EU-RISK MANAGEMENT PLAN FOR PLAVIX®/ISCOVER® (CLOPIDOGREL HYDROGEN SULFATE)

Rsik Management Plan (RMP) Version number	Version 2.7
Data Lock Point (DLP)	17-NOV-2020
Date of final sign-off	22-NOV-2024

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk Management Plan (RMP) updated in response to the European Medicines Agency (EMA) request for revising Annex 4 - Follow-up Questionnaire (FUQ).
Summary of significant changes in this RMP	Part I – updated indication as per approved procedure EMEA/H/C/WS/2150 Annex 4 – revised FUQ. Annex 8 – updated Summary of changes to the RMP over time.

EMA/EMEA: European Medicines Agency; FUQ: Follow-Up Questionnaire; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	2.6
Approved with procedure	EMEA/H/C/WS/2150
Date of approval (opinion date)	Committee for Medicinal Products for Human Use (CHMP) opinion date 10-Nov-2022

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	Lisa Naditch-Brule[a], MD
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ABCD2:	Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnoses
ACS:	Acute Coronary Syndrome
ACTIVE:	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Event
ADP:	Adenosine Diphosphate
ADR:	Adverse Drug Reaction
AF:	Atrial Fibrillation
AGEP:	Acute Generalized Exanthematous Pustulosis
ASA:	Acetylsalicylic Acid
ATC:	Anatomical Therapeutic Chemical
B/R:	Benefit-Risk
CABG:	Coronary Artery Bypass Graft
CAD:	Coronary Artery Disease
CAPRIE:	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Event
CDC:	Centers for Disease Control and Prevention
CHADS:	Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke
CHANCE:	Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event
CHF:	Congestive Heart Failure
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CLARINET:	Clopidogrel to Lower Arterial Thrombotic Risk in Neonates and Infants Trial
CLARITY:	Clopidogrel as Adjunctive Reperfusion Therapy
COMMIT:	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COPD:	Chronic Obstructive Pulmonary Disease
COX:	Cyclo-oxygenase
CURE:	Clopidogrel in Unstable Angina to Prevent Recurrent Event
CURRENT-OASIS-7:	Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies for Ischemic Syndromes
CV:	Cardiovascular
CYP:	Cytochrome P450
DAPT:	Dual Antiplatelet Therapy
DDD:	Defined Daily Dose
DLP:	Data Lock Point
DOT:	Duration of Treatment
ECG:	Electrocardiogram
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EM:	Erythema Multiforme
EMA/EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report

ESC:	European Society of Cardiology
EU:	European Union
FU:	Follow-Up
FUQ:	Follow-Up Questionnaire
GBD:	Global Burden of Disease
GI:	Gastrointestinal
HCP:	Healthcare Professional
HR:	Hazard Ratio
ICH:	Intracranial Hemorrhage
IHD:	Ischemic Heart Disease
INN:	International Nonproprietary Name
IS:	Ischemic Stroke
ISS:	Investigator Sponsored Study
ITT:	Intent To Treat
LD:	Loading Dose
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MI:	Myocardial Infarction
mIS:	Minor Ischemic Stroke
NEDICES:	Neurological Disorders in Central Spain
NIHSS:	National Institutes of Health Stroke Scale
NOAC:	Non-Vitamin K Antagonist Oral Anticoagulant
NSAID:	Non-Steroidal Anti-inflammatory Drug
NSTEMI:	Non ST-Segment Elevation Myocardial Infarction
OAC:	Oral Anti-Coagulant
OASIS:	Organization to Assess Strategies for Ischemic Syndrome
p:	Probability
PAD:	Peripheral Arterial Disease
PARC:	Performance Analysis Reporting Center
PBRER:	Periodic Benefit-Risk Evaluation Report
PCI:	Percutaneous Coronary Intervention
PICOLO:	Platelet Aggregation Inhibition in Children on Clopidogrel
PL:	Package Leaflet
POINT:	Platelet-Oriented Inhibition in New Transient ischemic attack and minor ischemic stroke
PPI:	Proton Pump Inhibitor
PSUR:	Periodic Safety Update Report
PTC:	Product Technical Complaint
Q:	Quarter
QPPV:	Qualified Person Responsible for Pharmacovigilance
RCT:	Randomized Controlled Trial
RMP:	Risk Management Plan
SD:	Standard Deviation
SJS:	Stevens-Johnson Syndrome
SmPC:	Summary of Product Characteristics
SSRI:	Selective Serotonin Reuptake Inhibitor

STE:	ST Segment Elevation
STEMI:	ST-Segment Elevation Myocardial Infarction
TEN:	Toxic Epidermal Necrolysis
TIA:	Transient Ischemic Attack
TIMI:	Thrombosis in Myocardial Infarction
TTP:	Thrombotic Thrombocytopenic Purpura
UA:	Unstable Angina
UI:	Uncertainty Interval
US:	United States
VKA:	Vitamin K Antagonist
WHO:	World Health Organization

PART I: PRODUCT (s) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Clopidogrel hydrogen sulfate (also known and used as clopidogrel bisulfate) and herein after referred to as clopidogrel
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Platelet aggregation inhibitors excl. heparin (ATC Code: B01AC04)
Marketing Authorization Holder (MAH)	Sanofi-aventis groupe
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Plavix and Iscover
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Clopidogrel is a platelet aggregation inhibitor. It is a P2Y12 ADP receptor antagonist of the thienopyridine derivative class.
	Summary of mode action: It selectively inhibits the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex together with the binding of fibrinogen to this receptor, thereby inhibiting platelet aggregation.
	Important information about its composition: Not applicable
Hyperlink to the product information	Please refer to section 1.3.1 in electronic common technical document (e-CTD).
Indication(s) in the EEA	Current: *Secondary prevention of atherothrombotic events* Clopidogrel is indicated in: • Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. • Adult patients suffering from acute coronary syndrome: - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA). - ST segment elevation acute myocardial infarction, in combination with ASA in patients undergoing percutaneous coronary intervention (including

	patients undergoing a stent placement) or medically treated patients eligible for thrombolytic/fibrinolytic therapy. *In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)* Clopidogrel in combination with ASA is indicated in: • Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor ischemic stroke (NIHSS ≤3) within 24 hours of either the TIA or ischemic stroke event. *Prevention of atherothrombotic and thromboembolic events in atrial fibrillation* In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.
	Proposed: None
Dosage in the EEA	Current: Adults and elderly PLAVIX/ISCOVER 75 mg film-coated tablets: Clopidogrel should be given as a single daily dose of 75 mg. PLAVIX/ISCOVER 300 mg film-coated tablets: This 300 mg tablet of clopidogrel is intended for use as a loading dose. • In patients suffering from acute coronary syndrome: - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg or 600 mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended. Clopidogrel treatment should be continued at 75 mg once a day (with acetylsalicylic acid [ASA] 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months. • ST segment elevation acute myocardial infarction: - For medically treated patients eligible for thrombolytic / fibrinolytic therapy, clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics. For medically treated patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting. - When percutaneous coronary intervention (PCI) is intended: o Clopidogrel should be initiated at a loading dose of 600 mg in patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy. In patients ≥75 years old the 600 mg loading dose (LD) should be administered with caution. o Clopidogrel 300 mg loading dose should be given in patients undergoing PCI within 24 hours of receiving fibrinolytic therapy.

	Clopidogrel treatment should be continued at 75 mg once a day with ASA 75 mg -100 mg daily. Combined therapy should be started as early as possible after symptoms start and continued up to 12 months. • Adult patients with moderate to high-risk TIA or minor IS: Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg -100 mg once daily). Treatment with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy. • In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. Acetylsalicylic acid (75-100 mg daily) should be initiated and continued in combination with clopidogrel. If a dose is missed: - Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time. - For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose. <u>Method of administration</u> For oral use It may be given with or without food.
	<u>Proposed</u>: None
Pharmaceutical form(s) and strength(s)	75 mg and 300 mg film-coated tablets.
Is or will the product (be) subject to additional monitoring in the European Union (EU)?	No

ABCD2: Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnoses; ADP: Adenosine Diphosphate; ASA: Acetylsalicylic Acid; ATC: Anatomical Therapeutic Chemical; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; IS: Ischemic Stroke; LD: Loading Dose; MAH: Marketing Authorization Holder; NIHSS: National Institutes of Health Stroke Scale; PCI: Percutaneous Coronary Intervention; RMP: Risk Management Plan; TIA: Transient Ischemic Attack.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Clopidogrel is mainly indicated in adults for the secondary prevention of atherothrombotic events in recent myocardial infarction (MI), recent IS or established peripheral arterial disease (PAD) and in acute coronary syndrome (ACS); for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation (AF) and in combination with ASA in TIA and minor IS.

Ischemic stroke is classified as mild, moderate, severe and very severe and is described in the section "IS" (approved indication, see Table 7).

Table 6 - Epidemiology of transient ischemic attack

Indication	Transient ischemic attack (TIA)
Incidence	• **Europe** In a systematic review published in 2014, the incidences of TIA in Europe were estimated from 52 to 237 and from 5 to 114 per 100 000 persons in men and women aged 55-64, from 94 to 339 and from 71 to 147 per 100 000 persons in those aged 65-74, and from 304 to 720 and from 218 to 606 per 100 000 persons in those aged 75-84, respectively. The corresponding incidences are similar in the United States (US), and lower in Japan. (1) The crude annual incidence rate for traditional time-based TIA (TIA presumed to be vascular origin and confined to an area of the brain or eye perfused by a specific cerebral artery and of a duration <24 hours) in **Italy** was estimated at 35.2 per 1 000 000 (95% confidence interval [CI]: 30.6-40.3) in 2012, and 28.6 per 1 000 000 (95% CI: 4.1-33.5) when standardized to the 2011 European population. (2) In a recent study using community-based registers of first-ever TIA from 2009 to 2011 in **Portugal**, the crude annual incidence for TIA was reported higher: 74 per 100 000. (3) In a prospective registry population-based study conducted in Novosibirsk (**Russia**), a total of 211 patients with incident TIA were registered. The crude annual TIA incidence rate per 1 000 000 persons was 16 (95% CI: 8-33) in 1987-1988, and 29 (95% CI: 9-87) in 1996-1997. These rates standardized to European population were 17 (95% CI: 8-34) and 27 (95% CI: 9-79), respectively. (4) • **America** In the US, the age- and gender-adjusted incidence for TIA was estimated at 82.9 per 1 000 000 (95% CI: 77.9-88.0) in 1990. Blacks had significantly higher rates of TIA than whites. (5) In Canada, the age-adjusted incidence of TIA was estimated at 68.2 per 100 000 (95% CI: 65.3-70.9) in 1996. (6)
Prevalence	• **Europe** Using the Neurological Disorders in Central Spain (NEDICES), the prevalence of TIA adjusted to the standard European populations was estimated at 1.3% (95% CI: 1.0-1.6) in elderly population (65 years of age and older, n = 5278). (7) • **America** The estimated overall prevalence of TIA among adults in the US is approximately 2%. (8)

Indication	Transient ischemic attack (TIA)
	• **Asia** In China, a cross-sectional study including 98 658 Chinese adults in 2010 reported the age-standardized prevalence of TIA at 2.27%. (9)
Demographics of the population in the authorized/proposed indication	Higher incidences were revealed in men compared with women. The incidence of TIA increased very markedly with age, regardless of race or gender. (1) The prevalence of TIA increases with age, ranging from 0.4% in adults between the ages of 45 and 64 years to 4.1% in those between 75 to 79 years. (10) Also, in a study conducted in the US in 1994, blacks had significantly higher rates of TIA than whites. (5)
Main existing treatment options	Besides the supportive care required to keep the patient vitals normal in the acute setting. The American guidelines (stroke 2018) recommend the initiation of combination of Dual Antiplatelet Therapy (DAPT) of aspirin and clopidogrel within 24 hours of a TIA for up to 21 days which can be followed by monotherapy antiplatelet. Prior to the use of the DAPT, aspirin was the only approved drug for acute cerebral ischemic events and is still used for many patients. Besides aspirin and the DAPT, patients with intracranial arterial stenosis may require carotid endarterectomy/thrombolysis with tissue plasminogen activator to remove the clot for patients arriving within 3 hours of symptom onset. The most common reasons for ineligibility for thrombolysis are that the deficit is improving or too mild to warrant treatment; and most patients arrive outside the narrow 3-hour window. In the long term the treatment aims to keep the factors leading to stroke under control with the use of anti-hypertensives, statins or other lipid lowering drugs, anti-diabetic and antiplatelet.
Natural history of the indicated condition in the untreated population including mortality and morbidity	According to the Heart Disease and Stroke Statistics (US), approximately 15% of all strokes are heralded by a TIA. On average, the annual risk of future IS after a TIA or initial IS is 3 to 4%, with an incidence as high as 11% over the next 7 days and 24-29% over the following 5 years. Within 1 year of TIA, about 12% to 13% of patients will die. (11) In an American prospective study including 251 patients with first TIA, the time to death between 2000 and 2015, the presence of any of the 4 cardiometabolic conditions (diabetes mellitus, coronary artery disease (CAD), AF and heart failure) increased the mortality (Hazard ratio [HR]: 1.89; 95% CI: 1.17-3.03; probability [p] = 0.0089). (12) In an Australian registry-based study, including 22 157 patients with TIA from 2000 to 2007, TIA reduced survival by 4% in the first year and 20% within 9 years. Females had statistically significantly higher relative survival than males ($p < 0.001$). Increasing age was significantly associated with an increasing risk of excess death compared with age-matched population. (13)
Important co-morbidities	In an American prospective study, 251 patients with first TIA were examined for cardiometabolic co-morbidities (diabetes mellitus, CAD, heart failure and AF, 5-year incident hospitalization, and time to death between 2000 and 2015. Overall, 53% of the patients had one or other concurrent cardiometabolic condition. The frequency of cardiometabolic conditions were 19%, 32%, 22% and 12% for diabetes mellitus, CAD, AF and heart failure respectively. (12) In a retrospective study based on Israeli database, a total of 1457 patients admitted to neurology department for TIA or IS were included from 2010 and 2015. The most common risk factors were hypertension, hyperlipidemia, diabetes, AF, CAD, smoking, previous stroke or TIA. All co-morbidities except for diabetes and smoking were significantly higher ($p < 0.05$) in older patients (80 years and older, n = 487) compared with younger patients (less than 80 years old, n = 968). All co-morbidities reached statistical significance except for hyperlipidemia. (14)

Indication	Transient ischemic attack (TIA)
	In a prospective study conducted in Italy in 2012, the three most frequent risk factors observed in TIA patients (n = 210) were arterial hypertension (n = 151; 71.9%), hypercholesterolemia (n = 66; 33.4%), and diabetes mellitus (n = 48; 22.8%). (2)

AF: Atrial Fibrillation; CI: Confidence Interval; CAD: Coronary Artery Disease; DAPT: Dual Antiplatelet Therapy; HR: Hazard Ratio; IS: Ischemic Stroke; NEDICES: Neurological Disorders in Central Spain; p: Probability; TIA: Transient Ischemic Attack; US: United States.

