10 November 2022
EMA/55817/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iscover	clopidogrel
Plavix	clopidogrel
DuoPlavin	clopidogrel / acetylsalicylic acid

Procedure No. EMEA/H/C/xxxx/WS/2150

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACS – acute coronary syndrome

AHA – American Heart Association

ESC – European Society of Cardiology

LD – loading dose

NSTEMI – Non ST elevation myocardial infarction

PCI - percutaneous coronary intervention

STEMI – ST elevation myocardial infarction

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 2 December 2021 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIA

Extension of indication to include clopidogrel in combination with acetylsalicylic acid in ST segment elevation acute myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI); as a consequence section 4.1, 4.2 and 5.1 of the SmPC is updated. Version 1.5 of the RMP has also been submitted. In addition an editorial update has been made to the labelling.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Bruno Sepodes

Timetable	Actual dates
Submission date	02 Dec 2021
Start of procedure	25 Dec 2021
CHMP Rapporteur Assessment Report	21 Feb 2022
PRAC Rapporteur Assessment Report	21 Feb 2022

Timetable	Actual dates
Updated PRAC Rapporteur Assessment Report	03 Mar 2022
PRAC Outcome	10 Mar 2022
CHMP members comments	14 Mar 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 Mar 2022
Request for supplementary information (RSI)	24 Mar 2022
Restart of procedure	23 May 2022
CHMP Rapporteur Assessment Report	22 June 2022
PRAC Rapporteur Assessment Report	22 June 2022
PRAC Outcome	07 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur Assessment Report	15 July 2022
Request for supplementary information (RSI)	21 July 2022
Restart of procedure	12 Sept 2022
CHMP Rapporteur Assessment Report	14 Oct 2022
CHMP members comments	28 Oct 2022
Updated CHMP Rapporteur Assessment Report	07 Nov 2022
CHMP Opinion	10 Nov 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The currently approved posology of Clopidogrel (Plavix®/Iscover®) in patients suffering from ACS is as below (Plavix® /Iscover® SmPC):

- Non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg or 600 mg loading dose (LD). A 600 mg LD may be considered in patients <75 years of age when PCI is intended. Clopidogrel treatment should be continued at 75 mg once a day (with ASA 75 mg to 325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.
- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg LD in combination with ASA and with or without thrombolytics. For medically treated patients over 75 years of age clopidogrel should be initiated without a LD. Combined

therapy should be started as early as possible after symptoms start and continued for at least 4 weeks. The benefit of the combination of clopidogrel with ASA beyond 4 weeks has not been studied in this setting.

The currently approved posology of fixed-dose combination of clopidogrel and ASA (Duoplavin®) in patients suffering from ACS is as below (Duoplavin® SmPC):

- In patients with non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction): 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.
- In patients with STEMI: Therapy should be started as early as possible after symptoms start and continued for at least 4 weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting.

The MAH is now intending to include the changes below:

a. New Indication (Applicable to Plavix® / Iscover® and Duoplavin®)

- Extend the indication in STEMI patients undergoing a stent placement following PCI.

b. Posology and Administration

- Dosage in STEMI patients (Applicable to Plavix® / Iscover®) - When PCI is intended, the treatment with clopidogrel should be initiated with a single 300 mg or 600 mg LD.
- Treatment Duration (Applicable to Plavix® / Iscover® and Duoplavin®) - When PCI is intended, the treatment with clopidogrel should be continued at 75 mg once a day, in combination with ASA 75 mg to 100 mg up to 12 months. 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. However, in clinical practice the maintenance dose (MD) of ASA prescribing range is 75 mg to 325 mg daily. Combined therapy should be started as early as possible after symptoms start and continued daily up to 12 months (with ASA 75 mg to 100 mg daily).

The data submitted by the MAH is based on current clinical guidelines (2013 American College of Cardiology Foundation [ACCF]/American Heart Association [AHA] guidelines for the management of STEMI, 2017 European Society of Cardiology [ESC] guidelines for the management of STEMI and 2018 ESC/European Association for Cardio-Thoracic Surgery [EACTS] guidelines on myocardial revascularization) and a bibliographic review of published studies, retrieved through a comprehensive literature search covering the period 2001 to 2021 with the help of the Embase, PubMed, and Google scholar databases. The MAH has submitted a discussion of the existing relevant data on the use of clopidogrel in the treatment of STEMI patients undergoing PCI (with loading and maintenances doses and duration of treatment). A detailed literature search methodology has been submitted.

