Establishing the microcirculatory effects of ticagrelor on tissue perfusion in critical limb ischemia

Version Date: September 21, 2017

Protocol Number: Version 4.0

Protocol Amendment #3

Sponsor: Mehdi H. Shishehbor, D.O., M.P.H.

Funding: A grant from AstraZeneca

Primary Investigator: Mehdi H. Shishehbor, D.O., M.P.H.

Protocol Signature Page

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I have carefully read "Establishing the microcirculatory effects of ticagrelor on tissue perfusion in critical limb ischemia". I agree to conduct this study as outlined herein.

_____
Investigator Signature

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Printed Investigator Name

_____
Date

Table of Content

List of Abbreviations

ABI	Ankle-Brachial Index
ACS	Acute Coronary Syndrome
AE	Adverse Event
ANOVA	Analysis of Variance
B/P	Blood Pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CLI	Critical Limb Ischemia
COPD	Chronic Obstructive Pulmonary Disease
Crt	Creatinine
CVA	Cerebrovascular Accident
DAPT	Dual Antiplatelet Therapy
DM	Data Management
eCRF	Electronic Case Report Form
ESC	Executive Steering Committee
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c
Hct	Hematocrit
HDL	High-Density Lipoprotein
Hgb	Hemoglobin
HR	Heart Rate
INR	International Normalized Ratio
IRB	Institutional Review Board
ISS	Investigator Sponsored Study
LDL	Low-Density Lipoprotein
LS	Least Squares
mg	milligrams
mmHg	Millimeters Mercury
MMRM	Mixed Model Repeated Measures
PAD	Peripheral Arterial Disease
Plt	Platelet Count
PTA	Percutaneous Transluminal Angioplasty
PTT	Partial Thromboplastin Time
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event

SAS	Statistical Analysis System
SD	Standard Deviation
SOC	Standard of Care
SPSS	Statistical Package for the Social Sciences
SSL	Secure Sockets Layer
SPP	Skin Perfusion Pressure
TBI	Toe-Brachial Index
Tchol	Total Cholesterol
TcPO2	Transcutaneous Oxygen Concentration
Tg	Triglycerides
TIA	Transient Ischemic Attack
TSP	Toe-Systolic Pressure
ULN	Upper Limit of Normal

Study Synopsis

Title	Establishing the microcirculatory effects of ticagrelor on tissue perfusion in critical limb ischemia
Sponsor	Mehdi H. Shishehbor, D.O., M.P.H.
Rationale	Ticagrelor has emerged as a novel P2Y12 adenosine receptor antagonist studied primarily in the treatment of coronary heart disease, but with properties that make the drug suitable for study in PAD. Beyond its antiplatelet effects, ticagrelor's ability to inhibit uptake of adenosine may provide cytoprotective and reparative properties that could prove therapeutic to patients with advanced PAD. Indeed, oral administration of ticagrelor to animals prevents contraction of vascular smooth muscle: an effect not seen with clopidogrel or prasugrel (5). Similar to effects seen with clopidogrel, ticagrelor may reduce leukocyte-platelet adhesion and improve microcirculatory function during ischemia by reducing blood viscosity (6). In addition to these beneficial antiplatelet effects, ticagrelor may provide additional benefit in smooth muscle relaxation by promoting serum adenosine concentrations.
Study Center	Cleveland Clinic and University Hospital in Cleveland
Indication	Rutherford Classification Stage IV through VI PAD
Study Objectives	The primary goal of the proposed research is to determine if ticagrelor can induce a clinically significant change in transcutaneous oxygen concentration (TcPO2) superior to that induced by clopidogrel, among advanced cases of recently revascularized peripheral arterial disease (PAD). Secondary objectives include: 1) to compare the rate of wound healing at 6 months between treatment groups among Rutherford Classification Stage V-VI patients 2) to determine if other markers of blood flow improve with treatment with ticagrelor.
Study Design	This is a 2-arm randomized, active-controlled, pilot study. Patients over the age of 18 presenting with Rutherford Classification Stage IV-VI PAD will be included. Sixty (N=60) eligible patients who have given their consent to participate will be randomized to one of the following treatments: • Clopidogrel (75 mg by mouth daily) • Ticagrelor (90 mg by mouth twice daily) All patients will be followed for 6 months after enrollment, with the primary endpoint assessed at 6 months after randomization.
Number of Patients	A sample size of 60 patients (30 per group) provides 90% power to detect an 8±8 mmHg difference in TcPO2 between groups.

Target Population	Patients with critical limb ischemia either Rutherford Stage IV (without wounds) or Stage V-VI (with concomitant vascular insufficiency wounds) that have been recently revascularized.
Duration of patient participation and duration of the study	The total duration of the study is expected to be 54 months including 48 months for patient recruitment and 6 months for final patient follow-up. Patients will participate in the study for approximately 6 months.
Key Selection Criteria	**INCLUSION CRITERIA** • Adults age 18-100 years with Rutherford Classification Stage IV through VI PAD with a percutaneous lower extremity arterial angiography with arterial intervention in the past 2 weeks • Willingness to sign informed consent • Ability to return for follow-up visits • A female patient of childbearing potential who is sexually active must agree to use adequate contraception from screening until 30 days after receiving the last dose of study drug. **EXCLUSION CRITERIA** • Intolerance to thienopyridines • Hypersensitivity to ticagrelor or any component of the product • Concomitant use of oral anticoagulation with vitamin K antagonist, factor Xa inhibitor, or direct thrombin inhibitor • History of intracranial hemorrhage • History of severe hepatic impairment defined by baseline transaminase greater than or equal to 3x ULN or any elevation in bilirubin • Active bleeding • Allergy to aspirin • Baseline TcPO2 < 10 mmHg post angiography • Resting pre-procedure heart rate < 50 beats-per-minute without a permanent pacemaker and not on an atrioventricular nodal blocking agent • Severe COPD on home oxygen therapy • Patients on strong CYP3A inhibitors and/or CYP3A inducers that cannot be stopped for the course of the study.
Study Visit Schedule and Assessments	Visits will occur at screening (baseline) post angiography, and at 3 and 6 months.
Test Product, Dose, and Mode of Administration	Patients will be randomized to either ticagrelor 90 mg by mouth twice daily or clopidogrel 75 mg by mouth daily.
Concomitant Medications	Aspirin 81 mg by mouth every day

Prohibited Medications	• Concomitant use of oral anticoagulation with a vitamin K antagonist, factor Xa inhibitor, or direct thrombin inhibitor • Aspirin > 100mg per day
Endpoints	**Primary endpoint** • Absolute change in TcPO2 from baseline to 6 months **Secondary endpoints** • Rate of wound healing from baseline to month 6 in treatment groups for patients with Rutherford Stage V-VI PAD • Change in ankle-brachial index (ABI), toe-brachial index (TBI), toe-systolic pressure (TSP) and skin perfusion pressure (SPP) from baseline to month 6 in treatment groups • Major adverse limb events including a composite of surgical limb loss or any major vascular repeat revascularization, including thrombectomy, thrombolysis, or major lower-extremity surgical procedure from baseline to month 6 in treatment groups • Percent change in TcPO2 from baseline to 6 months • Percent change and absolute change in TcPO2 from baseline to month 3
AE/ SAE Collection	**AEs** • Self-reported shortness of breath with symptomatic bradycardia • Events that are not listed in the current labeling for the drugs • Events that lead to discontinuation of drug or result in a dose modification **SAEs** • Death. • Life threatening AEs. • Requires inpatient hospitalization or prolongation of existing hospitalization. • A disability/incapacity. • A congenital anomaly/birth defect in the offspring of a patient who received drug. • Important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. **Other SAEs of Special Interest** • Major bleeding defined as a composite of fatal bleeding, intracranial bleeding, hypovolemic shock or severe hypotension due to bleeding requiring pressors, or need for transfusion of at least 2 units in any 24-hour period. • Major adverse limb events (surgical limb loss, major repeat revascularizations including thrombectomy, thrombolysis, or major lower extremity surgical procedure.

Safety Evaluations	Safety endpoints to be assessed include major bleeding, self-reported dyspnea and reported symptomatic bradycardia.
Statistical Methodology	Analysis of the Primary and Secondary Endpoints Baseline covariates will be compared with Fisher's exact test for categorical variables and two-sample t-test for continuous variables with a normal distribution or rank sum test if non-normally distributed between treatment groups. All comparisons between treatment groups will be performed as intent-to-treat using two-tailed significance testing at a value of 0.05. Mixed model repeated measures analysis (MMRM) will be used to conduct the between-group comparison of absolute change in TcPO2 at 3 months and 6 months follow-up, with adjustment of baseline TcPO2 level following revascularization. Estimated within-group least squares (LS) means of TcPO2 and between-group differences of LS means in TcPO2 at 3- and at 6-month follow-up time points will be obtained from the MMRM modeling. If the TcPO2 data is not normally distributed, the same MMRM method will be performed to analyze the rank transformed TcPO2 data, however the descriptive data is presented with median (interquartile range), and the between-group differences are shown using F statistics. Meanwhile, relevant nonparametric methods will be applied as sensitivity analysis. Friedman test will be conducted to compare the TcPO2 repeated measures from baseline to 6 months follow-up between the treatment groups. A Wilcoxon signed rank test will be used to assess intragroup change in TcPO2 at 3- and at 6-month follow-up. The absolute change in TcPO2 over time and other continuous secondary endpoints will be analyzed using the same strategies. Safety endpoints, adverse events and other categorical secondary endpoints will be analyzed using Fisher's exact test. The relationships between the primary endpoint of change in TcPO2 at 6 months follow-up and the continuous secondary endpoints will be explored by regression analysis.