Table 7 - Epidemiology of ischemic stroke

<table>
<tr><th>Indication</th><th>Ischemic stroke (IS)</th></tr>
<tr><td>Incidence</td><td>The global incidence of IS was estimated at 98.62 95% CI: (84.90-115.80) per 100 000 in 2019. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved. https://clients.ihme.services/
Table 7a: Incidence of four world regions in 2019
<table>
<tr><th></th><th>Africa</th><th>America</th><th>Asia</th><th>Europe</th></tr>
<tr><td>Incidence (per 100 000)</td><td>55.73 (95% CI: 48.87- 63.68)</td><td>75.22 (95% CI: 64.54-88.29)</td><td>108.52 (95% CI: 91.85-128.26)</td><td>139.96 (95% CI: 121.31-161.67)</td></tr>
</table>
CI: Confidence Interval.
Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
The severity of IS is most commonly assessed using the NIHSS composing of 15 items (each item between a 0 and 4) with the minimum score being a 0 and maximum score of 42, IS is then classified as minor (1-4), moderate (5-15), severe (16-20), very severe (21-42). (15)
There is very limited data available on the incidence of stroke in relation to its severity.</td></tr>
<tr><td>Prevalence</td><td>In 2019, the global prevalence for IS was estimated at 997.65 per 100 000 (95% CI: 889.92-1117.39), or 1.00 % 95% CI: (0.89-1.12). Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
Table 7b: Prevalence of four world regions in 2019
<table>
<tr><th></th><th>Africa</th><th>America</th><th>Asia</th><th>Europe</th></tr>
<tr><td>Prevalence (%)</td><td>0.61 (95% CI: 0.55-0.67)</td><td>1.13 (95% CI: 1.00-1.27)</td><td>1.02 (95% CI: 0.90-1.16)</td><td>1.26 (95% CI: 1.12-1.40)</td></tr>
</table>
CI: Confidence Interval.
Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.</td></tr>
<tr><td>Demographics of the population in the authorized/proposed indication</td><td>According to the Centers for Disease Control and Prevention (CDC), stroke risk increases with age, but strokes can and do occur at any age. In 2009, 34% of people hospitalized for stroke were less than 65 years old.
Also, CDC reported that the risk of having a stroke is nearly twice as high for blacks as for whites, and blacks have the highest rate of death to stroke. Though stroke death rates have declined for decades among all race/ethnicities, Hispanics have seen an increase in death rates since 2013.
Gender-specific risk factors, such as pregnancy and puerperium, use of oral contraceptives, and higher incidences of auto-immune disorders (eg, antiphospholipid syndrome), might explain a higher incidence observed among women than men (especially those younger than 30 years of age). However other studies have found no difference or an increased risk among men, possibly because patients aged between 50 years and 65 years were included. (16)</td></tr>
</table>

Indication	Ischemic stroke (IS)
Main existing treatment options	For the management of patients with any kind of stroke besides the supportive care required to keep the patient vitals normal in the acute setting, many treatment modalities are required to prevent any recurrence of stroke or any other cardiovascular (CV) event. Various mono or dual antiplatelet treatments have been recommended by the Guidelines for the Prevention of Stroke in Patients with Stroke and TIA, a Guideline for Healthcare Professionals(HCPs) from the American Heart Association/American Stroke Association Jul-2014. (17) For preventing secondary strokes in patients with TIA/stroke: aspirin, ticlopidine, clopidogrel, dipyridamole plus ASA, and clopidogrel plus ASA have been recommended. The other potent P2Y12 agents like ticagrelor and prasugrel are not indicated in this patient population as of now. This antiplatelet therapy is recommended lifelong following an IS. The choice of antiplatelet for each of the patients depends upon each of their baseline characteristics, physician and patient choice. For patients with minor stroke the American guidelines (stroke 2018) recommend the initiation of combination of DAPT of aspirin and clopidogrel within 24 hours of a minor IS for up to 21 days which can be followed by monotherapy antiplatelet. Prior to the use of the DAPT, aspirin was the only approved drug for acute cerebral ischemic events and is still used for many patients. Besides aspirin and the DAPT, patients with intracranial arterial stenosis may require carotid endarterectomy/ thrombolysis with tissue plasminogen activator to remove the clot for patients arriving within 3 hours of symptom onset. The most common reasons for ineligibility for thrombolysis are that the deficit is improving or too mild to warrant treatment; and most patients arrive outside the narrow 3-hour window. In the long term, the treatment of stroke aims to keep the factors leading to stroke under control with the use of anti-hypertensives, statins or other lipid lowering drugs, anti-diabetic and antiplatelet. Besides the supportive care required to keep the patient vitals normal in the acute setting.
Natural history of the indicated condition in the untreated population including mortality and morbidity	The global mortality rate for IS was estimated at 42.56 per 100 000, 95% CI: (38.43- 45.70) in 2019. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.* In a prospective study including 209 patients aged 40 to 80, the overall mortality in the TIA group (n = 129) was significantly higher than in the minor stroke group (n = 80) (44% versus 20%, p <0.0006 after correction for age), and that in the general population in Malmo. Pre-existing vascular disease was slightly more prevalent in the TIA than in the minor stroke group (27% versus 21%, with no statistical significance). Regarding the risk of death in the study population as a whole, mortality was greater among those with vascular disease than among without (81% versus 20%, p = 0.0001). (18)
Important co-morbidities	In a retrospective study based on Israeli database, a total of 1457 patients admitted to neurology department for TIA or IS were included from 2010 and 2015. The most common risk factors were hypertension, hyperlipidemia, diabetes, AF, CAD, smoking, previous stroke or TIA. All co-morbidities except for diabetes and smoking were significantly higher (p <0.05) in older patients (80 years and older, n = 487) compared with younger patients (less than 80 years old, n = 968). All co-morbidities reached statistical significance except for hyperlipidemia. (14)

AF: Atrial Fibrillation; ASA: Acetylsalicylic Acid; CAD: Coronary Artery Disease; CDC: Centers for Disease Control and Prevention, CI: Confidence Interval; CV: Cardiovascular; DAPT: Dual Antiplatelet Therapy; HCP: Healthcare Professional; NIHSS: National Institutes of Health Stroke Scale; IS: Ischemic Stroke; p: Probability; TIA: Transient Ischemic Attack.

Table 8 - Epidemiology of acute coronary syndrome/recent myocardial infarction

<table>
<tr><th>Indication</th><th>Acute Coronary Syndrome (ACS)/recent Myocardial Infarction (MI)</th></tr>
<tr><td>Incidence</td><td>
Acute coronary syndrome is defined as any clinical syndrome of acute and prolonged ischemia related to CAD. It comprises unstable angina (UA), Non ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).

Acute coronary syndrome is a subcategory of CAD, which is the origin of Ischemic Heart Disease (IHD).

In 2019, the global incidence of IHD was estimated at 274.04 (95% CI: 242.96-306.36) per 100 000) for all ages and both sexes. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

Table 8a: Incidence of four world regions in 2019
<table>
<tr><th></th><th>Africa</th><th>America</th><th>Asia</th><th>Europe</th></tr>
<tr><td>Incidence (per 100 000)</td><td>152.53 (95% CI: 136.62-168.70)</td><td>210.89 (95% CI: 189.93-234.45)</td><td>275.43 (95% CI: 242.28-309.80)</td><td>527.97 (95% CI: 471.00-586.93)</td></tr>
</table>
CI: Confidence Interval.
Source: Institute for Health Metrics and Evaluation Used with permission. All rights reserved.
</td></tr>
<tr><td>Prevalence</td><td>
In 2019, the global prevalence of IHD was 2.55% (95% CI: 2.30-2.84). Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

Table 8b: Prevalence of four world regions in 2019
<table>
<tr><th></th><th>Africa</th><th>America</th><th>Asia</th><th>Europe</th></tr>
<tr><td>Prevalence (%)</td><td>1.25 (95% CI: 1.14-1.37)</td><td>2.14 (95% CI: 1.93-2.36)</td><td>2.65 (95% CI: 2.36-2.97)</td><td>4.47 (95% CI: 4.04-4.95)</td></tr>
</table>
CI: Confidence Interval.
Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
</td></tr>
<tr><td>Demographics of the population in the authorized/proposed indication</td><td>
In a recent cross-sectional study conducted in Sri Lanka in 2019, male sex showed higher association with three types of ACS (STEMI, NSTEMI and UA) compared to female (p = 0.001). Higher mean age of 62.2±11.4 years was observed amongst UA patients and 61.9±14.5 years amongst NSTEMI patients compared to 59.2±11.2 years for STEMI patients with no significant statistical difference (p = 0.246).

A Canadian prospective study using data from Montreal heart institute from 1986 to 2003 included 18 719 patients admitted to coronary care unit. The mean age increased from 58.4 to 63.4 years and the proportion of men remained stable at approximately 70%. (19)
</td></tr>
<tr><td>Main existing treatment options</td><td>
Patients of ACS (UA, STEMI or NSTEMI) following an event either managed medically and in most instances undergo stenting (PCI). Dual Anti-platelet Therapy with P2Y12 inhibitors as clopidogrel, ticagrelor, cangrelor or prasugrel are used along with aspirin. DAPT for a period of 12 months is recommended by guidelines and decided by clinicians upon the evaluation of patients' baseline ischemic and bleeding risks. Of these ticagrelor, prasugrel are more potent than clopidogrel and got approvals after they showed their superiority in clinical trials in terms of efficacy over clopidogrel in large randomized controlled trials (RCTs), along with increased rates of bleeding. (20)

The European Society of Cardiology (ESC) guideline recommend use of these potent P2Y12 inhibitors over clopidogrel, nevertheless clopidogrel is still the most commonly used P2Y12 inhibitor in ACS patients, mostly due to availability/lower cost of generics and better safety profile in patients with multiple comorbidities and more prone to bleeding. Also, the international and domestic guidelines recommend the use of clopidogrel in ACS patients who cannot tolerate ticagrelor/prasugrel or contradicted. Other factors, which impact selection of P2Y12 inhibitors, include type of clinical setting and patient's ischemic and bleeding risk and other comorbidities. (20)(21)(22)
</td></tr>
</table>

Indication	Acute Coronary Syndrome (ACS)/recent Myocardial Infarction (MI)
	Ticagrelor 60 mg twice a day along with aspirin as a DAPT is approved for patients with CAD but no prior MI or stroke.
Natural history of the indicated condition in the untreated population including mortality and morbidity	The global mortality rate for PAD was estimated at 116.88, 95% CI: (115.05-119.61) in 2017. Data for AF specifically was not available in Global Burden of Disease (GBD) 2017. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.*
Important co-morbidities	In a recent published cross-sectional study conducted in Sri Lanka, almost 51.8% NSTEMI patients, 47.8% UA patients and 29.9% STEMI patients had hypertension (p = 0.008) indicating significant association of hypertension with UA and NSTEMI. About 33.6% UA patients and 30.0% NSTEMI patients had diabetes mellitus whilst only 22.1% of STEMI patients had diabetes mellitus of no significance (p = 0.225). Around 15.0% patients with UA, 25.5% with NSTEMI and 11.7% with STEMI had dyslipidemia (p = 0.032). There was a very strong association between a past history of ACS or stable angina with NSTEMI and UA (p = 0.001). (23) In a prospective case-control study conducted in Iraq in 2018, the most prevalent risk factors in patients with ACS and aged below 40 years were obesity (86% of ACS cases), hypertension (26%), diabetes mellitus (n = 22%), and positive family history of ACS (n = 24%). (24)

ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation; CAD: Coronary Artery Disease; CI: Confidence Interval; DAPT: Dual Antiplatelet Therapy; ESC: European Society of Cardiology; GBD: Global Burden of Disease; IHD: Ischemic Heart Disease; MI: Myocardial Infarction; NSTEMI: Non ST-Segment Elevation Myocardial Infarction; p: Probability; PAD: Peripheral Arterial Disease; PCI: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; STEMI: ST-Segment Elevation Myocardial Infarction; UA: Unstable Angina.

