toxicity studies were conducted with clopidogrel bisulfate which evaluated the systemic, carcinogenic, genotoxic, reproductive, immunogenic and ancillary effects of the compound.

Acute toxicity: At very high single doses by oral administration of clopidogrel (≥1500 mg/kg in rodents, and ≥500 mg/kg in baboons), lung congestion or labored breathing, and a poor gastric tolerability (gastric erosions and/or vomiting) were reported in rats, mice and baboons. In mice, the oral LD50 value was about 2603 mg/kg in males and 2379 mg/kg in females. The intravenous LD50 value was about 160 mg/kg in males and females. In rats, the oral LD50 value was about 2420 mg/kg in males and 1910 mg/kg in females. The intravenous LD50 value was about 110 mg/kg in males and females.

Chronic toxicity: During preclinical studies in rats and baboons, the most frequently observed effects at very high doses (>300x the therapeutic dose of 75 mg/day on a mg/kg basis) were acute gastritis, gastric erosions and/or vomiting. At lower doses, an increase in liver weight was observed in mice, rats and baboons associated with increases in cholesterol plasma levels in rats and baboons, and a slight hypertrophy of the smooth endoplasmic reticulum in centrilobular hepatocytes in rats. No histopathological changes were seen in mice or baboons. The liver findings were a consequence of an effect on hepatic metabolising enzymes observed at high doses, a phenomenon that is generally recognized as having no relevance to humans receiving lower therapeutic doses. After one year of treatment at doses representing between 7- 9x (rats) or between 10-23x (baboon), the exposure seen in humans receiving the clinical dose of 75 mg/day, none of these effects were observed.

Carcinogenicity: There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages ≤77 mg/kg/day, which afforded plasma exposures >25x that in humans at the recommended daily dose of 75 mg/day.

Mutagenicity: 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 chromosome aberration test in human lymphocytes). *In vivo*, clopidogrel had no clastogenic activity in the micronucleus test performed in mice by the oral route.

Teratogenicity and impairment of fertility: Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits (at doses ≤52x the recommended human dose on a mg/m^2 basis). When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies

performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

Other studies: Clopidogrel was not toxic to bone marrow pluripotent stem cells in mice and did not cause any immunotoxic effects in rats and baboons. In the guinea pig, clopidogrel has no antigenic activity and had no phototoxic or photoallergic activity.

Clopidogrel had no promoting activity using an *in vitro* assay for inhibition of intercellular communication of liver cells in culture.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PLAVIX® (Tablets, 75 mg), submission control number. 264401, Product Monograph, sanofi-aventis Canada Inc., October 20, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] ACT CLOPIDOGREL

Clopidogrel Tablets, USP
Read this carefully before you start taking **ACT CLOPIDOGREL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ACT CLOPIDOGREL**.

What is ACT CLOPIDOGREL used for?

ACT CLOPIDOGREL is used in adults to help prevent blood clots and reduce the risk of having conditions caused by blood clots (such as strokes, unstable angina (chest pain at rest), heart attacks, or peripheral arterial disease (leg pain on walking or at rest)).

How does ACT CLOPIDOGREL work?

ACT CLOPIDOGREL belongs to a group of medicines known as antiplatelet drugs. Platelets are very small structures in the blood that clump together during blood clotting. Antiplatelet drugs such as ACT CLOPIDOGREL help prevent this clumping and reduce the chance of blood clots forming.

What are the ingredient in ACT CLOPIDOGREL?

Medicinal ingredients: Clopidogrel bisulfate

Non-medicinal ingredients: Hydrogenated vegetable oil, low substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, polyethylene glycol, red iron oxide.
The film coating contains hypromellose lactose, polyethylene glycol, red iron oxide and titanium dioxide.

ACT CLOPIDOGREL comes in the following dosage forms:

Tablets, 75 mg

Do not use ACT CLOPIDOGREL if:

- are allergic to clopidogrel bisulfate or any of the ingredients contained in the tablets.
- are taking replaglinide, a drug used to lower blood glucose.
- have a medical condition that may cause bleeding, such as a stomach ulcer.
- have liver problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ACT CLOPIDOGREL. Talk about any health conditions or problems you may have, including if you:

- have a medical condition that causes bleeding, such as a stomach ulcer, or a blood disorder that causes you to bleed more easily or tend to bleed longer than 10 minutes without taking any drugs.
- are taking any other medications such as:
    - acetylsalicylic acid (ASA);
    - other drugs used to reduce or prevent blood clotting, such as warfarin, heparin, abciximab, eptifibatide, tirofiban and dipyridamole;
    - oral antidepressants drugs (SSRIs – Selective Serotonin Reuptake Inhibitors) such as fluvoxamine and fluoxetine;
    - Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) used to treat painful and/or inflammatory conditions of muscles or joints;
    - drugs used to treat stomach ulcers and stomach acidity such as omeprazole;
    - rifampin, an antibiotic used to treat strong infections;
    - rosuvastatin, a drug used to lower the level of cholesterol;
- have kidney problems.
- are pregnant or become pregnant while taking ACT CLOPIDOGREL.
- are breast-feeding.
- have recently had surgery (including dental surgery), or plan on having surgery soon.