Study Visits

Study Procedures	Screening/ Baseline	3 Months (+/- 1 week)	6 Months (+/- 1 week)
Informed Consent	X		
Demographics	X		
Medical History	X		
Rutherford Classification	X	X	X
ABI, TBI, TSP	X	X	X
Wound Size	X	X	X
Vital Signs	X	X	X
Record Baseline Labs[1]	X		
Urine Pregnancy Test[2]	X		
Angiographic Data	X		
TcPO2 measurement	X[3]	X	X
SPP measurement	X	X	X
Concomitant Medications	X	X	X
Randomization	X		
Dispense Study Drug	X	X	
Assessment of wound healing		X	X
Study medication compliance		X	X
Collect AEs & SAEs		X	X

[1]Baseline labs will be obtained from local labs performed in the month prior to screening and include the following: Blood urea nitrogen, creatinine, HbA1c, hemoglobin, hematocrit, platelet count, international normalized ratio, partial thromboplastin time, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides
[2]For females of childbearing potential
[3]Post angiography

1 Introduction

1.1 Background

Treatment of critical limb ischemia (CLI), an advanced form of peripheral arterial disease (PAD), has lagged behind other forms of cardiovascular disease. Lacking are novel medical strategies that promote ambulatory ability and, when CLI-related wounds are present, reconstitution of tissue oxygenation and tissue healing. Wound healing remains a distinct challenge, characterized by a complex interplay of neuropathic and microvascular circulatory deficiencies that promote inflammation and tissue hypoxia (1). Recent interest has focused on the role of adenosine, a ubiquitous purine nucleoside, and its reparative biological effects through neuromodulation and wound healing via A (2A) and A (2B) cellular receptors (2,3). Herein, we propose a first-in-man pilot study among patients revascularized for advanced symptomatic PAD, including patients with CLI-related vascular insufficiency wounds. Ticagrelor will be compared to clopidogrel, the post-angioplasty standard-of-care thienopyridine, in an evaluation of interval improvement in tissue oxygenation as assessed by tissue partial pressure of oxygen (TcPO2).

1.2 Rationale for use of ticagrelor

Ticagrelor has emerged as a novel P2Y12 adenosine receptor antagonist studied primarily in the treatment of coronary heart disease, but with properties that make the drug suitable for study in PAD. Beyond its antiplatelet effects, ticagrelor's ability to inhibit uptake of adenosine may provide cytoprotective and reparative properties that could prove therapeutic to patients with advanced PAD. These beneficial properties may explain the striking reduction of adverse vascular outcomes observed in the PLATO Study and may represent a fundamental pharmacologic difference between ticagrelor – a carbocyclic nucleoside – and the thienopyridines (4). Indeed, oral administration of ticagrelor to animals prevents contraction of vascular smooth muscle: an effect not seen with clopidogrel or prasugrel (5). Similar to effects seen with clopidogrel, ticagrelor may reduce leukocyte-platelet adhesion and improve microcirculatory function during ischemia by reducing blood viscosity (6). In addition to these beneficial antiplatelet effects, ticagrelor may provide additional benefit in smooth muscle relaxation by promoting serum adenosine concentrations. In addition to its vasodilatory properties, adenosine has been shown to limit ischemia-related tissue injury. The addition of adenosine to thrombolytic therapy in acute myocardial infarction in 3 large randomized studies has demonstrated dramatic reduction in infarct size (7-9). To this end, a randomized, double-blind, phase IIIb multicenter study is underway comparing cardiovascular outcomes among an anticipated 11,500 patients with established PAD in the Examining Use of tiCagrelor In paD (EUCLID) Study (clinicaltrials.gov Identifier: NCT01732822). While this large clinical outcomes study is timely and highly important, a study demonstrating ticagrelor's microvascular effects is warranted. Ticagrelor's potentially beneficial pharmacologic properties may offer advantages of increased tissue oxygenation that promote wound healing and improve ambulatory ability in advanced PAD.

Similar to the endovascular treatment of coronary artery disease, percutaneous transluminal angioplasty (PTA) for PAD requires the use of dual-antiplatelet therapy (DAPT) to prevent thrombotic complications related to stent placement or balloon angioplasty. In a head-to-head comparison with clopidogrel among patients with acute coronary syndromes, ticagrelor has already shown impressive reductions in mortality without increasing the overall risk of major

bleeding (13). For patients undergoing PTA, DAPT is recommended for at least 30 days following the PTA procedure. The benefits of DAPT beyond 30-days after peripheral arterial intervention have been recently demonstrated; clopidogrel plus aspirin was superior to aspirin monotherapy for up to 6 months after PTA by preventing peri-procedural platelet activation and improved functional outcomes without increasing the risk of bleeding complications (14). Furthermore, even though costs associated with long-term DAPT are higher, clopidogrel has proven cost-effective over aspirin monotherapy for secondary prevention for vascular events among patients with PAD (15,16). With an anticipated antiplatelet benefit as robust as that of clopidogrel, ticagrelor may also demonstrate cost-effectiveness.

1.3 Rationale for use of TcPO2 and SPP

To assess the potential perfusion benefits of ticagrelor, baseline and follow-up assessment with TcPO2 will be used to compare relative effects of clopidogrel. TcPO2 requires cutaneous positioning of oximetry electrodes and has been validated as an appropriate clinical measure of tissue oxygenation in CLI (10). A distinct advantage of TcPO2 includes its ability to assess regional tissue oxygenation, such as at the external margins of a vascular insufficiency ulcer. TcPO2 also provides surrogate information of macro- and microvascular arterial perfusion with a prognostic signal; TcPO2 levels > 30 mmHg have been associated with higher rates of local wound healing (10,11).

Several noninvasive measures of local tissue perfusion provide complementary roles in management of patients with wounds related to tissue ischemia. Whereas ankle-brachial index (ABI) is a valid screening tool for PAD, advanced vascular calcification that often accompanies severe PAD also renders ABI less reliable, often by underestimating disease severity. Markers of microvascular perfusion, such as toe-brachial index, toe systolic pressure, TcPO2 and skin perfusion pressure have been suggested to be more accurate measures. TcPO2 may have improved accuracy in predicting wound healing relative to other modalities, including toe systolic pressure (TSP) (12). However, there exist no simultaneous comparisons of all four techniques among patients with advanced PAD. Therefore, an important feature of this study is to compare these techniques among patients with Rutherford Class IV-VI CLI.

Alternate noninvasive techniques to assess arterial flow in CLI have important limitations. Ankle-brachial index is the standard noninvasive test for PAD, although it can provide unreliable and overestimated results among those with advanced age, diabetes mellitus, and chronic kidney disease (10,11,17). Toe-blood pressure, including TBI and TSP, while prognostically useful in predicting wound healing, is not available among those with previous forefoot amputation. For these reasons, TcPO2 was selected for this study as a reliable assessment of regional tissue oxygenation, sensitive to improvements in microvascular perfusion. Similar to TcPO2, the utility of SPP has not been extensively characterized, although some studies suggest it is useful in assessing perivascular microcirculation of the wound (11). Distinct from the assessment of tissue oxygenation with TcPO2, SPP measures blood in the microcirculation around and within a wound. SPP is a painless test that measures microcirculatory blood flow using photoplethysmography with Doppler techniques. Therefore, SPP offers a complimentary and concurrent assessment of microcirculatory wound perfusion that may enhance understanding of healing in ischemic tissues.

2 Study Design

2.1 Summary

This is a prospective, randomized, unblinded, open-label, active controlled pilot study to evaluate the efficacy and safety of ticagrelor plus aspirin versus clopidogrel plus aspirin in patients with Rutherford Stage IV to VI PAD that have undergone a percutaneous transluminal angioplasty (PTA) of the lower extremities in the past 2 weeks.
This study will be conducted at the Cleveland Clinic and University Hospital in Cleveland, Ohio. A total of 60 patients are planned for this study.

3 Study Objectives and Endpoints

3.1 Primary Objective

The primary objective is to determine if ticagrelor, compared to clopidogrel, can induce a greater measurable change in transcutaneous oxygen concentration (TcPO2), a surrogate for tissue perfusion, among advanced cases of CLI.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the absolute change in TcPO2 from baseline to month 6 compared between treatment groups.

3.2.2 Secondary Endpoints

- Rate of wound healing from baseline to month 6 in treatment groups for patients with Rutherford Classification Stage V-VI PAD
- Change in ankle-brachial index (ABI), toe-brachial index (TBI), toe-systolic pressure (TSP) and skin perfusion pressure (SPP) from baseline to month 6 in treatment groups
- Major adverse limb events including a composite of surgical limb loss or any major vascular repeat revascularization, including thrombectomy, thrombolysis, or major lower-extremity surgical procedure from baseline to month 6 in treatment groups
- Percent change in TcPO2 from baseline to 6 months
- Percent change and absolute change in TcPO2 from baseline to month 3 compared between treatment groups

A subgroup analysis will be performed among patients with non-gangrenous wounds to include a secondary assessment comparing TcPO2 to changes in SPP, ABI, TBI, and TSP between treatment groups at baseline and over the course of the study.

4 Selection and Withdrawal of Patients

4.1 Study Population

Approximately 60 patients who meet all inclusion criteria and no exclusion criteria will be randomized into the study.

Enrollment into the study will require severe symptomatic CLI without wounds (Rutherford Stage IV) or CLI with concomitant vascular insufficiency wounds (Rutherford Stage V-VI PAD).
Potential participants will be identified and screened prior to discharge or at the time of the first out-patient visit (within 2 weeks after discharge) after a percutaneous lower extremity arterial angiography with arterial intervention (stent or balloon angioplasty) for the presence of lower extremity vascular insufficiency. Participants will be classified as Rutherford Class IV – VI (with or without ulcerations). Per SOC, patients will have been placed on clopidogrel after the arterial intervention.