Table 9 - Epidemiology of peripheral arterial disease

Indication	Peripheral Artery Disease (PAD)
Incidence	In 2019, the global incidence of PAD was estimated at 135.75, 95% CI: 118.42-155.09 per 100 000 for all ages and both sexes. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.* **Table 9a: Incidence of peripheral artery disease in four world regions in 2019** CI: Confidence Interval. Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
Prevalence	In 2019, the global prevalence of PAD was estimated at 1.46% (95% CI: 1.28-1.65) for all ages and both sexes. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.* **Table 9b: Prevalence of peripheral artery disease in four world regions in 2019** CI: Confidence Interval. Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.
Demographics of the population in the	In a meta-analysis performed in 2019, the global prevalence of PAD increased consistently with age. At younger ages, prevalence was slightly higher in low- and middle-income countries than high-income countries (4.32%, 95% CI: 3.01-6.29 versus 3.54, 95% CI: 1.17-10.24, at

Table 9a: Incidence of peripheral artery disease in four world regions in 2019

	Africa	America	Asia	Europe
Incidence (per 100 000)	47.89 (95% CI: 41.39 -55.01)	178.84 (95% CI: 154.87-203.96)	125.13 (95% CI: 108.36-142.99)	269.29 (95% CI: 234.63-309.54)

Table 9b: Prevalence of peripheral artery disease in four world regions in 2019

	Africa	America	Asia	Europe
Prevalence (%)	0.43 (95% CI: 0.37-0.50)	2.05 (95% CI: 1.82-2.29)	1.31 (95% CI: 1.13-1.50)	3.18 (95% CI: 2.76-3.63)

Indication	Peripheral Artery Disease (PAD)
authorized/proposed indication	40-44 years), but the increase with age was greater in high-income countries than low- and middle-income countries, leading to a higher prevalence in higher-income countries than low- and middle-income countries at older ages (21.24%, 95% CI: 15.22-28.90, versus 12.04%, 95% CI: 8.67-16.60, at 80-84 years). In high-income countries, prevalence was slightly higher in women than in men up to age 75 years (eg, 7.81%, 95% CI: 3.97-14.77, versus 6.60%, 95% CI: 3.74-11.38, at 55-59 years), whereas in low- and middle-income countries little difference was found between women and men (eg, 6.40%, 95% CI: 5.06-8.05, versus 6.37%, 95% CI: 4.74-8.49, at 55-59 years). Overall, the global prevalence of PAD individuals aged 25 years and older was 5·56%, 95% CI: 3.79-8.55, and the prevalence estimate was higher in high-income countries than that in low- and middle-income countries (7.37%, 95% CI: 4.35-13.66, versus 5.09%, 95% CI: 3.64-7.24). Globally, a total of 236.62 million people aged 25 years and older were living with PAD in 2015, among whom 72.91% were in low- and middle-income countries. The Western Pacific Region had the most PAD cases (74.08 million), whereas the Eastern Mediterranean Region had the least (14.67 million). More than two thirds of the global peripheral artery disease cases were concentrated in 15 individual countries in 2015. (25)
Main existing treatment options	Symptomatic patients with lower extremity PAD included both those with claudication and those with prior lower extremity revascularization, making the antiplatelets as one of the main treatments per se for such patients. Antiplatelet therapy with aspirin alone (range 75-325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD. The other treatment options would be chelation with cilostazol. Of these who do undergoing revascularization use of DAPT with clopidogrel and aspirin is recommended.
Natural history of the indicated condition in the untreated population including mortality and morbidity	The global mortality rate for PAD was estimated at 0.96 per 100000 95% CI: (0.53-1.66) in 2019. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.*
Important co-morbidities	In a recent meta-analysis (2019), smoking, diabetes, hypertension, and hypercholesterolaemia were the major risk factors for PAD. (25) In a prospective study including 1600 patients from the Department of cardiology of the Emergency Clinical Hospital Sfantul Spiridon Iasi (Roumania) in 2016, the association between co-morbidities and current risk of PAD was evaluated. The compound of two risk factors (heart failure with hypertension) had weak to moderate significance (p <.0001), whilst three risk factors (heart with diabetes mellitus and CAD, heart failure with hypertension and smoking, diabetes mellitus with CAD and smoking) had a strong significant association (p <.0001). (26) In a survey conducted in Italy in 2004, the risk factors that were associated significantly with PAD were smoking, diabetes mellitus and hypertension. (27)

CAD: Coronary Artery Disease; CI: Confidence Interval; DAPT: Dual Antiplatelet Therapy; MI: Myocardial Infarction; p: Probability; PAD: Peripheral Arterial Disease.

Table 10 - Epidemiology of atrial fibrillation

Indication	Atrial Fibrillation (AF)
Incidence	The global incidence of AF and flutter was estimated at 61.01 95% CI: (47.10-77.05) per 100 000 in 2019. Data for AF specifically was not available in GBD 2017. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.* For AF specifically, the most recent global incidence was available for year 2010. It was estimated at 77.5 (95% CI: 65.2-95.4) in men and 59.5 (95% CI: 49.9-74.9) in women. (28)

Indication	Atrial Fibrillation (AF)
Prevalence	The global prevalence of AF and flutter was estimated at 0.77% 95% CI: (0.59-0.97) in 2019. Data for AF specifically was not available in GBD 2019. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.* For AF specifically, the most recent global prevalence was available for year 2013. It was estimated at 191.3 per 100 000 (95% CI: 182.1-200.1). (29)
Demographics of the population in the authorized/proposed indication	There have been progressive increases in the worldwide prevalence and incidence of AF between 1990 and 2010 in both sexes. The incidence and prevalence rates of AF were generally higher in males than in females. There were significant variations in the AF burden by GBD region, with developed countries having a greater burden overall. The highest incidence rates were estimated in North America and the lowest rates in Asia Pacific. Higher rates of AF were observed in older age groups. For example, males 75-79 years have double the prevalence rate compared to males age 65-69 years, and more than 5-fold higher prevalence compared to males age 55-59 years. (28)
Main existing treatment options	Vitamin K antagonists warfarin and 4 non-vitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban have been approved for clinical use for patients with AF. NOACs are associated with comparable, or, in some cases, better efficacy, and reduced intracranial bleeding risk compared with vitamin K antagonist (VKA) and are the mainstay for patients with AF to prevent stroke. Clopidogrel along with ASA is one of the options for patients with AF who cannot tolerate VKA or do not want to be put on warfarin. Recent studies have shown that in patients with history of AF undergoing PCI, it is better to use dual therapy of novel oral anticoagulant with a P2Y12 agent like clopidogrel/ ticagrelor versus the use of triple therapy of warfarin and DAPT (clopidogrel/ ticagrelor with aspirin).
Natural history of the indicated condition in the untreated population including mortality and morbidity	The global mortality rate for AF and flutter was estimated at 4.08 per 100 000, 95% CI: (3.46-4.67) in 2019. Data for AF specifically was not available in GBD 2019. *Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.* The age-adjusted mortality rate was available for year 2010 and it was estimated at 1.6 (uncertainty interval [UI] 1.0-2.4) in males and 1.7 (UI 1.4-2.2) in females, in 2010. The mortality increased steadily through 1995, 2000 and 2005, especially in the developed world. Mortality associated with AF was higher in females overall. In 2010, the estimated numbers of total deaths (males and females) represented less than 1% of the global mortality in the vast majority of the 21 GBD regions. (28) The estimated age-adjusted disability-adjusted life years due to AF were 64.5 (UI 46.8-84.2) and 45.9 (UI 35.7-58.5) per 1 000 000 in 2010. (28)
Important co-morbidities	In a recent retrospective study using medical records of King Abdul-Aziz Hospital (Saudi Arabia) from 2010 to 2017, the most prevalent risk factors of AF among 167 patients were hypertension, valvular heart disease, and type 2 diabetes mellitus. (30) An American case-control study reported that the most common chronic conditions in patients with AF were obesity, hypertension, congestive heart failure (CHF), CAD, chronic kidney disease, and chronic obstructive pulmonary disease (COPD) ($p < 0.05$). (31) In a retrospective study using data collected from 5382 patients admitted in the cardiology service of Kosavo, the associated comorbidities of AF were ischemic heart disease (21.4%), hypertensive heart disease (27.44%), valvular heart disease (17.4%), CHF (47%), COPD (6.7%), and diabetes (14.3%). (32)

AF: Atrial Fibrillation; ASA: Acetylsalicylic Acid; CAD: Coronary Artery Disease; CHF Congestive Heart Failure; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; DAPT: Dual Antiplatelet Therapy; GBD: Global Burden of Disease; MI: Myocardial Infarction; NOAC: Non-Vitamin K Antagonist Oral Anticoagulant; PCI: Percutaneous Coronary Intervention; UI: Uncertainty Interval; VKA: Vitamin K Antagonist.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

As part of the initial development program, the safety of clopidogrel was extensively evaluated in a comprehensive series of nonclinical studies and in clinical studies in healthy adults and patients. Since the first launch almost 22 years ago, substantial postmarketing experience has accumulated and safety evaluation continues through usual pharmacovigilance surveillance. No specific measures beyond labeling updates are considered necessary at this time.

Pharmacology studies to evaluate safety did not reveal any relevant effects for human use, involving the central nervous, CV, respiratory, gastrointestinal (GI) and renal systems.

The key non-clinical findings are presented in the following table.

Table 11 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity: • Key issues identified from Acute or repeat-dose toxicity studies: - GI tract tolerance: During preclinical studies in rat and baboon, the most frequently observed effects at very high doses (more than 300 times the therapeutic dose of 75 mg/day on a mg/kg basis) were acute gastritis, gastric erosions and/or vomiting.	The GI tract effects in animals were observed only at very high doses and the gastric effects of clopidogrel in humans are well documented, including common (eg, dyspepsia or diarrhoea), uncommon (eg, nausea, gastritis or gastric ulcer and duodenal ulcer) GI signs or symptoms or very rare cases of colitis. Some GI lesions may be expressed by GI bleeding due to the pharmacological activity of this antiplatelet drug. A statement regarding the association of clopidogrel and GI effects is included in the corresponding summary of product characteristics (SmPC) section.
- Hepatic tolerance: At doses ranging from 100 mg/kg/day upwards in rodents and from 200 mg/kg/day upwards in baboons after 1-year administration, an increase in liver weight was observed in mice, rats and baboons associated with increases in cholesterol plasma levels in rats and baboons, and a slight hypertrophy of the smooth endoplasmic reticulum in centrilobular hepatocytes in rats. No histopathological changes were seen in mice or baboons. After one year of treatment at doses representing at least 7 times (rats) or between 10 or 23 times (baboon) the exposure seen in humans receiving the clinical dose of 75 mg/day, none of these effects were observed.	The preclinical liver findings were attributed to an effect on hepatic metabolizing enzymes observed at high doses, a phenomenon that is generally recognized as having no relevance to humans receiving lower therapeutic doses. Enzyme induction has not been observed in humans, and thus is not relevant for the therapeutic use of clopidogrel. In human data, very rare observations acute liver failure, hepatitis or abnormal liver function tests have been reported through postmarketing surveillance; for which no specific mechanism has been suggested. These hepato-biliary disorders are included in the list of adverse reactions in the corresponding SmPC section.
• **Reproductive/developmental toxicity studies** Reproduction studies have been performed in rats at doses up to 500 mg/kg/day and in rabbits at doses up to 300 mg/kg/day and have revealed no evidence of impaired fertility or harm to the foetus due to clopidogrel.	Because animal reproduction studies are not always predictive of a human response, and in absence of adequate clinical studies in pregnant women, the use of clopidogrel is not recommended during pregnancy. A statement regarding the use of clopidogrel in pregnant women is included in the corresponding SmPC section.

Key Safety Findings	Relevance to human usage
• **Lactation** Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring.	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, the use of clopidogrel is not recommended during lactation. A statement regarding the use of clopidogrel in lactating women is included in the corresponding SmPC section.
• **Genotoxicity** Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity.	No safety issues expected in human based upon absence of genotoxic potential.
• **Carcinogenicity** There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and for 104 weeks to rats at dosages up to 100 mg/kg/day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg/day.	No safety issues expected in human based upon negative or absence of carcinogenic potential.
Safety pharmacology Safety pharmacology studies did not reveal any relevant effects on the central nervous, CV, respiratory, GI and renal systems. In vitro electrophysiological studies on rabbit Purkinje fibers performed with clopidogrel and its main circulating metabolite (carboxylic acid derivative, SR26334) did not reveal any effect on the conduction time or any proarrhythmic activity of clopidogrel or SR26334 at concentrations up to and including 3×10^{-5} M.	No safety issues expected in human.
Other toxicity-related information or data: Not applicable	Not applicable

CV: Cardiovascular; GI: Gastrointestinal; SmPC: Summary of Product Characteristics.

No additional non-clinical data have been collected on the use of clopidogrel in any special populations.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The safety and efficacy of clopidogrel have been evaluated in 6 double-blind studies involving over 113 000 patients: the clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE), a comparison of clopidogrel to ASA, and the clopidogrel in UA to prevent recurrent events (CURE), clopidogrel as adjunctive reperfusion therapy (CLARITY), clopidogrel and metoprolol in MI trial (COMMIT), clopidogrel high LD regimen versus standard dose in patients with UA or MI with an early invasive strategy (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies for Ischemic Syndromes [CURRENT-OASIS-7]) and atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE)-A studies, comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy. A description of the clinical trial program, including number of patients treated for each approved indication of the EU marketing authorization during the overall marketing authorization is provided below.

Recent MI, recent stroke or established peripheral arterial disease

The CAPRIE study included 19 185 patients with atherothrombosis as manifested by recent MI (<35 days), recent IS (between 7 days and 6 months) or established PAD. Patients were randomized to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the MI subgroup, most of the patients received ASA for the first few days following the acute MI.

Acute coronary syndrome

The CURE study included 12 562 patients with non-ST segment elevation (STE) ACS (UA or non-Q-wave MI), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia.

In patients with acute STEMI, safety and efficacy of clopidogrel have been evaluated in 2 randomized, placebo-controlled, double-blind studies: the CLARITY study and the COMMIT study.

The CLARITY trial randomized 3491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients were randomly assigned to receive clopidogrel (300 mg LD, followed by 75 mg/day, n = 1752) or placebo (n = 1739), both in combination with ASA (150 to 325 mg as a LD, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The total number of patients treated in the trial were 3452 out of which 1733 received clopidogrel and 1719 received placebo.

The PCI-CLARITY study was a planned subanalysis of patients undergoing PCI who were randomized to receive clopidogrel or placebo at presentation in the CLARITY trial. Out of 1863 patients who underwent PCI, 933 had been randomized to receive clopidogrel and 930 had been randomized to receive placebo at the time of initial presentation. Baseline data from CLARITY study by treatment group as randomized is provided in Table 12.

Table 12 - Demographic and other baseline data by treatment group and overall (ITT population)

	Clopidogrel 300/75 mg[a]	Placebo[a]	Overall
Total number of patients	1752	1739	3491
Age (yrs)			
n with data	1752	1739	3491
<65	1219 (69.6%)	1252 (72.0%)	2471 (70.8%)
≥65	533 (30.4%)	487 (28.0%)	1020 (29.2%)
Mean	57.7	57.2	57.4
Median	58	57	58
SD	10.3	10.3	10.3
Range	28-78	18-79	18-79
Gender			
N with data	1752	1739	3491
Female	352 (20.1%)	336 (19.3%)	688 (19.7%)
Male	1400 (79.9%)	1403 (80.7%)	2803 (80.3%)
Race			
n with data	1752	1739	3491
Asian/oriental	43 (2.5%)	30 (1.7%)	73 (2.1%)
Black	28 (1.6%)	35 (2.0%)	63 (1.8%)
Caucasian	1569 (89.6%)	1556 (89.5%)	3125 (89.5%)
Other	112 (6.4%)	118 (6.8%)	230 (6.6%)

a With background ASA and initial fibrinolytic therapy.
ASA: Acetylsalicylic Acid; ITT: Intent To Treat; SD: Standard Deviation.