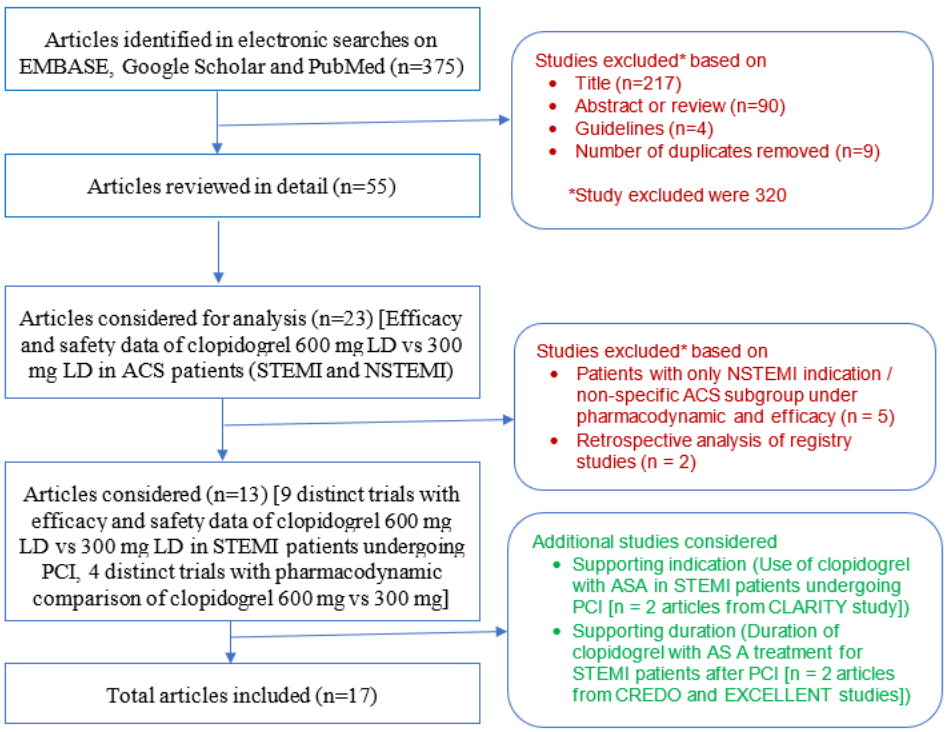
Source of data:

The literature for this submission consists of articles under 3 categories:

- Supporting indication (clopidogrel with ASA in STEMI patients undergoing PCI);
- Supporting LD of clopidogrel (600 mg in STEMI patients undergoing PCI);
- Supporting duration (clopidogrel with ASA in STEMI patients after PCI for 12 months).

LITERATURE SEARCH METHODOLOGY

Literature search flowchart



The literature review flowchart provided in Figure above details the 17 articles that were identified from the literature search databases and included in the analysis. The literature comprised articles under 3 categories:

- Supporting indication (use of clopidogrel with ASA in ST-elevation myocardial infarction [STEMI] patients undergoing percutaneous coronary intervention [PCI]
- Supporting loading dose of clopidogrel (use of 600 mg loading dose [LD] in STEMI patients undergoing PCI)
- Supporting duration (duration of use of clopidogrel with ASA in STEMI patients after PCI).

Epidemiology

ST elevation acute myocardial infarction is defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic ST elevation and subsequent release of biomarkers of myocardial necrosis. ST elevation acute myocardial infarction comprises approximately 25% to 40% of MI presentations.

Management

In STEMI patients, clinical guidelines recommend a primary PCI strategy over fibrinolysis within indicated timeframes. Treatment guidelines also recommend adjunctive antithrombotic therapy with ASA and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) to support reperfusion with primary PCI and maintained over 12 months.

The currently approved posology of Clopidogrel (Plavix/Iscover) in patients suffering from ACS is the following:

- Non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction):

- clopidogrel treatment should be initiated with a single 300 mg or 600 mg loading dose (LD). A 600 mg LD may be considered in patients <75 years of age when PCI is intended. Clopidogrel treatment should be continued at 75 mg once a day (with ASA 75 mg to 325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.