4.1.1 Inclusion Criteria

Eligible patients will be considered for inclusion in this study if they meet all of the following criteria:

1. Adults age 18-100 years with Rutherford Classification Stage IV through VI PAD with a recent percutaneous lower extremity arterial angiography with arterial intervention in the past 2 weeks
2. Willingness to sign informed consent
3. Ability to return for follow-up visits
4. A female patient of childbearing potential who is sexually active must agree to use adequate contraception from screening until 30 days after receiving the last dose of study drug. Women NOT of child bearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (defined as at least 2 years since last regular menses). The female patient should not be lactating and must have a negative pregnancy test at screening.

4.1.2 Exclusion Criteria

Patients will be ineligible for this study if they meet any one of the following criteria:

1. Intolerance to thienopyridines
2. Hypersensitivity to ticagrelor or any component of the product
3. Concomitant use of oral anticoagulation with vitamin K antagonist, factor Xa inhibitor, or direct thrombin inhibitor
4. History of intracranial hemorrhage
5. History of severe hepatic impairment defined by baseline transaminase greater than or equal to 3x ULN or any elevation in bilirubin
6. Active bleeding
7. Allergy to aspirin
8. Baseline TcPO2 < 10 mmHg post angiography
9. Resting pre-procedure heart rate < 50 beats-per-minute without a permanent pacemaker and not on an atrioventricular nodal blocking agent
10. Severe COPD on home oxygen therapy
11. Patients on strong CYP3A inhibitors and/or CYP3A inducers that cannot be stopped for the course of the study. *

* Strong inhibitors of CYP3A are the following medications: ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin.
  Potent inducers of CYP3A include the following medications: rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital.
  In addition, ticagrelor will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4 and doses greater than 40 mg with these medications should be avoided.

4.2 Patient Enrollment and Randomization

Enrollment will occur when a patient signs and dates an informed consent form and provides authorization to use protected health information.

A total of 60 patients will be randomized into 2 treatment groups in a 1:1 ratio (ticagrelor to clopidogrel). Permuted block randomization will be used to allocate patients to treatment groups. Fixed block sizes will be used to allocate treatment groups, thereby ensuring that sample size in each group is similar as the study progresses. Blocked randomization lists will be computer generated and blinded to the investigators. The investigator will not know the assigned treatment for a patient until the patient is randomization. Patients will not be blinded to their treatment group.

4.3 Study Withdrawal

Patients are free to withdraw their participation at any time during this clinical study. The investigator also has the right to discontinue treatment with study drug if a serious adverse reaction to the study drug occurs. Patients will be encouraged to remain in the study even if study drug is discontinued. Reasons for early withdrawal of any patient from the study will be documented in the medical records. If the reason for discontinuation of the study drug is from an adverse event it will be documented in the medical records and the case report forms.

4.4 Study Discontinuation

The sponsor has the right to terminate the study at any time based on a recommendation from the Medical Monitor.

5 Treatment of Patients

5.1 Treatment Regimen

Patients are placed on clopidogrel after their arterial intervention per SOC. They will remain on clopidogrel up to the time that randomization occurs. For patients that are randomized to ticagrelor, the clopidogrel will be stopped.

Study Drug	Dose Level and Frequency
clopidogrel	75 mg by mouth daily
ticagrelor	90 mg by mouth twice daily

5.2 Description of Study Drug

Clopidogrel (Plavix®) is an FDA approved P2Y12 platelet inhibitor indicated for use in patients with acute coronary syndrome, recent MI, recent stroke, or established peripheral arterial disease. See Appendix A for a complete description of the drug.

Ticagrelor (Brilinta®) is an FDA approved P2Y12 platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). See the Investigator Brochure for a complete description of the drug.

5.3 Obtaining Study Drugs

Study medication (ticagrelor) will be provided for the patients from randomization until the time of the 6 month visit.

5.4 Concomitant Medications

Patients should receive aspirin 81 mg by mouth every day as per labeling recommendations for ticagrelor and clopidogrel.

5.5 Prohibited Medications

Treatment with the following medications are excluded during this study:

- Aspirin doses greater than 100 mg per day
- Oral anticoagulation with a vitamin K antagonist
- Factor Xa inhibitors
- Direct thrombin inhibitors

6 Study Procedures

6.1 Screening/Baseline

The following procedures will be performed on all patients at screening:

- Informed consent
- Demographics (see section 6.4.1)
- Medical History (see section 6.4.1)
- Rutherford Classification (see Appendix B)
- ABI, TBI, TSP

- Measurement of wound size if Rutherford Classification Stage V or VI
- Vital signs (B/P, HR, temperature, respirations)
- The results of the following will be recorded from local laboratory tests that were performed in the month prior to screening: BUN, crt, Hgb, Hct, plt, INR, PTT, HbA1c, Tchol, tg, LDL and HDL.
- Urine pregnancy test for females of childbearing potential
- Recent angiographic data
- TcPO2 measurement (see section 6.4.2)
- SPP measurement
- Concomitant medications
- Randomization
- Dispense study drug

6.2 Month 3 follow up

The patient will return to the clinic 3 months (90 days) after the date of randomization (+/- 2 weeks) and the following procedures will be performed:

- Rutherford Classification (see Appendix B)
- ABI, TBI, TSP
- Measurement of wound size and assessment of healing if Rutherford Classification Stage V or VI at Baseline
- Vital signs (B/P, HR, temperature, respirations)
- TcPO2 measurement (see section 6.4.2)
- SPP measurement
- Concomitant medications
- Dispense study drug
- Assess study medication compliance
- Collect SAEs and AEs

6.3 Month 6 follow up

The patient will return to the clinic 6 months (180 days) after the date of randomization (+/- 2 weeks) and the following procedures will be performed:

- Rutherford Classification (see Appendix B)
- ABI, TBI, TSP
- Measurement of wound size and assessment of healing if Rutherford Classification Stage V or VI at Baseline
- Vital signs (B/P, HR, temperature, respirations)
- TcPO2 measurement

- SPP measurement
- Concomitant medications
- Assess study medication compliance
- Collect SAEs and AEs

Once a patient has been assessed at the 6-month follow-up visit they will exit the study. If ongoing use of ADP-receptor antagonist is required, patients will continue with either medication as indicated and approved although it will not be provided as part of the study. If no other indication exists for an ADP-receptor antagonist, either ticagrelor or clopidogrel will be discontinued, as per routine clinical practice.

6.4 Study Procedures

The following procedures will be considered as study procedures:

- TcPO2 measurement
- SPP measurement

Other procedures (Rutherford Classification, ABI, TBI, TSP, assessment of wound size and healing, vital signs, labs and angiographic procedures) are considered as SOC clinical procedures.

6.4.1 Demographics and Medical History

Demographic and medical history information to be collected include: age, race, gender, body-mass index, wound size, wound location, medical comorbidities including tobacco use history, duration of claudication, duration of lower extremity wound (if applicable), hypertension, hyperlipidemia, diabetes mellitus, prior cerebrovascular accident (CVA) or transient ischemic attack (TIA), carotid artery stenosis > 50%, chronic kidney disease (CKD), and complications related to prior PAD, such as prior wounds, forefoot amputation, below knee amputation, above knee amputation. Angiographic data relevant to revascularization procedures, including a record of arterial segment treated and vascular anatomy, will also be recorded.

6.4.2 Measurement of TcPO2

Assessment of TcPO2 will be performed using the Perimed Periflux System 5000 (Perimed Inc., Ardmore, PA) equipped with laser Doppler and transcutaneous oximetry function units. Before each measurement, the device will be calibrated as per manufacturer's specifications. Patients will be asked to refrain from tobacco use or caffeine 12 hours prior to TcPO2 assessment. All measurements will be performed in the supine position. A site distant from the diseased area (right subclavicular region) will be used as a reference value (12, 18).

Skin perfusion is strongly dependent upon skin temperature. Accurate and reproducible assessment of tissue oxygenation requires measurement at maximal hyperemia. Measurement at peak blood flow provides consistency of measurements at peak cutaneous blood flow reserve. Therefore, assessment of TcPO2 requires local tissue warming around the cutaneous ulcer site to

a prespecified temperature. As part of the Perimed system, the PF 5020 Temp Unit will be used to gradually warm the perimeter of the wound at sites of measurement to a steady state of 44°C (43-45°C) as per manufacturer specifications.

In patients with Stage IV (no wound) the level of the great toe will be used as the site for measurement of TcPO2. In the event of previous amputations, the most distal aspect of the foot will be used for the measurement. In order to ensure that subsequent assessments are consistent with the index measurement, the area used will be documented in the records

From room temperature (30-34°C), thermal steady state is achieved in 3-5 minutes and is maintained during tissue assessment. All subsequent TcPO2 assessments will be made at 44°C (43-45°C) to ensure maximal hyperemia and measurement accuracy. After the site of TcPO2 adhesion is prepared, the instrument is calibrated at thermal steady state (3-5 minutes). Continuous TcPO2 monitoring then commences over 10-15 minutes until transcutaneous oxygen pressure also reaches steady state.

Follow-up TcPO2 measurements (Perimed © Periflux System 5000) will be performed at 3 and 6 months after revascularization for the purposes of this study. Repeated measures for this study at 3 and 6 months are necessary to assess the interval change of TcPO2 and to provide additional accuracy of statistical modeling of secondary efficacy endpoints.