The 2x2 factorial design COMMIT trial included 45 852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting electrocardiogram (ECG) abnormalities (ie, ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, n = 22 961) or placebo (n = 22 891), in combination with ASA (162 mg/day), for 28 days or until hospital discharge.

In the CURRENT-OASIS-7, randomized 2x2 factorial trial, 25 086 individuals with ACS intended for early PCI were randomly assigned to double-dose (600 mg on day 1, 150 mg on days 2-7, then 75 mg daily) (n = 12 520) versus standard-dose (300 mg on day 1 then 75 mg daily) (n = 12 566) clopidogrel, and high-dose (300-325 mg daily) versus low-dose (75-100 mg daily) aspirin. The total number of patients treated in the trial were 24 934 out of which 12 446 received clopidogrel 600/150/75 mg and 12 489 received clopidogrel 300/75/75 mg. A total of 24 835 randomized ACS patients underwent coronary angiography and 17 263 received PCI. Baseline data from CURRENT-OASIS-7 study is provided by treatment group as randomized in Table 13.

Table 13 - Summary of demographic and other baseline data - ITT population (clopidogrel)

	Clopidogrel 300/75/75 mg + ASA (N = 12 566)	Clopidogrel 600/150/75 mg + ASA (N = 12 520)	All (N = 25 086)
Age (yrs)[a]			
Mean (SD)	61.4 (11.7)	61.3 (11.9)	61.3 (11.8)
Min : Max	23 : 98	20 : 97	20 : 98
Age (yrs) (n [%])[a]			
<65	7532 (59.9%)	7522 (60.1%)	15 054 (60.0%)
65-74	3149 (25.1%)	3086 (24.6%)	6235 (24.9%)
≥75	1884 (15.0%)	1912 (15.3%)	3796 (15.1%)
Missing	1	0	1
Gender (n [%])			
Female	3458 (27.5%)	3413 (27.3%)	6871 (27.4%)
Male	9108 (72.5%)	9107 (72.7%)	18 215 (72.6%)
Race (n [%])			
Black	129 (1.0%)	131 (1.0%)	260 (1.0%)
Caucasian	7857 (62.5%)	7831 (62.6%)	15 688 (62.5%)
Asian/Oriental	2877 (22.9%)	2884 (23.0%)	5761 (23.0%)
Other	1702 (13.5%)	1672 (13.4%)	3374 (13.5%)
Missing	1	2	3
Ethnicity			
South Asian	1367 (10.9%)	1344 (10.7%)	2711 (10.8%)
Chinese	1031 (8.2%)	1058 (8.5%)	2089 (8.3%)
Japanese	39 (0.3%)	25 (0.2%)	64 (0.3%)
Malays	45 (0.4%)	51 (0.4%)	96 (0.4%)
Other Asian	395 (3.1%)	406 (3.2%)	801 (3.2%)
Arab	150 (1.2%)	145 (1.2%)	295 (1.2%)
Black African	129 (1.0%)	131 (1.0%)	260 (1.0%)
Coloured African	36 (0.3%)	44 (0.4%)	80 (0.3%)
European	7857 (62.5%)	7831 (62.6%)	15 688 (62.5%)
Missing	1	2	3

a Calculations do not include 1 patient in the 300/75/75 mg + ASA group with age 266 (patient is included in missing row).
ASA: Acetylsalicylic Acid; ITT: Intent To Treat; SD: Standard Deviation.

Atrial fibrillation

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

The ACTIVE-A study (N = 7554) was a multicenter, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA (N = 3772) to placebo + ASA (N = 3782). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Pediatric population

In a dose escalation study of 86 neonates or infants up to 24 months of age at risk for thrombosis (Platelet Aggregation Inhibition in Children on Clopidogrel [PICOLO]), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kg in neonates and infants and 0.15 mg/kg only in neonates. The dose of 0.2 mg/kg achieved the mean percent inhibition of 49.3% (5 µM ADP-induced platelet aggregation) which was comparable to that of adults taking Plavix 75 mg/day.

In a randomized, double-blind, parallel-group study (Clopidogrel to Lower Arterial Thrombotic Risk in Neonates and Infants Trial [CLARINET]), 906 pediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomized to receive clopidogrel 0.2 mg/kg (n = 467) or placebo (n = 439) along with concomitant background therapy up to the time of second stage surgery.

Transient Ischemic Attack/Minor Ischemic Stroke

Dual antiplatelet therapy with the combination of clopidogrel and aspirin was shown to reduce the early risk of new stroke in patients with minor IS or TIA in a Chinese population enrolled in the clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) trial. (33)

The efficacy of DAPT was further validated in North America, Europe, Australia and New Zealand in the platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial. (34)

Both trials were randomized, double-blind, controlled trials to assess the efficacy and safety of combined treatment with clopidogrel and aspirin versus aspirin alone for minor IS (NIHSS ≤3) and high-risk TIA (ABCD2 ≥4). The CHANCE trial used 21 days of DAPT followed by clopidogrel alone from 22 to 90 days in the clopidogrel-aspirin arm, whereas the POINT trial used 90 days of DAPT in the clopidogrel-aspirin arm.

By pooling data from the 2 trials, data for 10 051 participants was obtained, of whom 5016 patients were assigned to receive clopidogrel-aspirin and 5035 patients were assigned to receive aspirin alone. Among these patients, 6106 (60.8%) were male, and the median (interquartile range) age was 63.2 (55.0-72.9) years old; 6498 patients (64.7%) had a minor stroke as the qualifying event, and 3553 (35.3%) presented with TIA. Further characteristics are provided in Table 14, Table 15 and Table 16 below.

Table 14 - Characteristics of the CHANCE and POINT trials

Trial	CHANCE	POINT
Published Year	**2013**	**2018**
Study design	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial
Region of study cities	114 sites in China	269 sites in 10 countries in North America, Europe, Australia, and New Zealand
Sample size	5170 (2584 patients, 219 584 person-day for a LD of clopidogrel of 300 mg followed with 75 mg till 90 days)	4881
Age		
<65 years old	3029	Not provided in publication
>65 years old	2141	
Sex		
Male	3420	Not provided in publication
Female	1750	
Index event type		
Minor stroke	3725	Unknown
TIA	1445	
Ethnicity	100% Asian	3.0% Asian; 75.0% White; 20.4% Black; 1.5% Other

CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; LD: Loading Dose;
POINT: Platelet Oriented Inhibition in New Transient ischemic attack and minor ischemic stroke; TIA: Transient Ischemic Attack.

Table 15 - CHANCE study drug exposure (whole study treatment period of 90 days)

	Clopidogrel + Aspirin (N = 2584)		Placebo + Aspirin (N = 2586)	
Age	**Number of patients**	**Clopidogrel + Aspirin 1-21** **Clopidogrel + placebo 22-90**	**Number of patients**	**Placebo + Aspirin 1-21** **Placebo + Aspirin 22-90**
<65 years	1497 Total Duration: 120 062 days Mean DOT: 80.20 days/patients (SD = 25.85d) Median DOT: 90 days (Q1 87d Q3 90d)	Total Duration of exposure[a] Mean DOT[b] (SD) Median[c] (Q1-Q3)	1532 Total Duration: 119 697 days Mean DOT: 78.13 days/patients (SD = 28.32d) Median DOT: 90 days (Q1 90d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)
Total ≥65	1087 Total Duration: 84 299 days Mean DOT: 77.55 days/patients	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)	1054 Total Duration: 79 970 days Mean DOT: 75.87 days/patients	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)

	Clopidogrel + Aspirin (N = 2584)		Placebo + Aspirin (N = 2586)	
Age	**Number of patients**	**Clopidogrel + Aspirin 1-21** **Clopidogrel + placebo 22-90**	**Number of patients**	**Placebo + Aspirin 1-21** **Placebo + Aspirin 22-90**
	(SD = 28.94d) Median DOT: 90 days (Q1 90d Q3 90d)		(SD = 30.55d) Median DOT: 90 days (Q1 88d Q3 90d)	
65-74 years	710 Total Duration: 54 834 days Mean DOT: 77.23 days/patients (SD = 29.37d) Median DOT: 90 days (Q1 90d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)	680 Total Duration: 52 023 days Mean DOT: 76.50 days/patients (SD = 30.00d) Median DOT: 90 days (Q1 89d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)
75-84 years	352 Total Duration: 27 731 days Mean DOT: 78.78 days/patients (SD = 27.59d) Median DOT: 90 days (Q1 90d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)	349 Total Duration: 26 285 days Mean DOT: 75.32 days/patients (SD = 30.94d) Median DOT: 90 days (Q1 89d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)
≥85 years	25 Total Duration: 1734 days Mean DOT: 69.36 days/patients (SD = 34.66d) Median DOT: 90 days (Q1 27d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)	25 Total Duration: 1662 days Mean DOT: 66.48 days/patients (SD = 38.50d) Median DOT: 90 days (Q1 9d Q3 90d)	Total Duration of exposure Mean DOT[b] (SD) Median[c] (Q1-Q3)

a Total Duration of exposure- adding up all the days each of the patient has received the treatment for in that age group.
b Mean DOT- total duration of treatment for all patients in that age group/ number of patients in that age.
c Median DOT.
CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; DOT: Duration of Treatment; Q: Quarter; SD: Standard Deviation.

Table 16 - POINT study drug exposure (at 90 days)

	Treatment arm B (N = 2432)		Placebo A (N = 2449)	
Age	Clopidogrel Number of patients	Clopidogrel	Placebo Number of patients	Placebo
<65 years	1205	Total Duration of exposure[a] 77 408 Mean[b] DOT (SD) 64 (33.0)	1221	Total Duration of exposure 79 947 Mean[b] DOT (SD) 65 (31.4)

	Treatment arm B (N = 2432)		**Placebo A (N = 2449)**	
Age	Clopidogrel Number of patients	Clopidogrel	Placebo Number of patients	Placebo
		Median[c] (Q1-Q3) 89 (71-90)		Median[c] (Q1-Q3) 89 (76-90)
Total ≥65	1227	Total Duration of exposure 73 984 Mean[b] DOT (SD) 60 (35.3) Median[c] (Q1-Q3) 87 (28-90)	1228	Total Duration of exposure 76 525 Mean[b] DOT (SD) 62 (35.4) Median[c] (Q1-Q3) 87 (31-90)
65-74 years	622	Total Duration of exposure 39 230 Mean[b] DOT (SD) 63 (34.0) Median[c] (Q1-Q3) 87 (45-90)	645	Total Duration of exposure 41 450 Mean[b] DOT (SD) 64 (34.3) Median[c] (Q1-Q3) 88 (42-90)
75-84 years	429	Total Duration of exposure 25 519 Mean[b] DOT (SD) 59 (36.9) Median[c] (Q1-Q3) 87 (22-90)	448	Total Duration of exposure 27 014 Mean[b] DOT (SD) 60 (36.1) Median[c] (Q1-Q3) 87 (23-89)
≥85 years	176	Total Duration of exposure 9335 Mean[b] DOT (SD) 53 (37.3) Median[c] (Q1-Q3) 81 (10-89)	135	Total Duration of exposure 8061 Mean[b] DOT (SD) 60 (37.4) Median[c] (Q1-Q3) 87 (13-90)

a Total Duration of exposure is the sum of all days receiving the drug for all patients within each age group. Mean DOT is the total duration of exposure divided by the number of patients within each age group.

b Mean DOT- total duration of treatment for all patients in that age group/ number of patients in that age.

c Median DOT.

DOT: Duration of Treatment; POINT: Platelet-Oriented Inhibition in New Transient ischemic attack and minor ischemic stroke;
Q: Quarter; SD: Standard Deviation.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Due to the vast clinical experience with clopidogrel since its first approval obtained in the US on 17 November 1997, the data from postmarketing exposure compensate any effect of exclusion criteria in the clinical trial development in the exposed population.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Given the longstanding postmarketing experience (including in stroke), the limitations relative to adverse drug reaction (ADR) detection in clinical trials are no longer relevant.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Due to the vast postmarketing experience with clopidogrel since 17 November 1997, the data from postmarketing exposure compensate any limitations with respect to populations that may have been under represented in clinical trial development programs (including the 2 pivotal investigator sponsored study [ISS] trials [CHANCE and POINT] in TIA/minor stroke) and are reflected in the current labeling information.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1. Method used to calculate exposure

In 2019, the MAH transitioned from the Performance Analysis Reporting Center (PARC) application to Margin Consolidated (MARCO) for the reporting of sales data from postmarketing experience. The PARC application included sales data from major countries with the goal of capturing 85% to 90% of total world sales. For this reason, the extracted figures were an approximation of the total quantity sold because PARC does not have access to the total amount distributed in all countries. Data varied from one reporting interval to another due to changes in subscription agreements and the number of data channels available within a given country (examples when applicable to product distribution channels include direct to consumer sales, hospital sales, home care sales). The PARC application also collected data quarterly, which introduced a possible 3-month gap from closure of the previous quarter.

The MAH is currently utilizing the MARCO application for reporting of sales data from postmarketing experience. The MARCO application data reporting by country is not limited by subscription agreements and therefore represents the sales data from a greater number of countries than was available in PARC. For this reason, increases in the reporting of postmarketing exposure is observed due to the expansion in the availability of data utilized to estimate patient exposure. The MARCO application collects data monthly, as a result, the data may not correspond precisely to the current reporting interval. Using MARCO data, the presentation of the exposure is now in “patient days” (using World Health Organization [WHO] Defined Daily Dose [DDD]).

Methodology:

- Calculating total sales in mg by multiplying counting units of tablets with their respective strength in mg.
- Total patient days were calculated by dividing total sales in mg by WHO DDD of 75 mg for oral formulation.

SV.1.2. Exposure

Clopidogrel cumulative exposure assessment

In an effort to report the most inclusive estimate of cumulative exposure, the MAH is calculating the cumulative exposure by combining the PARC and MARCO data. Sales figures were obtained from PARC for the period from 01 October 2000 through 30 September 2018 and from MARCO for the period from 01 October 2018 through 30 November 2020.

- For the period from 01 October 2000 through 30 September 2018 (PARC): The exposure to clopidogrel tablets could be estimated to be 35 852.1 million patient days.
- For the period from 01 October 2018 through 30 November 2020 (MARCO): The exposure to clopidogrel tablets could be estimated to be 5756.7 million patient days.