• ST segment elevation acute myocardial infarction:

- clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg LD in combination with ASA and with or without thrombolytics. For medically treated patients over 75 years of age clopidogrel should be initiated without a LD. Combined therapy should be started as early as possible after symptoms start and continued for at least 4 weeks. The benefit of the combination of clopidogrel with ASA beyond 4 weeks has not been studied in this setting.

The currently approved posology of fixed-dose combination of clopidogrel and ASA (Duoplavin®) in patients suffering from ACS is the following:

• In patients with non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction):

- 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.

• In patients with STEMI: Therapy should be started as early as possible after symptoms start and continued for at least 4 weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting.

2.1.2. About the product

Clopidogrel (Plavix/Iscover) is currently approved in following conditions:

<u>Secondary prevention of atherothrombotic events</u>

• Adult patients suffering from myocardial infarction (MI) (from a few days until less than 35 days), ischemic stroke (IS) (from 7 days until less than 6 months) or established peripheral arterial disease.

• Adult patients suffering from acute coronary syndrome (ACS):

- Non-ST segment elevation ACS (unstable angina or non-Q-wave MI), including patients undergoing a stent placement following percutaneous coronary intervention (PCI), in combination with acetylsalicylic acid (ASA).

- ST segment elevation acute myocardial infarction (STEMI), in combination with ASA in medically treated patients eligible for thrombolytic therapy.

In patients with moderate to high-risk Transient Ischemic Attack or minor Ischemic Stroke Clopidogrel in combination with ASA is indicated in:

• Adult patients with moderate to high-risk Transient Ischemic Attack (TIA) (Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnosis [ABCD2] score ≥4) or minor IS (National Institute of Health Stroke Scale [NIHSS] ≤3) within 24 hours of either the TIA or IS 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 and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

Fixed-dose combination of clopidogrel and ASA (Duoplavin®) is currently approved in the following conditions (Duoplavin® SmPC):

• Secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and ASA.

• For continuation therapy in:

- Non-ST segment elevation ACS (unstable angina or non-Q-wave MI) including patients undergoing a stent placement following PCI.
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Table 1- Summary of main study results for Clopidogrel

Substance (INN/Invented Name): for Clopidogrel			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.76, 3.96 and 3.96 t pH, 5, 7 and 9 respectively	Potential PBT N < 4.5 the Phase I trigger value
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Persistence	DT50	28,8 d (12°C, whole system)	Not P (Clopidogrel) Potentially P (transformation products of Clopidogrel)

Bioaccumulation	BCF	296 L/kg (Whole fish Kinetic, 5% lipid)	Not B
Toxicity *Pimephales promelas* OECD310	NOEC	310 mg/L	Not T
PBT-statement:	**The compound is not considered as PBT nor as vPvB**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ default or refined (e.g. prevalence, literature)	0.382	μg/L	**> 0.01 μg/L**
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc=1698L/Kg Adsorption Log Koc= 3.23	Four soils and activated sludge The substance reversibly adsorbs primarily to organic matter. Koc≤4 threshold value Assessment of fate and effects in the terrestrial environment in Phase II tier B is not required
Ready Biodegradability Test	OECD 301B	Not readily biodegradable (-10,2% CO2, 28 d)	
Aerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 (Whole system): 7,5-13,5d significant shifting to sediment 3 transformation products >10% in water and sediment	. Transformation products were not identified
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	850	µg/L	*Pseudokirchneriella subcapitata*. EC50 72h (biomass) =4440mg/L NOEC was concluded to be 850 mg/L for both study endpoints
Daphnia sp. Reproduction Test	OECD 211	NOEC	710	µg/L	Treatment related reductions in growth at the 1400 mg/L test concentration and for survival, reproduction and growth at 2300 mg/L, over a 21day period.
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	310	µg/L	*Pimephales promelas* A statistically significant effects on total length, wet and dry weight and larvae survival exposed to the 840 mg/L treatment level.
Bioaccumulation	OECD 305	BCF	296 (Whole fish Kinetic, 5% lipid)	L/Kg	BCF values suggests a bioaccumulation in biota up to 296 L/kg (5% lipid, whole fish) BCFmax (kinetic, whole fish: 279 L/kg Lipid content: 4,72% (mean, whole fish at the time of steady state)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	582.6	mg/L	
Phase Iib Studies					
Sediment Dwelling Organism (*Chironomus riparius*)	OECD 218	NOEC	9	mg/Kg	It is not clear if the toxicity studies with sediment dwellers have been normalised to 10% o.c. for PNEC derivation (µg/Kgdw).