6.4.3 Measurement of Skin Perfusion Pressure

The skin perfusion pressure (SPP) is used to measure blood in the microcirculation around and within a wound using photoplethysmography with Doppler techniques and can be a useful predictor of wound healing potential. The SPP is performed by applying a pressure cuff to the extremity with the wound. Using a Doppler the measurement of the pressure at which perfusion first returns to the cutaneous microcirculation is obtained.

6.4.4 Ankle-Brachial Index

The ankle-brachial index (ABI) is a measurement that is the standard of care in the diagnosis of lower extremity PAD. The ABI also provides an objective baseline assessment that can be used to follow the progression of the disease process and evaluate the effectiveness of the disease plan. The ABI is performed by measuring the systolic blood pressure using a Doppler instrument from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries after the patient has been at rest in the supine position for 10 minutes (23).
ABI measurement will be obtained at baseline, month 3 and month 6.

6.4.5 Toe-Brachial Index and Toe-Systolic Pressure

The toe-brachial index (TBI) and toe-systolic pressure are a more reliable indicator of limb perfusion in patients with diabetes or the elderly because the small vessels of the toes are often spared from the medial calcification that may occur in the leg arteries. A small occlusive cuff is placed on the proximal portion of the great toe (or another toe in the event of an amputation). A photo-electrode is placed on the end of the toe to obtain an arterial waveform using infrared light. The return of toe pulsality is assessed by use of a plethysmographic detection device. The systolic pressure (TSP) is recorded at the point in which the baseline waveform is re-established. The ratio of the recorded toe systolic pressure (TSP) to the higher of

the two brachial pressures gives the TBI (23). TBI and TSP measurements will be obtained at baseline, month 3 and month 6.

7 Pharmacologic Loading Pre-revascularization

For patients requiring revascularization, pharmacologic loading of an ADP-receptor antagonist will have been ordered as per standard of care so as to minimize risks for post-procedural arterial thrombosis. For this study, patients will have been treated with clopidogrel up to, during, and immediately after the time of revascularization as is standard of care. After revascularization, an ADP-receptor antagonist (e.g., clopidogrel) is routinely continued for 6 months, and then discontinued. Patients will be screened and randomized for the study either in the hospital after the procedure prior to discharge or at the time of the first out-patient clinic visit following revascularization (approximately one to two weeks after the procedure). Patients will be randomized to either clopidogrel or ticagrelor. After randomization patients will receive study medication (ticagrelor) with a 90-day provision through 6 months follow-up, refilled at the 3 month clinic visit.

8 Safety Monitoring and Reporting

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. The term AE is used to include both serious and non-serious AEs.

An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

8.1 Adverse Events

The following adverse events will be collected from the time that informed consent is obtained for this study:

- Self-reported shortness of breath
- Symptomatic bradycardia defined as self-reported symptoms of shortness of breath, chest discomfort, or dizziness with a confirmed heart rate of < 45 bpm at the time of the symptoms.
- Adverse events that are not listed in the current labeling for the drugs (see Appendix A and Investigator Brochure for ticagrelor).
- Events that lead to discontinuation of drug or result in a dose modification.

8.2 Serious Adverse Events

The following SAEs will be collected from the time that informed consent is obtained until the month 6 visit:

- Death.
- Life threatening AEs.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- A disability/incapacity.
- A congenital anomaly/birth defect in the offspring of a patient who received drug.
- Important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

8.3 Other Events of Special Interest Considered as Serious

- Major bleeding defined as a composite of fatal bleeding, intracranial bleeding, hypovolemic shock or severe hypotension due to bleeding requiring pressors, or need for transfusion of at least 2 units in any 24-hour period.
- Major adverse limb events (surgical limb loss, major repeat revascularizations including thrombectomy, thrombolysis, or major lower extremity surgical procedure.

8.4 Documentation and Reporting of Adverse Events

Prompt reporting of the SAE to the Sponsor is essential so that legal and ethical obligations can be fulfilled. SAEs will be reported to the Sponsor within 24 hours of learning of the event. The causality of the SAE (the relationship to the study treatment/procedures) will be assessed by the investigator and reported to the Sponsor. The SAE will also be documented on the appropriate eCRF.

Since the Critical Limb Ischemia Study is exempted from IND reporting, the Sponsor does not have the responsibility to report any AEs/SAEs to the FDA. The Investigator will report all SAEs (regardless of causality or expectedness) and cases of pregnancy and overdose to the Sponsor and the Sponsor will report these events to AstraZeneca, so they can fulfill the regulatory reporting requirement.

The SAE awareness date will be the date that the investigator determines that the event meets protocol-specific criteria for an SAE. The SAE will be reported to AstraZeneca by the Sponsor within 24 hours of awareness.

The investigator is responsible for informing the IRB of the SAE as per local requirements.

The Sponsor will send the SAE report that will contain the MedWatch form and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com. The cover page will include the following:

- Investigator sponsored study (ISS)
- The Investigator's name and address

- The study name/title and AstraZeneca ISS reference number
- The causality of the SAE as reported by the Investigator.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca.

8.5 Safety Monitoring

Safety endpoints to be assessed include major bleeding and self-reported dyspnea and self-reported symptomatic bradycardia. Major bleeding is defined as a composite of fatal bleeding, intracranial bleeding, hypovolemic shock or severe hypotension due to bleeding requiring pressors, or need for transfusion of at least 2 units in any 24-hour period. Self-reported symptomatic bradycardia is defined as self-reported symptoms of shortness of breath, chest discomfort, or dizziness with a confirmed heart rate of < 45 bpm at the time of the symptoms.

9 Statistical Plan

9.1 Statistical Methods

Baseline covariates will be compared with Fisher's exact test for categorical variables and two-sample t-test for continuous variables with a normal distribution or rank sum test if non-normally distributed between treatment groups. All comparisons between treatment groups will be performed as intent-to-treat using two-tailed significance testing at a value of 0.05.
Mixed model repeated measures analysis (MMRM) will be used to conduct the between-group comparison of absolute change in TcPO2 at 3 months and 6 months follow-up, with adjustment of baseline TcPO2 level following revascularization. Estimated within-group least squares (LS) means of TcPO2 and between-group differences of LS means in TcPO2 at 3- and at 6-month follow-up time points will be obtained from the MMRM modeling.
If the TcPO2 data is not normally distributed, the same MMRM method will be performed to analyze the rank transformed TcPO2 data, however the descriptive data is presented with median (interquartile range), and the between-group differences are shown using F statistics. Meanwhile, relevant nonparametric methods will be applied as sensitivity analysis. Friedman test will be conducted to compare the TcPO2 repeated measures from baseline to 6 months follow-up between the treatment groups. A Wilcoxon signed rank test will be used to assess intragroup change in TcPO2 at 3- and at 6-month follow-up.
The percent change in TcPO2 over time and other continuous secondary endpoints will be analyzed using the same strategies. Safety endpoints, adverse events and other categorical secondary endpoints will be analyzed using Fisher's exact test. The relationships between the primary endpoint of change in TcPO2 at 6 months follow-up and the continuous secondary endpoints will be explored by regression analysis.

9.2 Sample size

The goal of this study is to compare the absolute change in TcPO2 among recently revascularized patients randomized to intervention (ticagrelor) or control (clopidogrel). With 60 patients, 30 per treatment group, this study will have 90% power at an acceptably low type I error rate (0.05) to detect a clinically significant 8 ± 8 mmHg difference in TcPO2, as discussed below.

It is anticipated that most revascularized patients will have a baseline TcPO2 result of approximately 40 mmHg, whereby a 25% change would reflect a final TcPO2 result of 50 mmHg. The standard deviation (SD) for TcPO2 among such a population is estimated to be 16 mmHg based on previously published data (11,19,20). The actual change in TcPO2 that might be induced by either ticagrelor or clopidogrel is unknown. However, based on our hypothesis of improved tissue oxygen tension with ticagrelor, it is anticipated that the ticagrelor group will increase TcPO2 to a greater degree with a SD for the intergroup difference approximately 50% of the baseline SD (16 mmHg). Therefore, we have designed this study to detect an intergroup difference in TcPO2 of 8 ± 8 mmHg assessed at 6 months. Even if clopidogrel induces no change in TcPO2 from baseline, an 8 mmHg increase in the ticagrelor group would represent a 20% improvement over baseline.

Given these assumptions, 26 patients per group will provide sufficient power to detect a large effect size that also reflects a clinically significant change in TcPO2 values. Adjusting for non-adherence and allowing for a 5% rate of crossover from ticagrelor to controls would require 28 patients per group. Attrition rates for this study are anticipated to be low and likely < 5%. However, given the severity of underlying illness among a population of severely symptomatic PAD, including previously reported mortality rates of 25% at 2 years (21), it seems reasonable to assume our population will have a baseline annual mortality rate of 5-10%. Adjusting the study with 30 patients per group would allow for 7.5% attrition while maintaining power to determine the desired effect.

Finally, our analysis will use 3 repeated measures to assess the TcPO2 endpoint at baseline, 3 months, and 6 months. The Friedman repeated measures ANOVA on ranks will be used to calculate the main effect differences among measurements repeated over time. This technique is particularly suitable if a great deal of variation between samples, especially at low TcPO2, where error variance estimates from standard ANOVA may be large.

10 Study Committees

The following committees will be responsible for the management of the study and the monitoring of the safety of the study patients.

10.1 Executive Steering Committee

The Executive Steering Committee (ESC) will have scientific responsibility for the study. They will review study conduct and progress, consider recommendations from the Medical Monitor and resolve any other study related issues.

10.2 Safety Monitoring Board

An independent Medical Monitor will be appointed to monitor the study by reviewing the case report forms, SAE and AE forms at specified intervals throughout the study and will be responsible for the oversight of safety.