The cumulative exposure utilizing the data obtained from PARC and MARCO is from 01 October 2000 through 30 November 2020. The total cumulative exposure to clopidogrel tablets could be estimated to be 41 608.8 million patient days.

Clopidogrel + acetylsalicylic acid fixed-dose combination cumulative exposure assessment

Methodology:

- Total patient days were calculated by dividing total sales (in number of tablets) with WHO DDD of 1 tablet for oral formulation.

In an effort to report the most inclusive estimate of cumulative exposure, the MAH is calculating the cumulative exposure by combining the PARC and MARCO data. Sales figures were obtained from PARC for the period from 01 January 2009 through 30 September 2018 and from MARCO for the period from 01 October 2018 through 30 November 2020.

- For the period from 01 January 2009 through 30 September 2018 (PARC): The exposure to clopidogrel + ASA tablets could be estimated to be 976.8 million patient days.
- For the period from 01 October 2018 through 30 November 2020 (MARCO): The exposure to clopidogrel + ASA tablets could be estimated to be 379.1 million patient days.

The total cumulative sales utilizing the data obtained from PARC and MARCO is from 01 January 2009 through 30 November 2020. The total cumulative exposure to clopidogrel + ASA tablets could be estimated to be 1355.9 million patient days from 01 January 2009 through 30 November 2020[1].

[1] In previous RMP with DLP 17 November 2019, a discrepancy in the cumulative data is observed due to change of database.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The properties of clopidogrel do not indicate a potential for misuse for illegal purposes.

In addition, the regular review of vast postmarketing experience in periodic benefit-risk evaluation report (PBRER) since clopidogrel first approval on 17 November 1997 confirm the lack of misuse for illegal purpose.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The safety profile of clopidogrel is well-established given the comprehensive large clinical development program conducted prior to and after its launch and the 23 years cumulative postmarketing safety experience.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
  - Thrombotic thrombocytopenic purpura (TTP)
  - Cross reactivity among thienopyridines
  - Acquired hemophilia A
  - Diminished antiplatelet response of clopidogrel in patients with genetically reduced cytochrome P450 (CYP) 2C19 function and potential clinical consequences
  - Reduction in pharmacological activity of clopidogrel in presence of CYP2C19 inhibitors: proton pump inhibitor (PPI) interaction (omeprazole) and potential clinical consequences
- Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated
  - Severe cutaneous reactions (including erythema multiforme [EM], Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], and acute generalized exanthematous pustulosis [AGEP])

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 17 - Important identified risk considered for inclusion in the list of safety concerns: Major bleeding (including Intracranial Hemorrhage [ICH][a])

Major bleeding (including ICH[a])	
Scientific evidence that has led to the inclusion	The PRAC, in its evaluation of the new indication TIA DAPT for the first 21 days of treatment (followed by anti-platelet monotherapy) for patient experiencing TIA at high risk of recurrence or minor ischemic stroke (mIS), requested to add Intracranial Hemorrhage (ICH) in very elderly patient (≥75 years) as important potential risk.

Major bleeding (including ICH[a])	
	However, the company considered the above-mentioned risk as already included in the important identified risk "major bleeding". It was developed for years in PBRER where the information of patient at risk of bleeding with Clopidogrel are very elderly patient and patient receiving additional drug acting on homeostasis such as patient treated with DAPT. Considering that ICH is by definition a major bleeding, the company proposed to rename the existing risk "major bleeding" to "major bleeding including ICH" and consider it as an important identified risk for the RMP. The proposal was accepted as part of EU-RMP v2.3 approval dated 10-Dec-2020 (Procedure no. EMEA/H/C/WS1769).
Risk-benefit impact	Bleeding is related to pharmacological activity of clopidogrel. Bleeding in populations at increased risk such as very elderly patients (≥75 years) or patient treated with DAPT or with drug-acting on hemostasis, is to be put in perspective with the observed benefit. Clopidogrel should be prescribed in the frame of exact labeling indications to maintain a positive benefit-risk (B/R) balance related to bleeding risk. Randomized phase 3 studies POINT and CHANCE showed a positive B/R balance in the new indication of DAPT for the first 21 days of treatment in TIA in patient at high risk of recurrence or in minor stroke. In CLARITY-PCI sub-group analysis of randomized phase 3 study CLARITY, no significant difference was observed in the rates of major or minor bleeding between both the treatments (2.0% with clopidogrel pre-treatment versus 1.9% with placebo, p >0.99). In the randomized phase 3 CURRENT-OASIS-7 study in the 17 236 patients who actually underwent a PCI procedure the double-dose clopidogrel regimen was associated with a reduction in the rates of both the primary and secondary outcome composites, and stent thrombosis. Major bleeding was more common with double-dose than with standard-dose clopidogrel (1.6% versus 1.1%, HR = 1.41, 95% CI 1.09 1.83, p=0.009). However, rates of severe bleeding and major bleeding defined by Thrombosis in Myocardial Infarction (TIMI) did not differ between groups (1.0% versus 0.7% HR 1.36, 95% CI 0.97-1.90 p = 0.074). Double dose clopidogrel did not increase the risk of bleeding that was fatal (0.07% versus 0.2% HR 0.46, 95% CI 0.18-1.22, p = 0.12) or intracranial (0.04% versus 0.05% HR 0.77, 95% CI 0.17-3.43, p = 0.73), nor bleeding that was related to coronary artery bypass graft (CABG) surgery (0.1% versus 0.07% HR 1.70, 95% CI 0.62-4.69, p = 0.30). (35) Before PCI, rates of ischaemic events or major bleeding did not differ between the groups. The differences in these outcomes occurred largely after PCI. Based on the risk assessment for addition of indication in STEMI PCI, the safety profile of clopidogrel remains unchanged.

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

B/R: Benefit-Risk; CABG: Coronary Artery Bypass Graft; CHANCE: Clopidogrel In High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; CI: Confidence Interval; CLARITY: Clopidogrel As Adjunctive Reperfusion Therapy; CURRENT-OASIS-7: Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies for Ischemic Syndromes; DAPT: Dual Antiplatelet Therapy; EMEA: European Medicines Agency; EU: European Union; HR: Hazard Ratio; ICH: Intracranial Hemorrhage; mIS: Minor Ischemic Stroke; p: Probability; PBRER: Periodic Benefit-Risk Evaluation Report; PCI: Percutaneous Coronary Intervention; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke; PRAC: Periodic Report Assessment Committee; RMP: Risk Management Plan; STEMI: ST-Segment Elevation Myocardial Infarction; TIA: Transient Ischemic Attack; TIMI: Thrombosis in Myocardial Infarction.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

Based on the risk assessment for addition of indication in STEMI PCI, the safety profile of clopidogrel remains unchanged:

- Clopidogrel pretreatment did not cause any significant difference in 30-day Major Bleeding or 30-day Minor Bleeding, compared to no pretreatment.
- One (1)-year treatment with Clopidogrel did not cause any significant difference in 30-day Major Bleeding or 30-day Minor Bleeding, compared to no pretreatment.
- Clopidogrel 600 mg LD did not demonstrate any significant difference compared to Clopidogrel 300 mg LD in 30-day Major Bleeding or 30-day Minor Bleeding.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for clopidogrel:

- Important identified risk:
  - Major bleeding (including ICH)

    Of note, ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.
- Important potential risk:
  - None
- Missing information:
  - None

SVII.3.1. Presentation of important identified risks and important potential risks

Table 18 - Important identified risk: Major bleeding (including ICH[a])

Identified Risk	Major bleeding (including ICH[a])
Potential mechanism	Clopidogrel acts as an inhibitor of platelet aggregation by selectively inhibiting the binding of ADP to its platelet receptor and the subsequent ADP mediated activation of the GP IIb/IIIa complex.
Evidence source(s) and strength of evidence	Clinical and epidemiological data, postmarketing experience and literature.
Characterization of the risk	**Frequency with 95% CI** Clinical studies Bleeding observed in CURE, CAPRIE, CLARITY, ACTIVE-A and ACTIVE-W:

Identified Risk	Major bleeding (including ICH[a])

In CURE study with over 12 500 patients (mean age 64.2 years) with ACS without STE followed between 3 and 12 months, there was an increase in major and minor bleeding between the clopidogrel + ASA FDC group compared with the placebo + ASA group (event rates 3.7% versus 2.7%, for major rate ratio 1.38 [1.13-1.67], p = 0.001, respectively, and 5.1% versus 2.4% for minor, rate ratio 2.12 [1.75-2.56], p <0.001). The principal sites for major bleeding included GI and at arterial puncture sites. The increase in life-threatening bleeding in the clopidogrel + ASA group compared to the placebo + ASA group was not statistically significant (2.2% versus 1.8%). There was no difference between the 2 groups in the rate of fatal bleeding (0.2% in both groups). The rate of non-life-threatening major bleeding was significantly higher in the clopidogrel + ASA FDC group compared with the placebo + ASA group (1.6% versus 1%), and the incidence of intracranial bleeding was 0.1% in both groups. The major bleeding event rate for clopidogrel + ASA FDC was dose-dependent on ASA (<100 mg: 2.6%; 100-200 mg: 3.5%; >200 mg: 4.9%) as was the major bleeding event rate for placebo + ASA (<100 mg: 2.0%; 100-200 mg: 2.3%; >200 mg: 4.0%). There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than 5 days prior to surgery (4.4% clopidogrel + ASA versus 5.3% placebo + ASA). In patients who remained on therapy within 5 days of bypass graft surgery, the event rate was 9.6% for clopidogrel + ASA and 6.3% for placebo + ASA. Ninety-two percent (92%) of the patients in the CURE study received heparin/low molecular weight heparin, and the rate of bleeding in these patients was similar to the overall results.

In CAPRIE study, the overall incidence of bleeding on clopidogrel and ASA was the same (9.3%). The incidence of severe reports was 1.4% and 1.6% in the clopidogrel and ASA groups, respectively. In patients receiving clopidogrel, GI bleeding occurred at a rate of 2.0% and required hospitalization in 0.7%. In patients receiving ASA, the corresponding rates were 2.7% and 1.1%, respectively. The overall incidence of other bleeding disorders was higher in the clopidogrel group (7.3%) compared to ASA (6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% versus 0.4%). The most frequent events reported were purpura/bruising and epistaxis. Other less frequently reported events were hematoma, hematuria and eye bleeding (mainly conjunctival). The incidence of intracranial bleeding was 0.4% for clopidogrel compared to 0.5% for ASA.

In CLARITY study, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin >5 g/dL) was similar between groups (1.3% versus 1.1% in the clopidogrel + ASA and in the placebo + ASA groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel + ASA and in the placebo + ASA groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups. The overall rate of non-cerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups.

CHANCE and POINT Time Course Analysis: There was no efficacy benefit of continuing DAPT beyond 21 days. A time-course distribution of major ischemic events and major hemorrhages by treatment assignment was done to analyze the impact of the short-term time-course of DAPT.

Table 18a: Time course distribution of major ischemic events and major hemorrhages by treatment assignment in CHANCE and POINT

		Number of events			
Outcomes in CHANCE and POINT	**Treatment assignment**	**Total**	**1st week**	**2nd week**	**3rd week**
Major ischemic events	ASA (n = 5035)	458	330	36	21
	Clopidogrel + ASA (n = 5016)	328	217	30	14

Identified Risk	Major bleeding (including ICH[a])

	Difference	130	113	6	7
Major Hemorrhage	ASA (n = 5035)	18	4	2	1
	Clopidogrel + ASA (n = 5016)	30	10	4	2
	Difference	-12	-6	-2	-1

ASA: Acetyl Salicylic Acid; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; POINT: Platelet-Oriented Inhibition in New Transient Ischemic Attack And Minor Ischemic Stroke.

Severity and nature of risk:

Clopidogrel prolongs bleeding time and thus increases the risk of bleeding in patients who have lesions with propensity to bleed. The intensity of bleeding may be increased if other drugs acting on hemostasis are associated to clopidogrel. Severe bleeding may be fatal. Major bleeding may be of various localizations primarily belonging to 4 main SOCs: GI disorders, nervous system disorders and injury disorders, poisoning and procedural complications, and eye disorders.

In clinical trial (**ACTIVE program**) all major bleeding defined per protocol, were to be reported as serious events. Major bleeding constituted the primary safety endpoint for this program, which were adjudicated by an event-adjudication committee, blinded to the treatment assignments. The results presented afterwards are based on ITT analysis.

Seriousness/outcomes:

In ACTIVE A study, all major bleedings were to be reported as serious events. They were more frequently reported in the clopidogrel in combination with ASA group than in the ASA alone group, and were mostly of an extra-cranial origin, ie, mainly GI. A fatal outcome was observed in the same proportion of major bleeds within each treatment group (ie, 16%). The frequency of fatal major bleeding was at 1.11% in the clopidogrel in combination with ASA group (versus 0.71% in the ASA alone group).

In ACTIVE W study, the rate of major bleeding was similar in both clopidogrel in combination with ASA group and VKAs group, ie, 3.03% and 2.76% respectively. However, ICH was higher in the VKAs group compared to the clopidogrel in combination with ASA group, due to an excess of hemorrhagic stroke. They were 7 (0.21%) and 11 (0.33%) fatal bleedings with clopidogrel in combination with ASA group and with VKAs group, respectively.