2.2.2. Discussion on non-clinical aspects

The ERA report for clopidogrel was updated in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 2006). The ERA was performed on the basis of available results from previously referenced study reports in previous approved products, and all relevant reports to the present ERA were provided. The additional data provide sound evidence that the ERA for clopidogrel is documented according to the ERA guidelines.

The ERA initially submitted by the MAH for Acetylsalicylic Acid was incomplete and the study results presented did not provide significant data to assess the effect of ASA in the environment. The MAH updated the report and provided significant data. It should be noted that although the value the PECsw value is higher than the action limit of 0.01 μg/L, it must be calculated according to guideline EMEA/CHMP/SWP/44609/2010, rev1, 2016.

Information have been given by the applicant as requested and is now considered sufficient to assess the environmental risk of clopidogrel. A conclusion on potential risk of DuoPlavin to the environment cannot be drawn as the applicant did not provide a complete ERA according to the requirements of the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2) for the active ingredient acetylsalicylic acid.

To complete the Phase II assessment in accordance with the ERA guideline EMEA/CHMP/SWP/4447/00 corr 2, 2006, and in the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP requests submission of the following study reports as soon as they are available and no later than January 2023:

Partition coefficient, OECD 107, study no. T101857-2, report no. R-9744

Fish FELS study, OECD 210, study no. T100876-2, report no. R-9273

Biodegradation study, OECD 301F, study no.T101073-2, report no. PH-37791

2.2.3. Conclusion on the non-clinical aspects

A final conclusion on potential risk of DuoPlavin to the environment is pending. The CHMP requests the MAH to provide a complete ERA according to the requirements of the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2) for the active ingredient acetylsalicylic acid no later than January 2023. The applicant committed to providing the Letter of Access and /or studies reports as soon as they are available, no later than January 2023.

2.3. Clinical aspects

GCP

2.3.1. Pharmacokinetics

The proposed changes apply to the three medicinal products (Plavix, Iscover and DuoPlavin) containing clopidogrel. The same supportive documentation is provided for the three products which belong to the same MAH, and similar labelling changes will apply to the three medicinal products (SmPC and Package leaflet).

No new pharmacokinetic studies were conducted by the MAH, and the proposed changes are supported by an overall level of clinical evidence (efficacy and safety data) from different sources.

2.3.2. Pharmacodynamics

The applicant proposes to add "patients undergoing percutaneous coronary intervention (PCI)" to the population already included in the therapeutic indication of clopidogrel in combination with acetylsalicylic acid (ASA): patients suffering from acute coronary syndrome with ST segment elevation acute myocardial infarction (STEMI).

No dedicated pharmacodynamics (PD) study is provided. The rational to include "patients with ST segment elevation acute myocardial infarction, undergoing percutaneous coronary intervention" (STEMI patients undergoing PCI) is based on clinical evidence from bibliographic review of 3 randomized trials and one observational trial (2005-2008) that provide PD data on the proposed new patient population, treated with clopidogrel in combination with ASA:

- **Gurbel et al., 2005** RCT, prospective, patients undergoing elective coronary stenting (n=190), Clopi 600 mg + Aspi 325 mg (n=52) or Clopi 300 mg + Aspi 325 mg (n=138) to determine the effect of clopidogrel LD on the incidence of nonresponsiveness (NR) and high post-treatment platelet aggregation (post-PA); Results: A lower rate of NR (<10% absolute change in platelet aggregation) with 600-versus 300 mg dose (8% versus 28% and 8% versus 32% with 5 and 20-µM ADP, respectively; p<0.001). Among the patients with high post-PA (>75th percentile aggregation after clopidogrel intake), after 300 mg clopidogrel, 62%-65% had NR, whereas after the 600 mg dose, all of the patients with high post-PA had NR.