  Your healthcare professional may ask you to stop taking ACT CLOPIDOGREL for 5-7 days before your surgery.
- have allergies to medications including prasugrel or ticlopidine.
- are lactose intolerant or have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  because lactose is a non-medicinal ingredient in ACT CLOPIDOGREL.

Other warnings you should know about:

ACT CLOPIDOGREL is not recommended for children or adolescents below 18 years of age.

If you experience any excessive bleeding, while taking ACT CLOPIDOGREL, do not stop taking ACT CLOPIDOGREL but see or call your healthcare professional right away.

If you should see another doctor or a dentist while you are using ACT CLOPIDOGREL, you should inform them that you are using ACT CLOPIDOGREL.

<u>Blood Tests: Monitoring and Tests:</u>

Your healthcare professional may want to do blood tests if you are on certain medication to follow your progress. It is important that you do have your blood tested.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
• **Repaglinide, used to lower blood sugar**

The following may interact with ACT CLOPIDOGREL:

- Aspirin (ASA), used to treat pain, fever and inflammation.
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), used to treat painful and/or inflammatory conditions of the muscles or joints.
- Opioids, used to treat severe pain. While you are treated with ACT CLOPIDOGREL, you should tell your healthcare professional before being prescribed any opioid.
- Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluvoxamine and fluoxetine, used to treat depression.
- Drugs use to reduce or prevent clotting, such as heparin, warfarin, abciximab, eptifibatide, tirofiban and dipyridamole.
- Antacids, such as omeprazole, used for indigestion or heartburn.
- Paclitaxel, used to treat many types of cancer.
- Rifampin, an antibiotic used to treat severe infections.
- Rosuvastatin, a drug used to lower the level of cholesterol.

How to take ACT CLOPIDOGREL:

ACT CLOPIDOGREL can be taken with or without food. You should take your medicine regularly and at the same time each day.

This product has been prescribed for you. You should not give it to others. ACT CLOPIDOGREL should be taken long term, under the supervision of your healthcare professional.

Usual adult dose:

You should take one 75 mg tablet of ACT CLOPIDOGREL per day, by mouth.

If you have had unstable angina (chest pain at rest) or a heart attack, a one-time 300 mg dose may be given to you, followed by one 75 mg tablet daily.

Overdose:

If you think you, or a person you are caring for, have taken too much ACT CLOPIDOGREL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose of ACT CLOPIDOGREL, but remember within 12 hours of your usual time, take your tablet immediately and then take your next tablet at the normal time. If you forget for more than 12 hours simply take the next single dose at the usual time. Do not take a double dose to make up for the one you missed.

What are possible side effects from using ACT CLOPIDOGREL?

These are not all the possible side effects you may have when taking ACT CLOPIDOGREL. If you experience any side effects not listed here, tell your healthcare professional.
Side effects may include:

- joint pain and/or muscle pain
- abdominal pain, diarrhea, indigestion (heartburn)
- nausea, vomiting, constipation, loss of taste, taste disturbance
- dizziness, headache
- tingling sensation in the arms and/or legs
- rash, itching
- bruising
- enlargement of breast tissue in men

If you cut or injure yourself, it may take slightly longer than usual for bleeding to stop. For minor cuts and injuries, like cutting yourself while shaving, this is of no concern. However, if you are in any doubt at all, you should contact your healthcare professional immediately.

ACT CLOPIDOGREL can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Nose bleeds	**√**		
Bleeding disorders: blood in the stool, urine or eye, vomiting blood, coughing up blood, purple spotted rash			**√**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			**√**
UNCOMMON			
Fever, signs of infection, extreme tiredness			**√**
Liver disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			**√**
Bleeding in the brain: sudden, severe headache, weakness, loss of speech or vision, confusion, nausea, vomiting, seizures, loss of consciousness			**√**
VERY RARE			
Eosinophilic pneumonia: cough, fever, difficulty breathing and sweating at night		**√**	
Kounis syndrome: a mixture of symptoms and signs of an allergic reaction and heart attack or unstable angina, with chest pain, shortness of breath, faintness, nausea, vomiting, fainting, itching, hives, sudden, heavy sweating, unusual paleness, palpitations, low blood pressure, slow heartbeat			**√**
UNKNOWN			
Low blood sugar: sweating, shakiness, dizziness, headache, and blurred vision		**√**	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

ACT CLOPIDOGREL tablets should be stored at room temperature (15-30°C). Protect from moisture and light.
Keep out of reach and sight of children.

If you want more information about ACT CLOPIDOGREL:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com ; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com .

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