Background incidence/prevalence:

Incidence of major bleeding in patients with ACS:

In the GRACE registry of 27 358 patients with a diagnosis of UA or NSTEMI, the incidence of major bleeding during their index admission was 2.4%. (36)

Among 34 146 patients with ACS, the incidence of major bleeding in the first 6 months of FU was 2%. In this study, individual patient data from the Organization to Assess Strategies for Ischemic Syndrome (OASIS) Registry, OASIS-2 and CURE were combined into a single database. (37)

In a study of 3193 patients hospitalized with an ACS admitted to the University of Michigan, Ann Arbor, USA between 1999 and 2004, the incidence of major bleeding during hospitalization was 6.2%. (38)

Incidence of major bleeding in patients with recent stroke:

In a study of 19 185 patients with atherosclerotic vascular diseases manifested as either recent IS (33.5%), recent MI (32.8%), or symptomatic PAD (33.6%) (**CAPRIE**-clopidogrel versus ASA), with more than 6300 patients in each of these 3 sub-clinical groups, the incidence of any severe bleeding disorder during the study (mean duration of FU of 1.91 years) was 1.38% in patients taking clopidogrel and 1.55% in those taking placebo. (39)

Identified Risk	Major bleeding (including ICH[a])
	In a study of 9190 patients from 690 medical centers in 23 countries, the incidence of serious bleeding during FU (median 366 days) was 2.4% in patients taking aspirin <162 mg/day and 3.3% in those taking aspirin ≥162 mg/day. The corresponding incidences for any bleeding were 11.2% and 15.3%. In this study, the patients had a history of UA or MI within 14 days, TIA within 30 days, stroke within 5-30 days, or vascular disease in 2 arterial beds (peripheral vascular and either CV or cerebrovascular). (40) In a study of 7599 patients with a recent IS or TIA with at least 1 additional vascular risk factor (MATCH), the incidence of major bleeding during 18 months of FU was 2% in patients taking clopidogrel and aspirin and 1% in those taking clopidogrel and placebo. (41) Incidence of major bleeding in patients with PAD: In a study of 2161 patients with PAD followed for an average of 35 months, the WAVE, the incidence of life-threatening bleeding was 4.0% in patients receiving combination therapy with anticoagulant and antiplatelet agents and 1.2% in those receiving an antiplatelet agent alone. (42) For moderate bleeding, the corresponding incidence was 2.9% and 1.0%. The antiplatelet agent used in this study was predominantly aspirin (over 91%); others used were ticlopidine (3.4%) and clopidogrel (3.4%). In a post-hoc analysis of 3096 patients with PAD from the CHARISMA trial, the incidence of severe bleeding was 1.7%; the incidence was not different from that in patients without PAD 1.5%. (43) Incidence of major bleeding in patients with AF: The reference treatment for AF patients at risk of vascular events is warfarin. Warfarin increased the risk of intracerebral hemorrhage by 128% and of extracranial bleeding by 70% compared to ASA. Among AF patients with atherothrombosis (44) the incidence of major bleeding (bleeding requiring hospitalization) was 1.51% per year, which was higher than the incidence of major bleeding in patients without AF (0.8% per year). In a study of 4060 AF patients taking anticoagulant therapy (warfarin) followed for an average of 3.5 years, the incidence of major bleeding was approximately 2% per year. (45) In another study of AF patients, the incidence of major bleeding was 2.3% per year for warfarin users and 3.9% for warfarin + aspirin users, and 1.9% per year for ximelagatran users. (46) In a study of AF patients undergoing PCI in 2 hospitals in Spain, the incidence of major bleeding during the FU period (mean 595 days) was 12.3%. (47) In the randomized phase 3 CURRENT-OASIS-7 study, major bleeding was more common with double-dose than with standard-dose clopidogrel (1.6% versus 1.1%, HR = 1.41, 95% CI 1.09 1.83, p = 0.009). TRITON-TIMI 38 study, reported 13% of the 13 608 patients (Prasugrel [N = 6813] Clopidogrel [N = 6795]) with age ≥75 years old. The study found no apparent net clinical benefit of prasugrel versus clopidogrel in patients ≥75 years old and in patients with low body weight (<60 kg). The study published by Matos Soeiro et al. (2019) involved very elderly patients (aged ≥75 years) with ACS, receiving clopidogrel 75 mg (Group I) or an LD of 300-600 mg (Group II), The study results showed increased bleeding rates in the LD group (8.5% in Group I versus 20% in Group II; odds ratio: 0.173; p = 0.007). This was driven by minor bleeding since major bleeding rate was nearly similar at 45.5% versus 44.4% (p = 0.672) in Group I versus Group II, respectively. Hemorrhagic stroke was the most prevalent bleeding disorder. The occurrence of any bleeding (major or minor) had an impact on higher in-hospital mortality rates. The mortality rate among patients who had any type of bleeding versus those who had no bleeding was 25% versus 4.5% (p<0.0001). Nevertheless, in the comparison between Groups I and II, there were no differences regarding mortality and combined events. CURRENT-OASIS-7 (Mehta, 2010): 13% of the study population had age ≥75 years old with balanced distribution between groups of clopidogrel double dose and single dose and ASA higher and lower dose. The analysis concluded that a 7 day, 600 mg LD regimen of clopidogrel is more effective than the standard 300 mg LD regimen in reducing ischemic events (primary outcome of CV death, MI, or stroke occurred in 330 (3.9%) individuals in the double-dose group, compared with 392 (4.5%) in the standard-dose group (adjusted HR 0.86, 95% CI 0.74-0.99, p = 0.039; [Table 18b]

Identified Risk	Major bleeding (including ICH[a])

[Figure 1]. Recurrent ischemia and stent thrombosis were also significantly lower in the double-dose than in the standard-dose clopidogrel group [Table 18b] in patients undergoing PCI for ACS.

Table 18b: Efficacy and safety outcomes for clopidogrel dose comparison

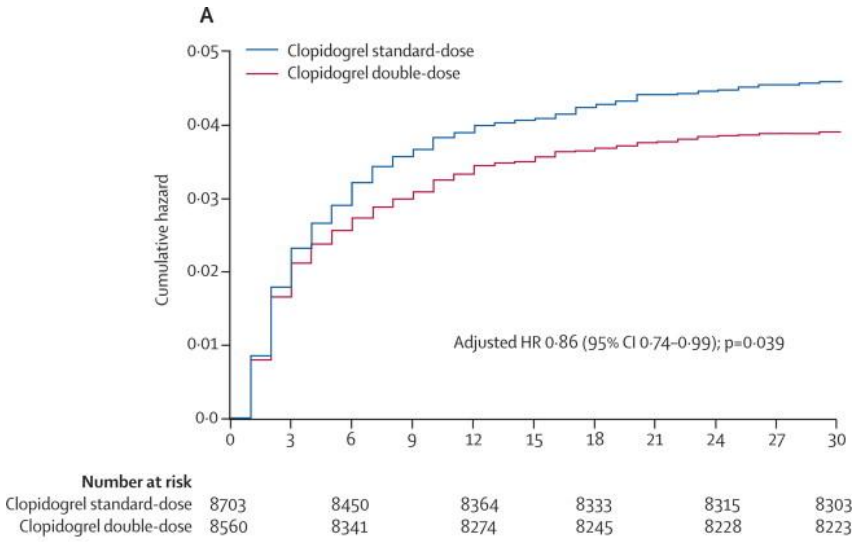
	Clopidogrel dose		Adjusted HR (95% CI)	p value
	Double (N=8560)	Standard (N=8703)		
CV death, MI, or stroke	330 (3.9%)	392 (4.5%)	0.86 (0.74-0.99)	0.039
CV death, MI, stroke or recurrent ischaemia	363 (4.2%)	435 (5.0%)	0.85 (0.74-0.98)	0.025
CV death	160 (1.9%)	169 (1.9%)	0.96 (0.77-1.19)	0.71
MI	172 (2.0%)	226 (2.6%)	0.79 (0.64-0.96)	0.018
Stroke	30 (0.4%)	36 (0.4%)	0.87 (0.53-1.41)	0.56
Recurrent ischaemia	39 (0.5%)	48 (0.6%)	0.85 (0.56-1.31)	0.47
Total mortality	166 (1.9%)	179 (2.1%)	0.94 (0.76-1.16)	0.57
CURRENT-defined major bleed	139 (1.6%)	99 (1.1%)	1.41 (1.09-1.83)	0.009
CURRENT-defined severe bleed	96 (1.1%)	72 (0.8%)	1.34 (0.99-1.82)	0.060
TIMI-defined major bleed	81 (1.0%)	60 (0.7%)	1.36 (0.97-1.90)	0.074
Fatal bleed	6 (0.07%)	13 (0.2%)	0.46 (0.18-1.22)	0.12
Intracranial bleed	3 (0.04%)	4 (0.05%)	0.77 (0.17-3.43)	0.73
Red cell transfusion >2 units	109 (1.3%)	77 (0.9%)	1.42 (1.06-1.91)	0.019
CABG-related bleed	10 (0.1%)	6 (0.07%)	1.70 (0.62-4.69)	0.30
Haemoglobin drop >50 g/L	47 (0.6%)	30 (0.3%)	1.60 (1.01-2.53)	0.045
Minor bleed	435 (5.1%)	368 (4.3%)	1.23 (1.07-1.41)	0.004
Events before PCI				
MI or stroke	25 (0.3%)	19 (0.2%)	1.34 (0.74-2.44)	0.33
MI	25 (0.3%)	17 (0.2%)	1.50 (0.81-2.78)	0.20
Stroke	0	2 (0.02%)	-	-
CURRENT-defined major bleed	9 (0.1%)	4 (0.04%)	2.31 (0.71-7.49)	0.16
CURRENT-defined severe bleed	5 (0.1%)	2 (0.02%)	2.55 (0.49-13.14)	0.26
TIMI-defined major bleed	5 (0.1%)	1 (0.01%)	5.09 (0.60-43.60)	0.14
Events after PCI				
CV death, MI, or stroke	305 (3.6%)	373 (4.3%)	0.83 (0.71-0.96)	0.015
CV death, MI, stroke or recurrent ischaemia	319 (3.7%)	397 (4.6%)	0.81 (0.70-0.94)	0.006
CV death	160 (1.9%)	169 (1.9%)	0.96 (0.77-1.19)	0.69

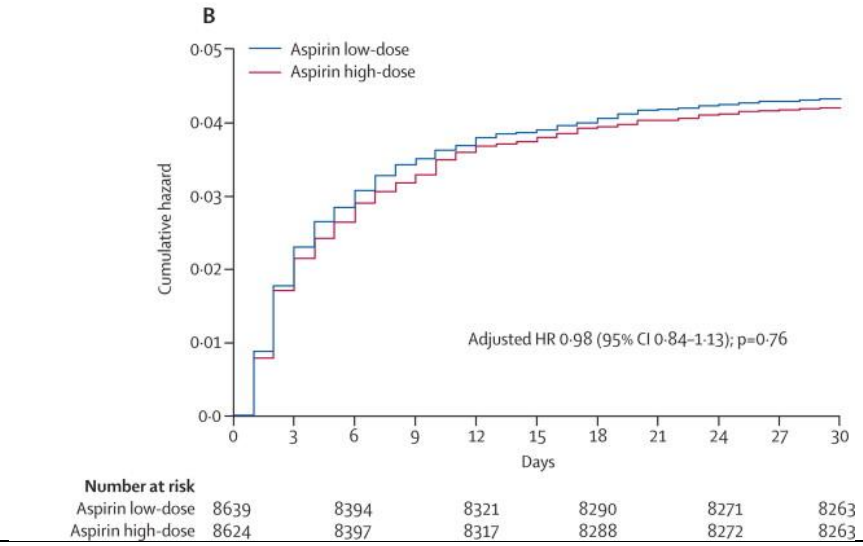
Identified Risk	Major bleeding (including ICH[a])

MI	147 (1.7%)	209 (2.4%)	0.72 (0.58-0.88)	0.002
Stroke	30 (0.4%)	34 (0.4%)	0.89 (0.55-1.46)	0.65
Recurrent ischaemia	20 (0.2%)	29 (0.3%)	0.70 (0.40-1.24)	0.23
Total mortality	166 (1.9%)	179 (2.1%)	0.94 (0.76-1.16)	0.55
CURRENT-defined major bleed	130 (1.5%)	95 (1.1%)	1.39 (1.07-1.81)	0.0141
CURRENT-defined severe bleed	91 (1.1%)	70 (0.8%)	1.32 (0.97-1.80)	0.080
TIMI-defined major bleed	76 (0.9%)	59 (0.7%)	1.31 (0.93-1.84)	0.12

Data are number (%), unless otherwise indicated.
CABG: Coronary Artery Bypass Graft Surgery; CI: Confidence Interval; CV: Cardiovascular; HR: Hazard Ratio; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; TIMI: Thrombosis in Myocardial Infarction.

Figure 1: Kaplan-Meier curves for the primary outcome of cardiovascular (CV) death, MI, or stroke, for the clopidogrel dose comparison (A) and the aspirin dose comparison

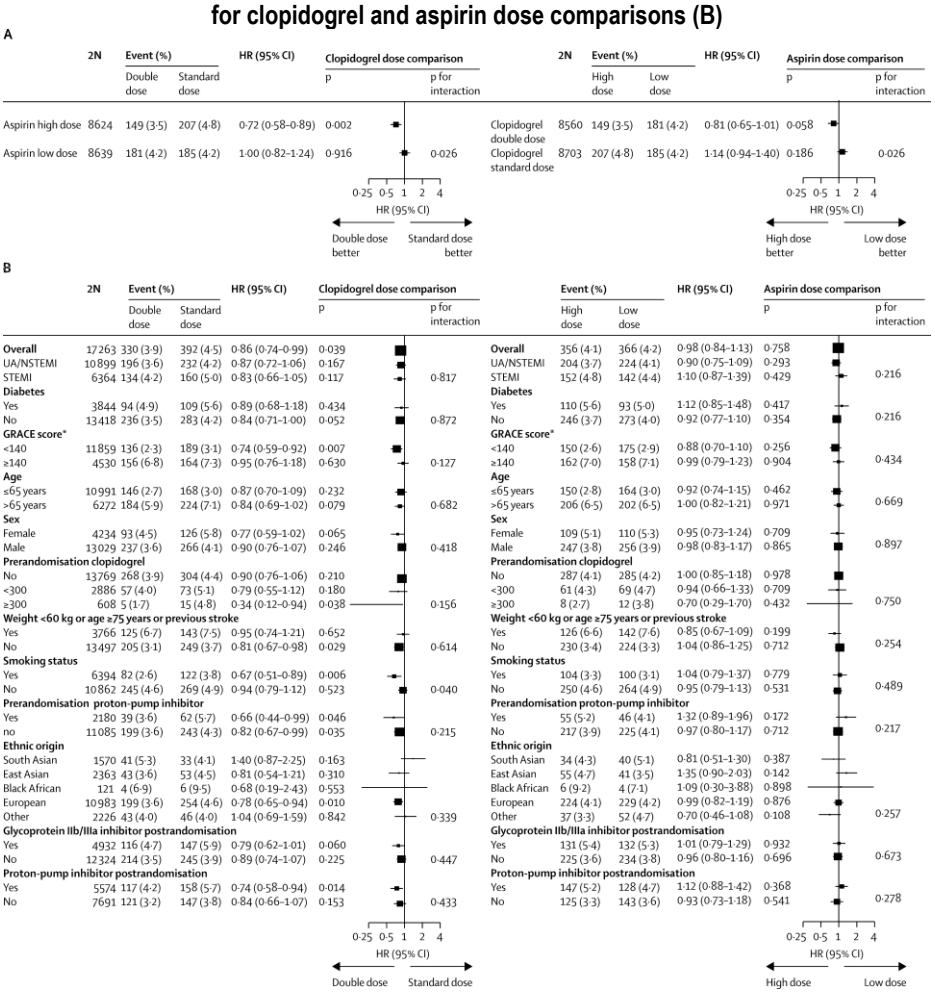




Identified Risk	**Major bleeding (including ICH[a])**

There was consistency in the treatment effect for each dose comparison in predefined subgroups [Figure 2]. Consistent effects were recorded with the double-dose clopidogrel regimen in patients with STEMI and patients with non-ST-segment elevation acute coronary syndromes [Figure 2].