Figure 1: Relation of post-treatment platelet aggregation (Post-PA) to nonresponsiveness in 300- and 600-mg groups as measured by 5 microM adenosinediphosphate- induced aggregation (Gurbel et al. 2005)

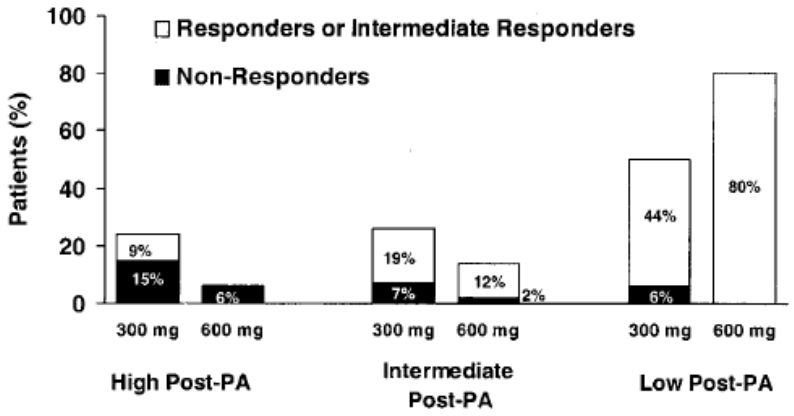


Figure 2: Distribution of the absolute change in adenosinediphosphate (ADP)-induced aggregation (Gurbel et al. 2005)

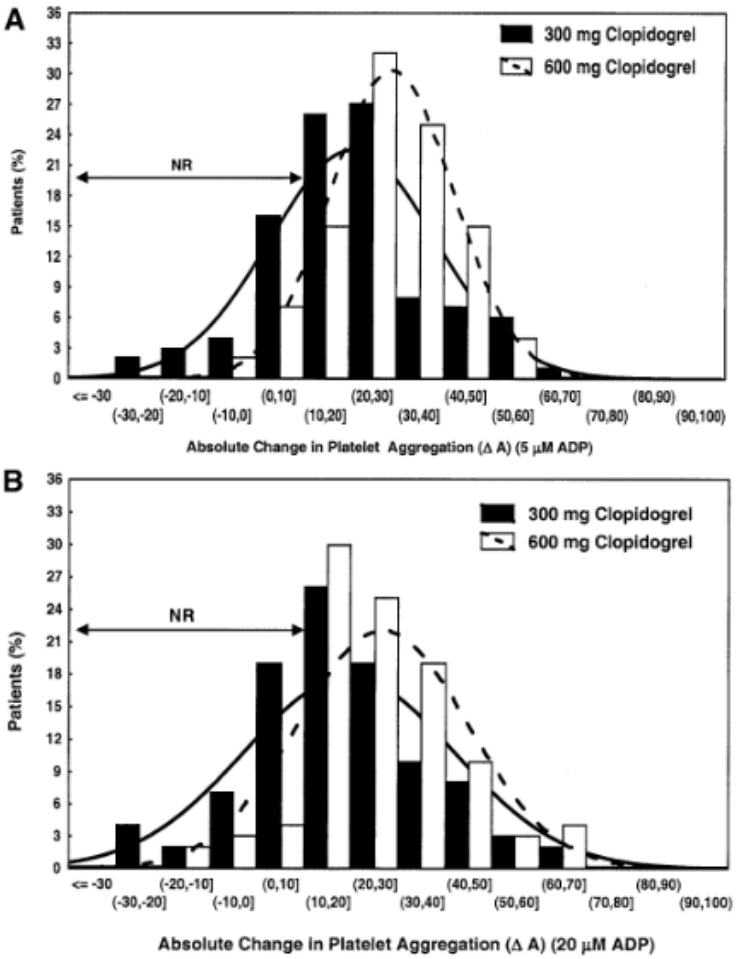


Figure 2. **(A)** Distribution of the absolute change in 5 μM adenosine diphosphate (ADP)-induced aggregation (ΔA). All of the patients under the **double-headed arrow** meet the definition for nonresponsiveness (NR). The distribution is shifted rightward in the 600-mg group, indicating greater inhibition (responsiveness to clopidogrel). **(B)** Distribution of the absolute change in 20 μM ADP-induced aggregation (ΔA). All of the patients under the **double-headed arrow** meet the definition for NR. The distribution is shifted rightward in the 600-mg group, indicating greater inhibition (responsiveness to clopidogrel).