11 Data Handling and Record Keeping

11.1 Data Collection

Data will be collected by the Nurse or Site Coordinator or designee. Data sources include patient reports and available medical records, including those from electronic medical record. Values for preoperative variables will be selected nearest to the date of the revascularization procedure, but used only if they were obtained within 30 days of the procedure.
C5Research Data Management will create a Case Report Form to document the agreed upon variables to be captured in the REDCap database.

11.2 REDCap Database:

Study data will be collected and managed by the site using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes Cleveland Clinic and was initiated at Vanderbilt University. The database is hosted at the Cleveland Clinic Datacenter. The system is protected behind a login and Secure Sockets Layer (SSL) encryption. There is an audit trail tracking all logins and activities in the database. Data collection is customized for each study or clinical study based on a study-specific data dictionary defined by the research team with guidance from the REDCap administrator in Quantitative Health Sciences at the Cleveland Clinic.

11.3 REDCap Completion Guidelines:

Cleveland Clinic Data Management (DM) will create a REDCap Completion Guidelines document to assist the site in data entry.

11.4 Retention of Records

Investigator files containing study related documents will be retained according to the agreed timeframe outlined in the contractual agreement and at least for a minimum of two (2) years after a marketing application is approved for the drug; or 2 years after investigational use is discontinued and FDA has been notified in accordance with the applicable regulations. Records shall be accessible for inspection by authorized representatives of the Sponsor, or the FDA. Records may be discarded upon written notification by the Sponsor. To avoid error, the Principal Investigator should contact C5Research / AstraZeneca, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be contacted if the Principal Investigator plans to leave the investigational site so that appropriate arrangements for file custodianship can be made.

12 Study Monitoring, Auditing, and Inspecting

C5Research is responsible for monitoring the safety and effectiveness of this study.

The study will be monitored according to the Monitoring Plan, per the applicable C5Research Standard Operating Procedures for clinical monitoring and in compliance with Title 21 CFR Part 312.

13 Ethical Considerations

This study will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines and the Cleveland Clinic IRB.
The Investigator has the ethical and legal responsibility to ensure that each patient is given a full explanation of the study. Written informed consent will be obtained from all patients before any study-specific procedures are performed.
The Cleveland Clinic IRB must review and approve the protocol and informed consent form before the study can begin.

14 Publication

The study investigators will present and publish the results of the study.

15 References

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Appendix A

CLOPIDOGREL BISULFATE- clopidogrel bisulfate tablet, film coated
Mylan Institutional Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use clopidogrel tablets safely and effectively.
See full prescribing information for clopidogrel tablets.

Clopidogrel Tablets, USP
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of clopidogrel tablets depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with clopidogrel tablets at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

RECENT MAJOR CHANGES

Dosage and Administration (2.4) 12/2011
Warnings and Precautions (5.1) 12/2011

INDICATIONS AND USAGE

Clopidogrel is a $P2Y_{12}$ platelet inhibitor indicated for:

- Acute coronary syndrome
  - For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)] including patients who are to be managed medically and those who are to be managed with coronary revascularization, clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. (1.1)
  - For patients with ST-elevation myocardial infarction (STEMI), clopidogrel has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown. (1.1)
- Recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Clopidogrel has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death. (1.2)

DOSAGE AND ADMINISTRATION

- Acute coronary syndrome (2.1)
  - Non-ST-segment elevation ACS (UA/NSTEMI): 300 mg loading dose followed by 75 mg once daily, in combination with aspirin (75 mg to 325 mg once daily)
  - STEMI: 75 mg once daily, in combination with aspirin (75 mg to 325 mg once daily), with or without a loading dose and with or without thrombolytics.
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg and 300 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

WARNINGS AND PRECAUTIONS

- Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with omeprazole or esomeprazole. (5.1)
- Bleeding: Clopidogrel increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)
- Discontinuation of clopidogrel: Premature discontinuation increases risk of cardiovascular events. (5.3)
- Recent transient ischemic attack or stroke: Combination use of clopidogrel and aspirin in these patients was not shown to be more effective than clopidogrel alone, but was shown to increase major bleeding. (5.4)
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with clopidogrel, including fatal cases. (5.5)

ADVERSE REACTIONS

Bleeding, including life threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

DRUG INTERACTIONS

- Nonsteroidal anti-inflammatory drugs (NSAIDs): Combination use increases risk of gastrointestinal bleeding. (7.2)
- Warfarin: Combination use increases risk of bleeding. (7.3)

USE IN SPECIFIC POPULATIONS

Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)
See Section 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of clopidogrel tablets is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1)]*. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel tablets at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see Clinical Pharmacology (12.5)]*. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers *[see Dosage and Administration (2.3)]*.

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome (ACS)

- For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST- elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, clopidogrel tablets have been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

- For patients with ST-elevation myocardial infarction (STEMI), clopidogrel tablets have been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of clopidogrel therapy in ACS is unknown.

1.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel tablets have been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

2 DOSAGE AND ADMINISTRATION

2.1 Acute Coronary Syndrome

Clopidogrel tablets can be administered with or without food *[see Clinical Pharmacology (12.3)]*.

For patients with non-ST-elevation ACS (UA/NSTEMI), initiate clopidogrel tablets with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75 mg to 325 mg once daily) and continue in combination with clopidogrel tablets *[see Clinical Studies (14.1)]*.

For patients with STEMI, the recommended dose of clopidogrel tablets is 75 mg once daily orally, administered in combination with aspirin (75 mg to 325 mg once daily), with or without thrombolytics. Clopidogrel tablets may be initiated with or without a loading dose *[see Clinical Studies (14.1)]*.

2.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of clopidogrel tablets is 75 mg once daily orally, with or without food *[see Clinical Pharmacology (12.3)]*.

2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response *[see Clinical Pharmacology (12.5)]*, an appropriate dose regimen for this patient population has not been established.

2.4 Use with Proton Pump Inhibitors (PPI)

Avoid using omeprazole or esomeprazole with clopidogrel. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite *[see Warnings and Precautions (5.1), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- 75 mg tablets: white film-coated, round, unscored tablets debossed with **M** on one side of the tablet

and **C27** on the other side.
- 300 mg tablets: white film-coated, oval, unscored tablets debossed with **M C28** on one side of the tablet and blank on the other side.

4 CONTRAINDICATIONS

4.1 Active Bleeding

Clopidogrel tablets are contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.2 Hypersensitivity

Clopidogrel tablets are contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 *[see Boxed Warning]* and by concomitant medications that interfere with CYP2C19.

Proton Pump Inhibitors

Avoid concomitant use of clopidogrel with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel *[see Drug Interactions (7.1) and Dosage and Administration (2.4)]*.

5.2 General Risk of Bleeding

Thienopyridines, including clopidogrel, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue clopidogrel 5 days prior to surgery. In patients who stopped therapy more than 5 days prior to CABG the rates of major bleeding were similar (event rate 4.4% clopidogrel + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within 5 days of CABG, the major bleeding rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7 to 10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

5.3 Discontinuation of Clopidogrel

Avoid lapses in therapy, and if clopidogrel must be temporarily discontinued, restart as soon as possible. Premature discontinuation of clopidogrel may increase the risk of cardiovascular events.

5.4 Patients with Recent Transient Ischemic Attack (TIA) or Stroke

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone, but the combination has been shown to increase major bleeding.

5.5 Thrombotic Thrombocytopenic Purpura (TTP)

TTP, sometimes fatal, has been reported following use of clopidogrel, sometimes after a short exposure (< 2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:
- Bleeding *[see Warnings and Precautions (5.2)]*
- Thrombotic thrombocytopenic purpura *[see Warnings and Precautions (5.5)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions and durations of follow up, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in

the clinical trials of another drug and may not reflect the rates observed in practice.

Clopidogrel has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for one year or more. The clinically important adverse reactions observed in trials comparing clopidogrel plus aspirin to placebo plus aspirin and trials comparing clopidogrel alone to aspirin alone are discussed below.

Bleeding

CURE

In CURE, clopidogrel use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

The overall incidence of bleeding is described in Table 1.

Table 1: CURE Incidence of Bleeding Complications (% Patients)

Event	Clopidogrel (+ aspirin)* (n = 6,259)	Placebo (+ aspirin)* (n = 6,303)
Major Bleeding†	3.7‡	2.7§
Life threatening bleeding	2.2	1.8
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 transfusion (≥ 4 units)	1.2	1
Other major bleeding	1.6	1
Significantly disabling	0.4	0.3
Intraocular bleeding with significant loss of vision	0.05	0.03
Requiring 2 to 3 units of blood	1.3	0.9
Minor Bleeding¶	5.1	2.4

* Other standard therapies were used as appropriate.

† Life threatening and other major bleeding.

‡ Major bleeding event rate for clopidogrel + aspirin was dose dependent on aspirin: < 100 mg = 2.6%; 100 mg to 200 mg = 3.5%; > 200 mg = 4.9% Major bleeding event rates for clopidogrel + aspirin by age were: < 65 years = 2.5%, ≥ 65 to < 75 years = 4.1%, ≥ 75 years = 5.9%

§ Major bleeding event rate for placebo + aspirin was dose dependent on aspirin: < 100 mg = 2%; 100 mg to 200 mg = 2.3%; > 200 mg = 4% Major bleeding event rates for placebo + aspirin by age were: < 65 years = 2.1%, ≥ 65 to < 75 years = 3.1%, ≥ 75 years = 3.6%

¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.

COMMIT

In COMMIT, similar rates of major bleeding were observed in the clopidogrel and placebo groups, both of which also received aspirin (see Table 2).