Figure 2: Primary outcome for clopidogrel and aspirin dose comparisons according to randomized factorial design (A), and subgroup analyses for primary outcome in subgroups for clopidogrel and aspirin dose comparisons (B)



CURRENT-defined major bleeding was more common with double-dose clopidogrel than with the standard dose (130 [1.5%] 95 [1.1%] 1.39 [1.07-1.81] p=0.0141). However, rates of severe bleeding and major bleeding defined by TIMI did not differ between groups [Table 18a]. Double dose clopidogrel did not increase the risk of bleeding that was fatal or intracranial, nor bleeding that was related to CABG surgery [Table 18a]. However, the results of the analysis for ≥75 years old subgroup were not provided

Postmarketing experience: As of the cut-off date, no change in the safety profile of clopidogrel was observed based on routine pharmacovigilance activities and no change in the safety information for the risk of bleeding.

Impact on individual patient:

Severe bleedings result in hospitalization, prolongation of hospitalization and may contribute to a worsening of ischemic status in atherothrombotic patients or sequelae.

Intracranial hemorrhage is the most devastating bleeding complication.

<table>
<tr><th>Identified Risk</th><th>Major bleeding (including ICH[a])</th></tr>
<tr><td>Risk factors and risk groups</td><td>
Generally, treated patients are at risk of increased bleeding in certain clinical circumstances, such as trauma, surgery or other pathological conditions. In some indications (eg, ACS), clopidogrel may be prescribed together with other antiplatelet agents or other medicinal products acting on hemostasis, which may increase the propensity or intensity of bleeding in these circumstances. Thus, special warnings and precautions for use are necessary for co-administration of clopidogrel with ASA, GP IIb/IIIa inhibitors, thrombolytics or heparin. Concomitant use of clopidogrel with oral anti-coagulant (OAC) (eg, warfarin) is not recommended. Concomitant use of Selective Serotonin Reuptake Inhibitors (SSRI)s should be undertaken with caution, since they can increase the propensity to bleed due to their spectrum of action on platelets. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase (COX)-2 inhibitors, should also be co-administered with caution, since they may increase the propensity to bleed, especially occult GI bleeding. Overall, patients concomitantly treated with any drugs known to cause bleeding can also be considered at risk due a potential additive effect with clopidogrel.
Very elderly patients:
In ACTIVE A study, in very elderly patients who are at greater risk for bleeding, as in the overall ACTIVE A population, the rate of adjudicated major bleeding was greater in the clopidogrel in combination with ASA group than in the ASA alone group (8.32% versus 5.98%); this increase was also noted for severe bleeding (6.19% versus 4.22%). Overall, the rates of major bleeding, severe bleeding, and ICH with clopidogrel in combination with ASA compared with ASA alone was independent of all relevant baseline demographic or previous history covariates (including bleeding risk or previous stroke, Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke [CHADS]2 score, and geographic region subgroups).
In POINT and CHANCE Pool analysis, a limited number of very elderly patient experienced ICH, reason why pooled data have been used for determining the risk of bleeding in population ≥75 years of age. No difference between treatment group regarding frequency was identified in this population.
Table 18c: Intracranial hemorrhage (ICH), CHANCE and POINT Pooled Analysis Dataset (ITT)
<table>
<tr><th>Age
(N Exposed patients)</th><th>No. of ICH in the clopidogrel + ASA group</th><th>No. of ICH in the ASA group</th><th>Total</th></tr>
<tr><td>75-84 years
(N = 1618)</td><td>4 (0.5%; 4/781)</td><td>3 (0.4%; 3/837)</td><td>7 (0.4; 7/1618)</td></tr>
<tr><td>≥85 years
(N = 361)</td><td>1 (0.5%; 1/201)</td><td>0 (0.0%; 0/160)</td><td>1 (0.3; 1/361)</td></tr>
<tr><td>Total
(N = 10 051)</td><td>13 (0.3%; 13/5016)</td><td>11 (0.2%;11/ 5035)</td><td>24 (0.2; 24/10 051)</td></tr>
</table>
ASA: Acetyl Salicylic Acid; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke.
Off-label use: No clinical benefit of clopidogrel has been demonstrated outside approved indications while patients remained at risk of bleeding.
</td></tr>
<tr><td>Preventability</td><td>
The following appropriate measures are recommended:

To use with precaution clopidogrel +/- ASA in populations or situations at higher risk of bleeding, such as medical conditions at risk of bleeding, concomitant use of pro-hemorrhagic drugs (eg, non-steroidal anti-inflammatory drugs (NSAIDs), SSRI, Heparin, GP IIb/IIa inhibitors), recent surgery, overdose, and to limit the prescription of ASA in association with clopidogrel to the clinical situation where the combination had proven the benefit.
To temporary discontinue 7 days prior to elective surgery if the antiplatelet effect is not desirable.
To contraindicate clopidogrel +/- ASA in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

</td></tr>
</table>

Identified Risk	Major bleeding (including ICH[a])
	• To avoid the LD in STEMI patients ≥75 years old taking fibrinolytic therapy. • To administrate a LD of 300 mg in non-STEMI patients ≥75 years old. • A LD of 600 mg clopidogrel in STEMI PCI patients ≥75 years old may be considered based on an individual benefit-risk assessment performed by the prescribing physician.
Impact on the benefit-risk balance of the product	Bleeding is related to pharmacological activity of clopidogrel. Bleeding in populations at increased risk such as very elderly patients (≥75 years) or patient treated with DAPT or with drug-acting on hemostasis, is to be put in perspective with the observed benefit. Clopidogrel should be prescribed in the frame of exact labeling indications to maintain a positive B/R balance related to bleedings risk. Due to limited data in patients ≥75 years old, who are usually excluded from the clinical trials and due to the increased risk of bleeding with the aging process, Clopidogrel LD of 300 mg is recommended in non-STEMI patients and no LD should be administered in STEMI patients taking fibrinolytic therapy. In STEMI patients undergoing PCI the LD of 600 mg can be administrated as the benefit is higher than the risk of bleeding in this case. Randomized phase 3 studies POINT and CHANCE showed a positive B/R balance in the new indication of DAPT for the first 21 days of treatment in TIA in patient at high risk of recurrence or in minor stroke. In CLARITY-PCI sub-group analysis of randomized phase 3 study CLARITY, no significant difference was observed in the rates of major or minor bleeding between both the treatments (2.0% with clopidogrel pre-treatment versus 1.9% with placebo, p >0.99). In the randomized phase 3 CURRENT-OASIS-7 study in the 17 236 patients who underwent a PCI procedure for acute coronary syndromes, a double dose clopidogrel regimen was associated with a reduction in cardiovascular events and stent thrombosis compared with the standard dose. Double dose reduced the rate of the primary outcome (330 events [3.9%] versus 392 events [4.5%]; adjusted HR 0.86, 95% CI 0.74-0.99, p=0.039) and definite stent thrombosis (58 [0.7%] versus 111 [1.3%]; 0.54 [0.39-0.74], p=0.0001). A double dose clopidogrel regimen can be considered for all patients with acute coronary syndromes treated with an early invasive strategy and intended early PCI. Major bleeding was more common with double-dose than with standard-dose clopidogrel (1.6% versus 1.1%, HR 1.41, 95% CI 1.09 1.83, p=0.009). However, rates of severe bleeding and major bleeding defined by TIMI did not differ between groups (1.0% versus 0.7% HR 1.36, 95% CI 0.97-1.90 p=0.074). Double dose clopidogrel did not increase the risk of bleeding that was fatal (0.07% versus 0.2% HR 0.46, 95% CI 0.18-1.22, p= 0.12) or intracranial (0.04% versus 0.05% HR 0.77, 95% CI 0.17-3.43, p=0.73), nor bleeding that was related to CABG surgery (0.1% versus 0.07% HR 1.70, 95% CI 0.62-4.69, p=0.30). (35) Before PCI, rates of ischemic events or major bleeding did not differ between the groups. The differences in these outcomes occurred largely after PCI. Based on the risk assessment for addition of indication in STEMI PCI, the safety profile of clopidogrel remains unchanged. Randomized Clinical trial CURRENT OASIS 7 showed statistical significance in reducing cardiovascular death, MI, stroke and stent thrombosis, thus supporting the recommendation of 600 mg clopidogrel regimen for patients ≥75 years old, however, the results of the analysis for ≥75 years old subgroup were not provided.
Public health impact	Major bleeding is balanced by the benefit of clopidogrel treatment (with or without ASA background therapy) to prevent atherothrombotic events in the frame of labelled indications including for clopidogrel + ASA FDC association to prevent stroke in a restricted population as per labeling (patients with AF, at increased risk of vascular events and who cannot take VKA). Given the positive benefit-risk profile of clopidogrel, the public health impact of major bleeding is considered to be low.

Identified Risk	Major bleeding (including ICH[a])

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

ACS: Acute Coronary Syndrome; ACTIVE: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Event; ADP: Adenosine Diphosphate; AF: Atrial Fibrillation; ASA: Acetyl Salicylic Acid; BR: Benefit-Risk; CABG: Coronary Artery Bypass Graft; CAPRIE: Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CHADS: Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; CI: Confidence Interval; CLARITY: Clopidogrel As Adjunctive Reperfusion Therapy; COMMIT: Clopidogrel And Metoprolol in Myocardial Infarction Trial; COX: Cyclo-Oxygenase; CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events; CURRENT-OASIS-7: Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies for Ischemic Syndromes; CV: Cardiovascular; DAPT: Dual Antiplatelet Therapy; FDC: Fixed-Dose Combination; FU: Follow-Up; GI: Gatrointestinal; GP: Glycoprotein; GPV: Global Pharmacovigilance; HR: Hazard Ratio; ICH: Intracranial Hemorrhage; IS: Ischemic stroke; ITT: Intent To Treat; LD: Loading Dose; MI: Myocardial Infarction; mIS: Minor Ischemic Stroke; NSAID: Non-Steroidal Anti-inflammatory Drug; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction; OAC: Oral Anti-Coagulant; OASIS: Organization to Assess Strategies for Ischemic Syndrome; p: Probability; PAD: Peripheral Arterial Disease; PCI: Percutaneous Coronary Intervention; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke; SOC: System Organ Class; SSRI: Selective Serotonin Reuptake Inhibitor; STE: ST Segment Elevation; STEMI: ST-Segment Elevation Myocardial Infarction; TIA: Transient Ischemic Attack; TIMI: Thrombosis in Myocardial Infarction; UA: Unstable Angina; USA: United States of America; VKA: Vitamin K Antagonist.

SVII.3.2. Presentation of the missing information

Not applicable.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 19 - Summary of the safety concerns

Important identified risks	Major bleeding (including ICH[a])
Important potential risks	None
Missing information	None

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; mIS: Minor Ischemic Stroke; TIA: Transient Ischemic Attack.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of clopidogrel will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports, product technical complaints (PTCs) relating to adverse events, and signal detection.

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place, including:

Specific adverse reaction FUQ for “Major bleeding (including ICH)” [Annex 4].

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable, since there are no additional pharmacovigilance activities planned for this product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable, since there are no additional pharmacovigilance activities ongoing or planned for clopidogrel.

No effectiveness evaluation is set up since there are no risk minimization activities beyond routine in place.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for clopidogrel.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 20 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Major bleeding (including ICH[a])	**Routine risk communication:** SmPC: Labeled in section 4.8 of Iscover and Plavix SmPC. Package Leaflet (PL): Labeled in section 4 of Iscover and Plavix PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labeled in sections 4.3 and 4.4 of Iscover and Plavix SmPC. PL: Labeled in sections 2 and 3 of Iscover and Plavix PL. **Other routine risk minimization measures beyond the product Information:** None

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; mIS: Minor Ischemic Stroke; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TIA: Transient Ischemic Attack.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concern of the medicinal product.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 21 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Major bleeding (including ICH[a])	**Routine risk minimization measures:** SmPC: Labeled in sections 4.3, 4.4 and 4.8 of Iscover and Plavix SmPC. PL: Labeled in sections 2, 3 and 4 of Iscover and Plavix PL.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific targeted FUQ form **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; FU: Follow-Up; mIS: Minor Ischemic Stroke PL: Package Leaflet; SmPC: Summary of Product Characteristics; TIA: Transient Ischemic Attack.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Plavix (Clopidogrel hydrogen sulfate)

This is a summary of the RMP for Plavix. The RMP details important risks of Plavix how these risks can be minimized, and how more information will be obtained about Plavix's risks and uncertainties (missing information).

Plavix's SmPC and its PL give essential information to HCPs and patients on how Plavix should be used.

This summary of the RMP for Plavix should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Plavix's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Plavix is authorized in adults for the secondary prevention of atherothrombotic events in recent MI, recent IS or established PAD and moderate to high-risk TIA or minor IS, and in ACS. It is also indicated for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation (AF) (see SmPC for the full indication). It contains clopidogrel as the active substance and it is given by oral route.

Further information about the evaluation of Plavix's benefits can be found in Plavix's (EMEA/H/C/000174) EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpages:

https://www.ema.europa.eu/en/medicines/human/EPAR/plavix

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Plavix together with measures to minimize such risks and the proposed studies for learning more about Plavix's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Plavix are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Plavix. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 22 - List of important risks and missing information (Plavix)

Important identified risk	Major bleeding (including ICH[a])
Important potential risk	None
Missing information	None

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; mIS: Minor Ischemic Stroke; TIA: Transient Ischemic Attack.