- **Von Beckerath et al., 2005 (ISAR-CHOICE trial)** RCT, Patients with suspected/documented acute coronary disease admitted for coronary angiography (n=60), Clopi 600 mg + Aspi 100 mg (n=20) or Clopi 900 mg + Aspi 100 mg (n=20) or Clopi 300 mg + Aspi 100 mg (n=20) to compare the antiplatelet effects exerted by the higher LD (900 mg) versus the 300 mg and 600 mg LDs. Results: Higher plasma concentrations of the active metabolite, clopidogrel, and the carboxyl metabolite with 600 mg versus 300 mg ($p \leq 0.03$) and lower values for ADP - induced platelet aggregation 4 h after administration ($p=0.01$ and 0.004 for 5 and 20 µmol/L, respectively). No additional effect of 900 mg compared with 600 mg, as regards an increase in plasma concentrations of active metabolite and clopidogrel ($p \geq 0.38$); suppression of ADP-induced platelet aggregation 4 h after drug administration ($p=0.59$ and 0.39 for 5 and 20 µmol/L, respectively)
-

Figure 3: Maximal adenosine diphosphate (ADP)-induced platelet aggregation 4 hours after administration of a 300-, 600-, and 900- mg loading dose (Von Beckerath, 2005)

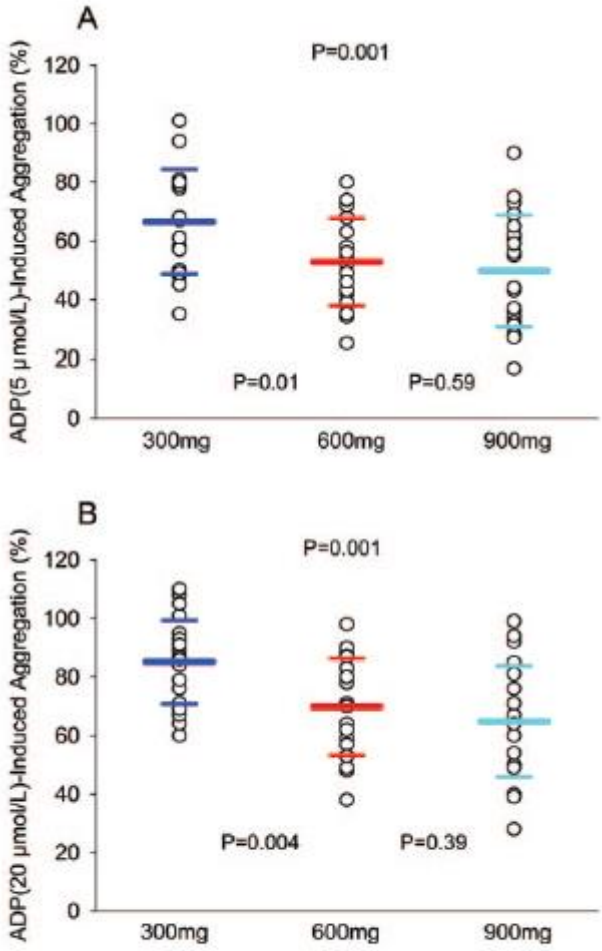


Figure 2. Maximal adenosine diphosphate (ADP)-induced platelet aggregation 4 hours after administration of a 300-, 600-, and 900- mg loading dose. Platelets were stimulated with a final concentration of 5 µmol/L (A) and 20 µmol/L (B) ADP. Circles represent single measurements; bars denote mean±SD.

- **Abuzahra et al. 2008** prospective RCT, Patients undergoing PCI with drug-eluting stents (n=119)**;** Clopi 600 mg + Aspi 325 mg immediately before PCI, followed by Clopi 75 mg two times/day + Aspi 81 mg/day for 1 month (high-dose group, n = 77) or Clopi 300 mg immediately before PCI + Aspi 325 mg, followed by Clopi 75 mg/day + Aspi 81 mg/day for 1 month (low-dose group, n = 42) to evaluate the effect of the higher clopidogrel dosing (600 mg) on platelet aggregation, cardiac, and bleeding events at 30 days in patients undergoing PCI. Results: Percent inhibition of platelet activity was 41% and 27% in the high-dose group versus 18% and 10% in the low-dose group at 4 h and 30 days (p=0.046 and 0.047, respectively). The incidence rate of the primary composite endpoint (cardiovascular death, MI, and target vessel revascularization [TVR] events) was significantly lower in the high-dose group compared with the low-dose group (10.3% versus 23.8%; p=0.04). Major and minor bleedings were similar in the 2 groups.