Table 2: Incidence of Bleeding Events in COMMIT (% Patients)

Type of bleeding	**Clopidogrel (+ aspirin) (n = 22,961)**	**Placebo (+ aspirin) (n = 22,891)**	**p-value**
Major* noncerebral or cerebral bleeding†	0.6	0.5	0.59
Major noncerebral	0.4	0.3	0.48
Fatal	0.2	0.2	0.90
Hemorrhagic stroke	0.2	0.2	0.91
Fatal	0.2	0.2	0.81
Other noncerebral bleeding (non-major)	3.6	3.1	0.005
Any noncerebral bleeding	3.9	3.4	0.004

* Major bleeds were 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 + aspirin by age were: < 60 years = 0.3%, ≥ 60 to < 70 years = 0.7%, ≥ 70 years = 0.8%. Event rates for placebo + aspirin by age were: < 60 years = 0.4%, ≥ 60 to < 70 years = 0.6%, ≥ 70 years = 0.7%.

CAPRIE (Clopidogrel vs. Aspirin)

In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2% in those taking clopidogrel vs. 2.7% in those taking aspirin; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for clopidogrel compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis and hematoma.

Other Adverse Events

In CURE and CHARISMA, which compared clopidogrel plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between clopidogrel and placebo.

In CAPRIE, which compared clopidogrel to aspirin, pruritus was more frequently reported in those taking clopidogrel. No other difference in the rate of adverse events (other than bleeding) was reported.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of clopidogrel. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders:* Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP)
- *Eye disorders:* Eye (conjunctival, ocular, retinal) bleeding
- *Gastrointestinal disorders:* Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- *General disorders and administration site condition:* Fever, hemorrhage of operative wound
- *Hepato-biliary disorders:* Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- *Immune system disorders:* Hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Musculoskeletal, connective tissue and bone disorders:* Musculoskeletal bleeding, myalgia, arthralgia, arthritis
- *Nervous system disorders:* Taste disorders, fatal intracranial bleeding, headache
- *Psychiatric disorders:* Confusion, hallucinations
- *Respiratory, thoracic and mediastinal disorders:* Bronchospasm, interstitial pneumonitis, respiratory tract bleeding
- *Renal and urinary disorders:* Increased creatinine levels
- *Skin and subcutaneous tissue disorders:* Maculopapular or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, erythema multiforme, skin bleeding, lichen planus, generalized pruritus
- *Vascular disorders:* Vasculitis, hypotension

7 DRUG INTERACTIONS

7.1 CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition *[see Warnings and Precautions (5.1) and Dosage and Administration (2.4)]*.

Proton Pump Inhibitors (PPI)

Avoid concomitant use of clopidogrel with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with clopidogrel. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of clopidogrel than did omeprazole or esomeprazole *[see Dosage and Administration (2.4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Coadministration of clopidogrel and NSAIDs increases the risk of gastrointestinal bleeding.

7.3 Warfarin (CYP2C9 Substrates)

Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration

of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category B

Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric populations have not been established.

Additional information describing a clinical study in which efficacy was not demonstrated in neonates and infants is approved in the package insert for Bristol-Myers Squibb's clopidogrel tablets. However, due to Bristol-Myers Squibb's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

8.5 Geriatric Use

Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with clopidogrel were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with clopidogrel were 60 years and older, 26% of whom were 70 years and older.

The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 1 and Table 2 for the CURE and COMMIT trials, respectively *[see Adverse Reactions (6.1)]*. No dosage adjustment is necessary in elderly patients.

8.6 Renal Impairment

Experience is limited in patients with severe and moderate renal impairment *[see Clinical Pharmacology (12.2)]*.

8.7 Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment *[see Clinical Pharmacology (12.2)]*.

10 OVERDOSAGE

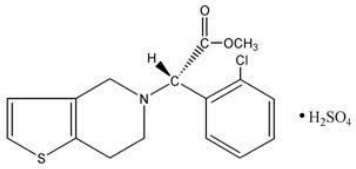
Platelet inhibition by clopidogrel is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.

Based on biological plausibility, platelet transfusion may restore clotting ability.

11 DESCRIPTION

Clopidogrel bisulfate is a thienopyridine class inhibitor of $P2Y_{12}$ADP platelet receptors. Chemically it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(*4H*)-acetate sulfate (1:1). The molecular formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S{\cdot}H_2SO_4$ and its molecular weight is 419.9.

The structural formula is as follows:



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

Clopidogrel tablets, USP for oral administration are provided as either white, round, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or white, oval, film-coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

Each tablet contains anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.

12.2 Pharmacodynamics

Clopidogrel must be metabolized 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 $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady-state between Day 3 and Day 7. At steady-state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Geriatric Patients

Elderly (≥ 75 years) and young healthy subjects had similar effects on platelet aggregation.

Renally-Impaired Patients

After repeated doses of 75 mg clopidogrel per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

Hepatically-Impaired Patients

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Gender

In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

12.3 Pharmacokinetics

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of Food

Clopidogrel can be administered with or without food. In a study in healthy male subjects when clopidogrel 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC_{0-24} was unchanged in the presence of food, while there was a 57% decrease in active metabolite C_{max}. Similar results were observed when a clopidogrel 300 mg loading dose was administered with a high fat breakfast.

Metabolism

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel 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. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

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. In the 75 mg to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2- and 2.7-fold increases in C_{max} and AUC, respectively.

Elimination

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

Drug Interactions

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain inhibitors of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

Proton Pump Inhibitors (PPI)

The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of clopidogrel 75 mg evaluated in dedicated drug interaction studies is presented in Figure 1.

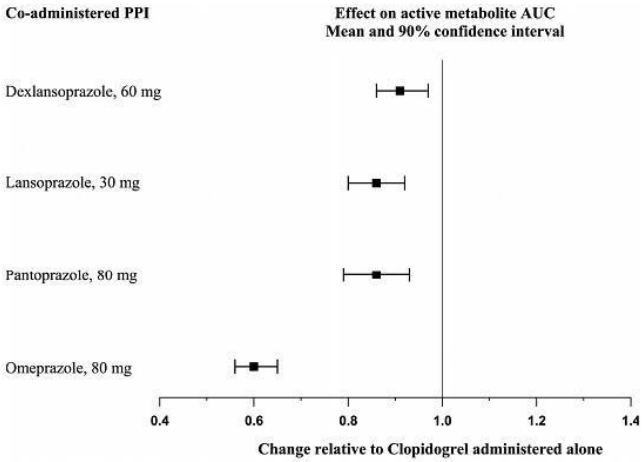


Figure 1: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Clopidogrel 75 mg Alone or with Proton Pump Inhibitors (PPIs)

Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

12.5 Pharmacogenomics

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 *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolizers. 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 metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, ten each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. 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 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

	Dose	Ultrarapid (n = 10)	Extensive (n = 10)	Intermediate (n = 10)	Poor (n = 10)
C_{max} (ng/mL)	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (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)
VASP-PRI (%)†	300 mg (24 h)	73 (12)	68 (16)	78 (12)	91 (12)
	600 mg (24 h)	51 (20)	48 (20)	56 (26)	85 (14)
	75 mg (Day 5)	40 (9)	39 (14)	50 (16)	83 (13)
	150 mg (Day 5)	20 (10)	24 (10)	29 (11)	61 (18)

Values are mean (SD)

* Inhibition of platelet aggregation with 5 mcM ADP; larger value indicates greater platelet inhibition

† Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition

Some published studies suggest that intermediate metabolizers have decreased active metabolite exposure and diminished antiplatelet effects.

The relationship between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in retrospective analyses of clopidogrel-treated subjects in CHARISMA (n = 2.428) and TRITON-TIMI 38 (n = 1,477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Acute Coronary Syndrome

CURE

The CURE study included 12,562 patients with ACS without ST-elevation (UA or NSTEMI) 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 ST-elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥ 65 years of age.

Patients were randomized to receive clopidogrel (300 mg loading dose followed by 75 mg once daily) or placebo, and were treated for up to one year. Patients also received aspirin (75 mg to 325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for 3 days prior to randomization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10% to 28%; p < 0.001) for the clopidogrel-treated group (see Table 4).

Table 4: Outcome Events in the CURE Primary Analysis

Outcome	Clopidogrel (+ aspirin)* (n = 6,259)	Placebo (+ aspirin)* (n = 6,303)	Relative Risk Reduction (%) (95% CI)
Primary outcome (Cardiovascular death, MI, stroke)	582 (9.3%)	719 (11.4%)	20% (10.3, 27.9) p < 0.001
All Individual Outcome Events:†			
CV death	318 (5.1%)	345 (5.5%)	7% (-7.7, 20.6)
MI	324 (5.2%)	419 (6.6%)	23% (11, 33.4)
Stroke	75 (1.2%)	87 (1.4%)	14% (-17.7, 36.6)

* Other standard therapies were used as appropriate.

† 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.

Most of the benefit of clopidogrel occurred in the first 2 months, but the difference from placebo was maintained throughout the course of the trial (up to 12 months) (see Figure 2).

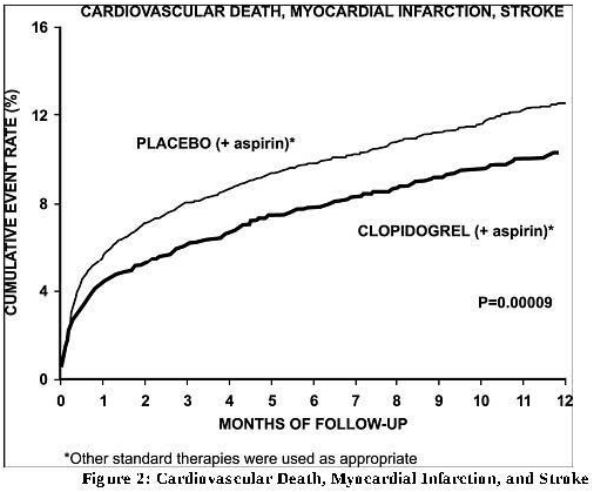


Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study

In CURE, the use of clopidogrel was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics, as shown in Figure 3. The benefits associated with clopidogrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH, intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of clopidogrel was observed independently of the

dose of aspirin (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study anti-platelet drugs, and chronic NSAIDs was not allowed in CURE.