II.B Summary of important risks

Table 23 - Important risks and missing information with corresponding risk minimization activities: Major bleeding (including ICH[a])

Important identified risk: **Major bleeding (including ICH[a])**	
Evidence for linking the risk to the medicine	Postmarketing experience, clinical and epidemiological data, and literature.
Risk factors and risk groups	Generally, treated patients are at risk of increased bleeding in certain clinical circumstances, such as trauma, surgery or other pathological conditions. In some indications (eg, ACS), clopidogrel may be prescribed together with other antiplatelet agents or other medicinal products acting on hemostasis, which may increase the propensity or intensity of bleeding in these circumstances. Thus, special warnings and precautions for use are necessary for co-administration of clopidogrel with ASA, GP IIb/IIIa inhibitors, thrombolytics or heparin. Concomitant use of clopidogrel with OAC (eg, warfarin) is not recommended. Concomitant use of SSRIs should be undertaken with caution, since they can increase the propensity to bleed due to their spectrum of action on platelets. Non-steroidal anti-inflammatory drugs, including COX-2 inhibitors, should also be co-administered with caution, since they may increase the propensity to bleed, especially occult GI bleeding. Overall, patients concomitantly

<table>
<tr><th colspan="2">Important identified risk: Major bleeding (including ICH[a])</th></tr>
<tr><td></td><td>treated with any drugs known to cause bleeding can also be considered at risk due a potential additive effect with clopidogrel.
<u>Very elderly patients:</u>
In ACTIVE A study, in very elderly patients who are at greater risk for bleeding, as in the overall ACTIVE A population, the rate of adjudicated major bleeding was greater in the clopidogrel in combination with ASA group than in the ASA alone group (8.32% versus 5.98%); this increase was also noted for severe bleeding (6.19% versus 4.22%). Overall, the rates of major bleeding, severe bleeding, and ICH with clopidogrel in combination with ASA compared with ASA alone was independent of all relevant baseline demographic or previous history covariates (including bleeding risk or previous stroke, CHADS2 score, and geographic region subgroups).
In POINT and CHANCE Pool analysis, a limited number of very elderly patient experienced ICH, reason why pooled data have been used for determining the risk of bleeding in population ≥75 years of age. No difference between treatment group regarding frequency was identified in this population.
Table 23a: Intracranial hemorrhage, CHANCE and POINT Pooled Analysis Dataset (ITT)
<table>
<tr><th>Age
(N Exposed patients)</th><th>No. of ICH in the clopidogrel + ASA group</th><th>No. of ICH in the ASA group</th><th>Total</th></tr>
<tr><td>75-84 years
(N = 1618)</td><td>4 (0.5%; 4/781)</td><td>3 (0.4%; 3/837)</td><td>7 (0.4; 7/1618)</td></tr>
<tr><td>≥85 years
(N = 361)</td><td>1 (0.5%; 1/201)</td><td>0 (0,0%; 0/160)</td><td>1 (0.3; 1/361)</td></tr>
<tr><td>Total
(N = 10 051)</td><td>13 (0.3%; 13/5016)</td><td>11 (0.2%;11/ 5035)</td><td>24 (0.2; 24/10 051)</td></tr>
</table>
ASA: Acetyl Salicylic Acid; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke.
Off-label use: No clinical benefit of clopidogrel has been demonstrated outside of approved indications while patients remained at risk of bleeding.</td></tr>
<tr><td>Risk minimization measures</td><td>Routine risk minimization measures:
<u>SmPC</u>:
Labeled in sections 4.3, 4.4 and 4.8 of Plavix SmPC.
<u>PL</u>:
Labeled in sections 2, 3 and 4 of Plavix PL.
Additional risk minimization measures:
None</td></tr>
</table>

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

ACTIVE: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Event; ACS: Acute Coronary Syndrome; ASA: Acetylsalicylic Acid; CHADS: Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; COX: Cyclo-Oxygenase; DAPT: Dual Antiplatelet Therapy; GI: Gastrointestinal; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; mIS: Minor Ischemic Stroke; OAC: Oral Anti-Coagulant; PL: Package Leaflet; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke; SmPC: Summary of Product Characteristics; SSRI: Selective Serotonin Reuptake Inhibitor; TIA: Transient Ischemic Attack.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Plavix.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Plavix.

Summary of risk management plan for Iscover (Clopidogrel hydrogen sulfate)

This is a summary of the RMP for Iscover. The RMP details important risks of Iscover how these risks can be minimized, and how more information will be obtained about Iscover's risks and uncertainties (missing information).

Iscover's SmPC and its PL give essential information to HCPs and patients on how Iscover should be used.

This summary of the RMP for Iscover should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Iscover's RMP.

III. THE MEDICINE AND WHAT IT IS USED FOR

Iscover is authorized in adults for the secondary prevention of atherothrombotic events in recent MI, recent IS or established PAD, and moderate to high-risk TIA or minor IS, and in ACS. It is also indicated for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation (AF) (see SmPC for the full indications). It contains clopidogrel as the active substance and it is given by oral route.

Further information about the evaluation of and Iscover's benefits can be found in Iscover's (EMA/H/C/000175) EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpages:

https://www.ema.europa.eu/en/medicines/human/EPAR/iscover

IV. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Iscover together with measures to minimize such risks and the proposed studies for learning more about Iscover's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

IV.A List of important risks and missing information

Important risks of Iscover are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Iscover. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 24 - List of important risks and missing information (Iscover)

Important identified risk	Major bleeding (including ICH[a])
Important potential risk	None
Missing information	None

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; mIS: Minor Ischemic Stroke; TIA: Transient Ischemic Attack.

IV.B Summary of important risks

Table 25 - Important risks and missing information with corresponding risk minimization activities: Major bleeding (including ICH[a])

Important identified risk: **Major bleeding (including ICH[a])**	
Evidence for linking the risk to the medicine	Postmarketing experience, clinical and epidemiological data, and literature.
Risk factors and risk groups	Generally, treated patients are at risk of increased bleeding in certain clinical circumstances, such as trauma, surgery or other pathological conditions. In some indications (eg, ACS), clopidogrel may be prescribed together with other antiplatelet agents or other medicinal products acting on hemostasis, which may increase the propensity or intensity of bleeding in these circumstances. Thus, special warnings and precautions for use are necessary for co-administration of clopidogrel with ASA, GP IIb/IIIa inhibitors, thrombolytics or heparin. Concomitant use of clopidogrel with OAC (eg, warfarin) is not recommended. Concomitant use of SSRIs should be undertaken with caution, since they can increase the propensity to bleed due to their spectrum of action on platelets. Non-steroidal anti-inflammatory drugs, including COX-2 inhibitors, should also be co-administered with caution, since they may increase the propensity to bleed, especially occult GI bleeding. Overall, patients concomitantly treated with any drugs known to cause bleeding can also be considered at risk due a potential additive effect with clopidogrel. Very elderly patients: **In ACTIVE A study**, in very elderly patients who are at greater risk for bleeding, as in the overall ACTIVE A population, the rate of adjudicated major bleeding was greater in the

<table>
<tr><th colspan="2">Important identified risk: Major bleeding (including ICH[a])</th></tr>
<tr><td></td><td>clopidogrel in combination with ASA group than in the ASA alone group (8.32% versus 5.98%); this increase was also noted for severe bleeding (6.19% versus 4.22%). Overall, the rates of major bleeding, severe bleeding, and ICH with clopidogrel in combination with ASA compared with ASA alone was independent of all relevant baseline demographic or previous history covariates (including bleeding risk or previous stroke, CHADS2 score, and geographic region subgroups).

In POINT and CHANCE Pool analysis, a limited number of very elderly patient experienced ICH, reason why pooled data have been used for determining the risk of bleeding in population ≥75 years of age. No difference between treatment group regarding frequency was identified in this population.

Table 25a: Intracranial hemorrhage, CHANCE and POINT Pooled Analysis Dataset (ITT)
<table>
<tr><th>Age
(N Exposed patients)</th><th>No. of ICH in the clopidogrel + ASA group</th><th>No. of ICH in the ASA group</th><th>Total</th></tr>
<tr><td>75-84 years
(N = 1618)</td><td>4 (0.5%; 4/781)</td><td>3 (0.4%; 3/837)</td><td>7 (0.4; 7/1618)</td></tr>
<tr><td>≥85 years
(N = 361)</td><td>1 (0.5%; 1/201)</td><td>0 (0,0%; 0/160)</td><td>1 (0.3; 1/361)</td></tr>
<tr><td>Total
(N = 10 051)</td><td>13 (0.3%; 13/5016)</td><td>11 (0.2%;11/ 5035)</td><td>24 (0.2; 24/10 051)</td></tr>
</table>
ASA: Acetyl Salicylic Acid; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke.

Off-label use: No clinical benefit of clopidogrel has been demonstrated outside of approved indications while patients remained at risk of bleeding.</td></tr>
<tr><td>Risk minimization measures</td><td>Routine risk minimization measures:
SmPC:
Labeled in section 4.3, 4.4 and 4.8 of Iscover SmPC.
PL:
Labeled in section 2, 3 and 4 of Iscover PL.
Additional risk minimization measures:
None</td></tr>
</table>

a ICH is applicable especially in TIA/mIS indication of DAPT for the first 21 days after TIA/mIS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

ACTIVE: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Event; ACS: Acute Coronary Syndrome; ASA: Acetylsalicylic Acid; CHADS: Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; COX: Cyclo-Oxygenase; DAPT: Dual Antiplatelet Therapy; GI: Gastrointestinal; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; mIS: Minor Ischemic Stroke; OAC: Oral Anti-Coagulant; PL: Package Leaflet; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke; SmPC: Summary of Product Characteristics; SSRI: Selective Serotonin Reuptake Inhibitor; TIA: Transient Ischemic Attack.

IV.C Post-authorization development plan

IV.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Iscover.

IV.C.2 Other studies in post-authorization development plan

There are no studies required for Iscover.

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PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

CLOPIDOGREL + ASA INTRACRANIAL/INTRACEREBRAL HEMORRHAGE (ICH) IN VERY ELDERLY (≥75-YEAR-OLD) PATIENT WITH TIA (TRANSIENT ISCHEMIC ATTACK) OR MINOR ISCHEMIC STROKE TREATED WITH DUAL ANTI-PLATELET THERAPY (DAPT)

FOLLOW-UP QUESTIONNAIRE (FUQ) FOR HEALTH CARE PROFESSIONALS (HCP)

Clopidogrel + ASA
Intracranial/Intracerebral Hemorrhage (ICH)
in very elderly (≥ 75-year-old) patient with TIA (Transient Ischemic Attack) or Minor Ischemic Stroke treated with Dual Anti-Platelet Therapy (DAPT)

Follow-up Questionnaire (FUQ) for Health Care Professionals (HCP)

The goal of this questionnaire is to collect the very essential information on reported event(s) of **ICH (Intracranial / Intracerebral hemorrhage) in very elderly (≥ 75-year-old) patients with TIA (Transient Ischemic Attack) or minor Ischemic Stroke treated with Dual Anti-Platelet Therapy (DAPT) with Clopidogrel+ASA**. For any other additional adverse event(s), please complete the corresponding "other experienced adverse event(s)" section at the end of this form
By providing this information, you will make a useful contribution to the safety of this product for the benefit of patients.

Sanofi Case ID:	**Program ID:**
Reporter Information *(person who provides the information reported on this form)*: Name or Initials: Qualification: ☐Health Care Professional (HCP) ☐non-HCP Email address: Phone Number:	
Patient Information: Name or Initials or ID: Gender: ☐Male ☐Female ☐Unknown Date of Birth: Age or Age Group: Age group category: ≥ 75-year-old (mandatory): ☐ Yes ☐ No	

SPECIFIC INFORMATION

Treatment Information

Dates of prescriptions (start/stop) of dual antiplatelet therapy of clopidogrel + low dose aspirin (i.e., ASA or ASL):

Start Date	Stop Date	Duration of treatment

Dose of ASA or ASL in DAPT: ☐ ≤100 mg ☐ >100mg–325mg

DAPT indication:
- ☐ Transient ischemic attack (TIA)
- ☐ Minor ischemic stroke
- ☐ Other (antithrombotic indication/prevention of cardiovascular event at time of ICH first symptoms)

Sanofi (Clopidogrel+ASA) Batch Number(s):

Adverse Event Information

If ICH is:	**ICH type**:
☐ spontaneous ☐ traumatic ☐ symptomatic ☐ asymptomatic **ICH severity**: _____	☐ Subdural hemorrhage ☐ Microvascular hemorrhage ☐ Other (specify): _____

Seriousness: ☐ Non-Serious ☐ Serious (select at least one criterion below)

☐Death	☐Life-threatening	☐Hospitalization or prolongation of hospitalization
☐Persistent or significant disability or incapacity		☐Medically significant (as per HCP)
☐Suspected transmission of infectious agent		☐Congenital anomaly, birth defect

Outcome:
☐ Recovered/Resolved ☐ Recovered/Resolved with Sequelae ☐ Not Recovered/Not Resolved
☐ Recovering/Resolving ☐ Fatal ☐ Unknown
Specify date of resolution or date of death, if applicable: _____
If patient recovered with sequelae, describe sequelae: _____

Event Relationship to Sanofi Product (Clopidogrel+ASA): ☐Related ☐Not Related ☐Unknown

Medical History/Risk Factors

Risk factors other than medications:
☐ Cerebral aneurysm
☐ Cerebral hemangioma
☐ Other (specify): _____

If DAPT indication is TIA, provide **ABCD² score** (if known): _____

If DAPT indication is minor ischemic stroke, provide **NIHSS score** (if known): _____

Previous history of bleeding: ☐Yes - specify diagnosis: _____
☐No ☐Unknown

Previous history of ICH with details: ☐Yes - specify onset date, exact diagnosis, and risk factors: _____

☐No ☐Unknown

IRM / Scanner

Date (DD-MMM-YYYY) and Results:

ADDITIONAL INFORMATION

Please provide any other relevant additional information **regarding the reported event** (e.g., other suspect product(s), other additional information on reported adverse event, patient's medical history, concomitant medications, etc.):

Please provide relevant information regarding **any other experienced adverse event(s)** (e.g., event onset date(s), outcome(s), if it led to hospitalization, relationship(s) with Sanofi product, etc.):

Additional requests for the reporter (if any):

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

NOT APPLICABLE