- **Gurbel et al., 2007** Comparative observational study of patients undergoing nonemergent coronary stenting (n=120); Clopi 300 mg + Aspi 325 mg after stent, followed by Clopi 75 mg/day (n= 73) or

Clopi 600 mg + Aspi 325 mg after stent, followed by Clopi 75 mg/day (n= 47); to analyze the relation between clopidogrel LD and the rate of thrombin-induced platelet-fibrin clot formation. Results: Significantly lower 5-µM ADP-induced platelet aggregation with 600 versus 300 mg (36.1 ±2.1 versus 41.7 ±1.9, p=0.03); Significantly lower 20-µM ADP-induced platelet aggregation with 600 versus 300 mg (53.4 ±2.3 versus 60.2 ±1.7, p=0.009); Significantly longer time to platelet-fibrin clot formation with 600 versus 300 mg (5.9 ±0.26 versus 5.0 ±0.2, p=0.004)

Figure 4: Effect of clopidogrel on absolute change in ADP-induced platelet aggregation and the time to platelet fibrin clot formation (Gurbel et al. 2007)

	Total group (n=120)	300 mg clopidogrel (n=73)	600 mg clopidogrel (n=47)	p-value (300 mg vs. 600 mg)
Absolute change in platelet aggregation (5 µM ADP)	21.0 ± 1.6	16.4 ± 1.8	26.2 ± 1.6	0.002
Absolute change in platelet aggregation (20 µM ADP)	17.8 ± 1.7	13.6 ± 1.5	22.7 ± 1.8	0.003
Absolute change in time to platelet–fibrin clot formation (min)	0.91 ± 0.17	0.73 ± 0.15	1.42 ± 0.14	0.01

2.3.3. Discussion on clinical pharmacology

No dedicated pharmacodynamics (PD) study is provided. The rationale to include the proposed new population of STEMI patients undergoing PCI is based on bibliographic data relevant for PD assessment of 3 randomised trials and one observational trial that compares the PD aspects of 600 mg LD of clopidogrel *versus* the standard dose (300 mg) in patients with acute coronary disease undergoing elective coronary stenting.

The presented studies support the strategy based on the 600 mg LD (as compared with the standard 300 mg LD) that shortens time to maximal platelet inhibition compared with 300 mg and results in superior antiplatelet effect that is maintained up to 24 hours without increasing bleeding risk, providing sufficient protection in patients undergoing PCI.

According to the results from these studies, although with some limitations related to small sample size, the dose-related effect of clopidogrel may contribute to the overall antithrombotic properties of the drug in patients undergoing stenting, with the effect being more prominent in patients receiving 600 mg, making the higher dose more effective than the standard 300-mg dose.

The pharmacodynamic data presented supports a superior efficacy and greater inhibition of platelet function with 600 mg LD compared with 300 mg LD of clopidogrel in patients suffering from ACS undergoing PCI. The SmPC amendments proposed by the applicant to update the posology information for STEMI patients undergoing PCI, are in line with these results and can be therefore acceptable.

2.3.4. Conclusion on clinical pharmacology

No new pharmacokinetic studies were conducted by the MAH, and the proposed changes are supported by an overall level of clinical evidence (efficacy and safety data) from different sources.

The pharmacodynamic data presented supports the strategy based on the 600 mg LD (as compared with the standard 300 mg LD) that shortens time to maximal platelet inhibition compared with 300 mg and results in superior antiplatelet effect that is maintained up to 24 hours without increasing bleeding risk, providing sufficient protection in patients undergoing PCI. From a clinical pharmacodynamic point of view,

the loading dose of 600 mg clopidogrel has shown to have greater inhibition of platelet function in patients suffering from ACS undergoing PCI and this variation is approvable.