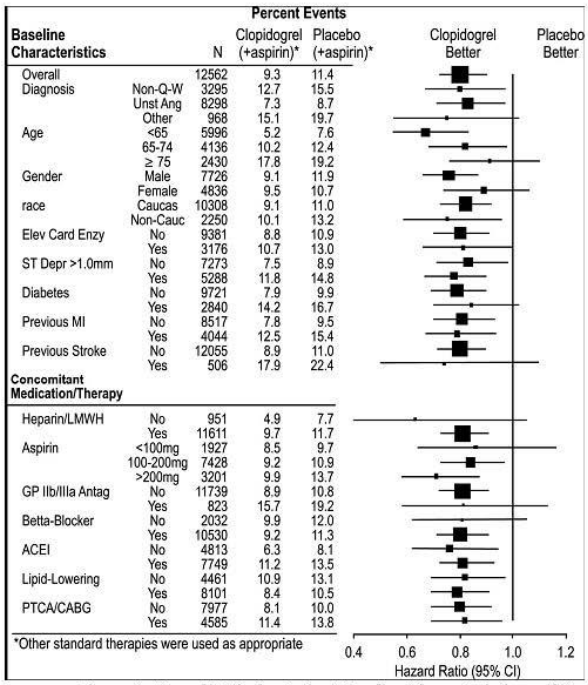


Figure 3: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study

The use of clopidogrel in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the clopidogrel group, 126 patients [2%] in the placebo group; relative risk reduction of 43%), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the clopidogrel group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%). The use of clopidogrel in CURE did not affect the number of patients treated with CABG or PCI (with or without stenting), (2,253 patients [36%] in the clopidogrel group, 2,324 patients [36.9%] in the placebo group; relative risk reduction of 4%).

COMMIT

In patients with STEMI, the safety and efficacy of clopidogrel were evaluated in the randomized, placebo-controlled, double-blind study, COMMIT. COMMIT included 45,852 patients presenting within 24 hours of the onset of the symptoms of myocardial infarction with supporting ECG abnormalities (i.e., ST-elevation, ST-depression or left bundle-branch block). Patients were randomized to receive clopidogrel (75 mg once daily) or placebo, in combination with aspirin (162 mg per day), for 28 days or until hospital discharge, whichever came first.

The primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death.

The patient population included 28% women, 58% age ≥ 60 years (26% age ≥ 70 years), 55% patients who received thrombolytics, 68% who received ACE-inhibitors, and only 3% who underwent PCI.

As shown in Table 5 and Figure 4 and Figure 5 below, clopidogrel significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002).

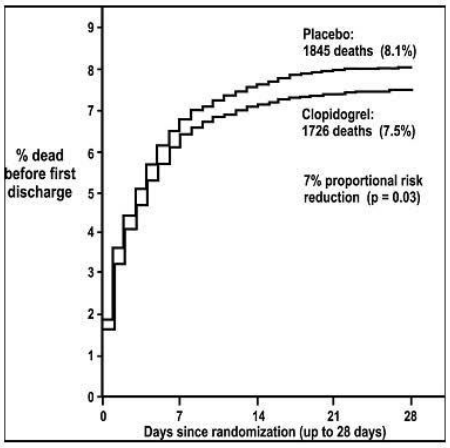
Table 5: Outcome Events in the COMMIT Analysis

Event	Clopidogrel (+ aspirin) (N = 22,961)	Placebo (+ aspirin) (N = 22,891)	Odds ratio (95% CI)	p-value
Composite endpoint: Death, MI, or Stroke*	2,121 (9.2%)	2,310 (10.1%)	0.91 (0.86, 0.97)	0.002
Death	1,726 (7.5%)	1,845 (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

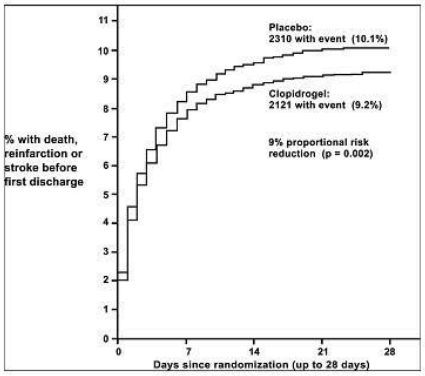
* The difference between the composite endpoint and the sum of death + non-fatal MI + non-fatal stroke indicates that nine patients (two clopidogrel and seven placebo) suffered both a non-fatal stroke and a non-fatal MI.

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



* All treated patients received aspirin.

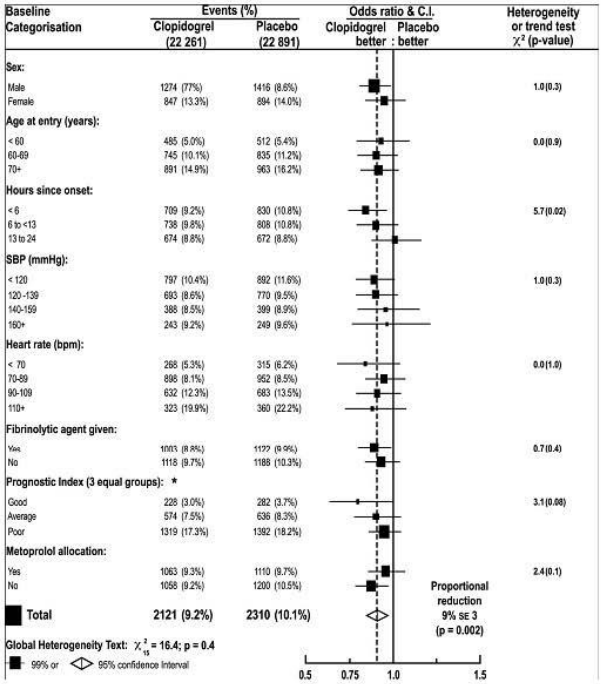
Figure 4: Cumulative Event Rates for Death in the COMMIT Study*



* All treated patients received aspirin.

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

The effect of clopidogrel did not differ significantly in various pre-specified subgroups as shown in Figure 6. The effect was also similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history (see Figure 7). Such subgroup analyses should be interpreted cautiously.



* Three similar-sized prognostic index groups were based on absolute risk of primary composite outcome for each patient calculated from baseline prognostic variables (excluding allocated treatments) with a Cox regression model.

Figure 6: Effects of Adding Clopidogrel to Aspirin on the Combined Primary Endpoint Across Baseline and Concomitant Medication Subgroups for the COMMIT Study

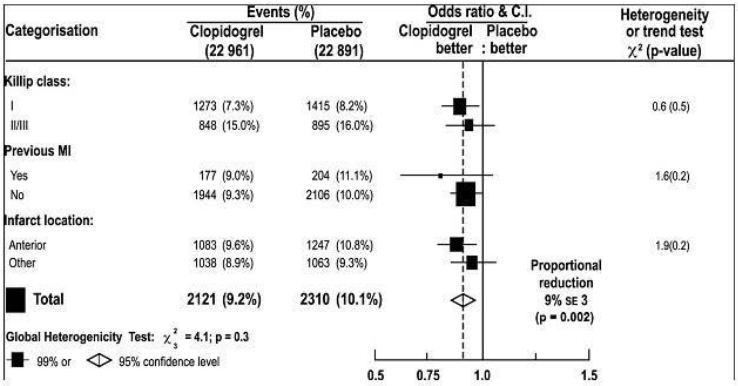


Figure 7: Effects of Adding Clopidogrel to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study

14.2 Recent Myocardial Infarction, Recent Stroke, or Established Peripheral Arterial Disease

CAPRIE

The CAPRIE trial was a 19,185 patient, 304 center, international, randomized, double-blind, parallel-group study comparing clopidogrel (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new

myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

Table 6: Outcome Events in the CAPRIE Primary Analysis

Patients	Clopidogrel n = 9,599	Aspirin n = 9,586
Ischemic stroke (fatal or not)	438 (4.6%)	461 (4.8%)
MI (fatal or not)	275 (2.9%)	333 (3.5%)
Other vascular death	226 (2.4%)	226 (2.4%)
Total	939 (9.8%)	1,020 (10.6%)

As shown in Table 6, clopidogrel was associated with a lower incidence of outcome events, primarily MI. The overall relative risk reduction (9.8% vs. 10.6%) was 8.7%, p = 0.045. Similar results were obtained when all-cause mortality and all-cause strokes were counted instead of vascular mortality and ischemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was lower in the clopidogrel group.

The curves showing the overall event rate are shown in Figure 8. The event curves separated early and continued to diverge over the 3-year follow-up period.

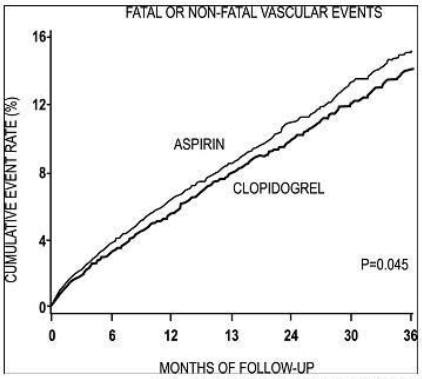


Figure 8: Fatal or Non-Fatal Vascular Events in the CAPRIE Study

The statistical significance favoring clopidogrel over aspirin was marginal (p = 0.045). However, because aspirin is itself effective in reducing cardiovascular events in patients with recent myocardial infarction or stroke, the effect of clopidogrel is substantial.

The CAPRIE trial included a population that was randomized on the basis of three entry criteria. The efficacy of clopidogrel relative to aspirin was heterogeneous across these randomized subgroups (p = 0.043). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of clopidogrel over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was not numerically superior to aspirin.

14.3 Lack of Established Benefit of Clopidogrel Plus Aspirin in Patients with Multiple Risk Factors or Established Vascular Disease

CHARISMA

The CHARISMA trial was a 15,603 subject, randomized, double-blind, parallel group study comparing clopidogrel (75 mg daily) to placebo for prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75 mg to 162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the clopidogrel group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p = 0.22). Bleeding of all severities was more common in the subjects randomized to clopidogrel.

16 HOW SUPPLIED/STORAGE AND HANDLING

Clopidogrel Tablets, USP are available as tablets containing clopidogrel bisulfate, USP equivalent to

75 mg or 300 mg of clopidogrel.

The 75 mg tablet is a white film-coated, round, unscored tablet debossed with **M** on one side of the tablet and **C27** on the other side. They are available as follows:

NDC 51079-557-20 - Unit dose blister packages of 100 (10 cards of 10 tablets each).

The 300 mg tablet is a white film-coated, oval, unscored tablet debossed with **M C28** on one side of the tablet and blank on the other side. They are available as follows:

NDC 51079-558-03 - Unit dose blister packages of 30 (5 cards of 6 tablets each).

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

[See Medication Guide (17.6).]

17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of clopidogrel.
- Tell patients to take clopidogrel exactly as prescribed.
- Remind patients not to discontinue clopidogrel without first discussing it with the physician who prescribed clopidogrel.

17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with clopidogrel and other drugs in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking clopidogrel before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping clopidogrel.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take, including prescription or over-the-counter proton pump inhibitors (e.g., omeprazole), warfarin, or NSAIDs *[see Warnings and Precautions (5)]*.

17.6 Medication Guide

MEDICATION GUIDE
CLOPIDOGREL TABLETS, USP
(kloe pid' oh grel)
75 mg and 300 mg

Read this Medication Guide before you start taking clopidogrel tablets and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about clopidogrel tablets?

1. Clopidogrel tablets may not work as well in people who:

- **have certain genetic factors that affect how the body breaks down clopidogrel.** Your doctor may do genetic tests to make sure clopidogrel tablets are right for you.
- **take certain medicines, especially omeprazole (Prilosec®*) or esomeprazole (Nexium®*).** Your doctor may change the medicine you take for stomach acid problems while you take clopidogrel tablets.

2. **Clopidogrel tablets can cause bleeding which can be serious and can sometimes lead to death.** Clopidogrel tablets are a blood thinner medicine that lowers the chance of blood clots forming in your body. While you take clopidogrel tablets:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer for any bleeding to stop

Call your doctor right away if you have any of these signs or symptoms of bleeding:
- unexpected bleeding or bleeding that lasts a long time
- blood in your urine (pink, red or brown urine)
- red or black stools (looks like tar)
- bruises that happen without a known cause or get larger
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds

Do not stop taking clopidogrel tablets without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking clopidogrel tablets too soon, have a higher risk of getting a blood clot on the stent, having a heart attack, or dying. If you must stop clopidogrel tablets because of bleeding, your risk of a heart attack may be higher.

What are clopidogrel tablets?

Clopidogrel tablets are a prescription medicine used to treat people who have any of the following:
- chest pain due to heart problems
- poor circulation in their legs (peripheral arterial disease)
- a heart attack
- a stroke

Clopidogrel tablets are used alone or with aspirin to lower your chance of having another serious problem with your heart or blood vessels such as heart attack, stroke, or blood clot that can lead to death.

Platelets are blood cells that help your blood clot normally. Clopidogrel tablets help to prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if clopidogrel tablets are safe and effective in children.

Who should not take clopidogrel tablets?

Do not take clopidogrel tablets if you:
- currently have a condition that causes bleeding, such as a stomach ulcer
- are allergic to clopidogrel or other ingredients in clopidogrel tablets. See the end of this leaflet for a complete list of ingredients in clopidogrel tablets.

What should I tell my doctor before taking clopidogrel tablets?

Before you take clopidogrel tablets, tell your doctor if you:
- have a history of bowel (gastrointestinal) or stomach ulcers
- have a history of bleeding problems
- plan to have surgery or a dental procedure. See "**How should I take clopidogrel tablets?**"
- are pregnant or plan to become pregnant. It is not known if clopidogrel tablets will harm your unborn baby
- are breast-feeding or plan to breast-feed. It is not known if clopidogrel passes into your breast milk. You and your doctor should decide if you will take clopidogrel tablets or breast-feed. You should not do both without talking to your doctor.

Tell all of your doctors and your dentist that you are taking clopidogrel tablets. They should talk to the doctor who prescribed clopidogrel tablets for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription, non-prescription medicines, vitamins and herbal supplements.

Clopidogrel tablets may affect the way other medicines work, and other medicines may affect how clopidogrel tablets work. See "**What is the most important information I should know about clopidogrel tablets?**"

Taking clopidogrel tablets with certain other medicines may increase your risk of bleeding.

Especially tell your doctor if you take:
- aspirin, especially if you have had a stroke. Always talk to your doctor about whether you should take aspirin along with clopidogrel tablets to treat your condition.
- Non-steroidal anti-inflammatory drugs (NSAIDs). Ask your doctor or pharmacist for a list of NSAID medicines if you are not sure.
- warfarin (Coumadin®*, Jantoven®*)

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take clopidogrel tablets?
- Take clopidogrel tablets exactly as your doctor tells you.

- Do not change your dose or stop taking clopidogrel tablets without talking to your doctor first. Stopping clopidogrel tablets may increase your risk of heart attack or stroke.
- Take clopidogrel tablets with aspirin as instructed by your doctor.
- You can take clopidogrel tablets with or without food.
- If you miss a dose, take clopidogrel tablets as soon as you remember. If it is almost time for your next dose, skip the missed dose. Take the next dose at your regular time. Do not take two doses of clopidogrel tablets at the same time unless your doctor tells you to.
- If you take too much clopidogrel tablets, call your doctor or go to the nearest emergency room right away.
- Talk with your doctor about stopping your clopidogrel tablets before you have surgery. Your doctor may tell you to stop taking clopidogrel tablets at least 5 days before you have surgery to avoid excessive bleeding during surgery.

What are the possible side effects of clopidogrel tablets?

Clopidogrel tablets can cause serious side effects including:

- See "**What is the most important information I should know about clopidogrel tablets?**"
- **A blood clotting problem called Thrombotic Thrombocytopenic Purpura (TTP).** TTP can happen with clopidogrel tablets, sometimes after a short time (less than 2 weeks). TTP is a blood clotting problem where blood clots form in blood vessels; and can happen anywhere in the body. TTP needs to be treated in a hospital right away, because it may cause death. Get medical help right away if you have any of these symptoms and they can not be explained by another medical condition:

- purplish spots (called purpura) on the skin or in the mouth (mucous membranes) due to bleeding under the skin
- your skin or the whites of your eyes are yellow (jaundice)
- you feel tired or weak
- your skin looks very pale
- fever
- fast heart rate or feeling short of breath
- headache
- speech changes
- confusion
- coma
- stroke
- seizure
- low amount of urine, or urine that is pink or has blood in it
- stomach area (abdominal) pain
- nausea, vomiting, or diarrhea
- vision changes

Tell your doctor if you have any side effect that bothers you or that does not go

away.

These are not all the possible side effects of clopidogrel tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store clopidogrel tablets?

- Store clopidogrel tablets at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Keep clopidogrel tablets and all medicines out of the reach of children.

General information about clopidogrel tablets

Medicines are sometimes used for purposes other than those listed in a Medication Guide. Do not take clopidogrel tablets for a condition for which it was not prescribed. Do not give clopidogrel tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about clopidogrel tablets. If you would like more information, talk to your doctor. Ask your doctor or pharmacist for information about clopidogrel tablets that was written for healthcare professionals.

For more information, call 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in clopidogrel tablets?

Active ingredient: clopidogrel bisulfate

Inactive ingredients: anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate and titanium dioxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.

*The brands listed are trademarks of their respective owners.

Manufactured by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Distributed by:
UDL Laboratories, Inc.
Rockford, IL 61103

S-11223
4/12

PRINCIPAL DISPLAY PANEL - 75 mg

NDC 51079-557-20

CLOPIDOGREL
TABLETS, USP
75 mg*

100 Tablets (10 x 10)

*Each film-coated tablet
contains 97.875 mg of
clopidogrel bisulfate, USP
equivalent to 75 mg of
clopidogrel base.

Usual Dosage: See accompanying
prescribing information.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

Manufactured by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Rx only

S-11224

Packaged and Distributed by:

UDL LABORATORIES, INC.

ROCKFORD, IL 61103

This unit dose package is not child resistant.

For institutional use only.

Keep this and all drugs out of the reach of children.

This container provides light-resistance.

See window for lot number and expiration date.

Appendix B

Rutherford Classification

- Stage 0 – Asymptomatic
- Stage 1 – Mild claudication
- Stage 2 – Moderate claudication
- Stage 3 – Severe claudication
- Stage 4 – Rest pain
- Stage 5 – Ischemic ulceration not exceeding ulcer of the digits of the foot
- Stage 6 – Severe ischemic ulcers or frank gangrene