2.4. Clinical efficacy

ACCF/AHA guidelines for the management of ST-elevation myocardial infarction (2013)

Antiplatelet Therapy to Support Primary PCI

The guidelines recommends that a loading dose of a P2Y12 receptor inhibitor should be given as early as possible or at the time of primary PCI to patients with STEMI. One of the options recommended is a loading dose of 600 mg of aspirin along with a loading dose of aspirin 162-325 mg (Class of recommendation I, Level of evidence B). Further, the guidelines recommend that P2Y12 inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (bare metal stent or drug-eluting stent) during primary PCI, with one of the recommended options being a MD of clopidogrel 75 mg daily along with daily MD of aspirin 81 to 325 mg (Class of recommendation I, Level of evidence B and Class of recommendation IIb, Level of evidence C respectively).

The guidelines also state that a loading dose of 600 mg of clopidogrel is preferred to a 300 mg loading dose, given the more extensive and rapid platelet inhibition achieved with the higher dose, as well as the beneficial effects reported in a clopidogrel and aspirin optimal dose usage to reduce recurrent events.

Antiplatelet Therapy to Support Reperfusion with Fibrinolytic Therapy

In patients with STEMI who receive fibrinolytic therapy, the guidelines recommend the use of aspirin (162 mg to 325 mg LD) and clopidogrel for patients ≤75 years of age (300 mg LD), >75 years of age (75 mg dose) (Class of recommendation I, Level of evidence A). The guidelines further specify that aspirin should be continued indefinitely (81 mg to 325 mg MD) and clopidogrel (75 mg daily MD) should be continued for at least 14 days and up to 1 year in patients with STEMI who receive fibrinolytic therapy

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy

With regards to antiplatelet therapy to support PCI after fibrinolytic therapy, the guideline recommends that aspirin should be continued indefinitely after PCI. In addition, clopidogrel should be provided as follows:
A) A 300 mg LD should be given before or at the time of PCI to patients who did not receive a previous LD and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy (Class of recommendation I, Level of evidence C).
B) A 600 mg LD should be given before or at the time of PCI to patients who did not receive a previous LD and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy (Class of recommendation I, Level of evidence C).
C) A dose of 75 mg daily should be given after PCI as a MD along with aspirin 81 to 325 mg. (Class of recommendation I, Level of evidence C).

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (2017)

Antiplatelet Therapy to Support Primary PCI

The ESC guidelines recommend that as periprocedural pharmacotherapy, patients undergoing primary PCI should receive DAPT, a combination of aspirin and a P2Y12 inhibitor, and a parenteral Anticoagulant. It is stated in the guidelines that "A potent P2Y12 inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding " (Class I, level A).

A table published in the ESC guidelines indicates the use of clopidogrel at a LD of 600 mg followed by a MD of 75 mg in patients undergoing primary PCI. Maintenance dose of aspirin recommended is 75 to 100 mg/day. There is no class or level of recommendation attached to these dosages in the ESC guidelines.

ESC / EACTS Guidelines on myocardial revascularization (2018)

These guidelines recommend that Dual antiplatelet therapy with ASA and clopidogrel is recommended for patients undergoing CAS for a duration of at least 1 month (Class of recommendation I, Level of evidence B). In patients undergoing percutaneous coronary intervention with stable coronary artery disease, the guidelines suggest dual antiplatelet therapy including a 150–300 mg oral loading dose of acetylsalicylic acid (or 80–150 mg i.v.) followed by 75–100mg per os (p.o.) daily plus a clopidogrel 300–600 mg loading dose followed by 75 mg daily

In STEMI patients undergoing PCI, the guidelines recommend a potent P2Y12 inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at the time of PCI at the latest) PCI and should be maintained over 12 months along with aspirin, unless there are contraindications such as an excessive risk of bleeding

1.1.1. Main studies

Clinical efficacy of clopidogrel in combination with ASA in STEMI patients undergoing PCI was demonstrated in a randomized clinical trial (CLARITY, Sabatine et al. 2005) and in a prespecified subgroup analysis of the same trial (CLARITY PCI, Sabatine et al. 2005).

An overview of this studies is shown in Table 2.

Table 2 – Overview of the CLARITY and CLARITY-PCI studies

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures
Sabatine, 2005 (CLARITY STUDY)	Multiple countries (23)	Double-blind RCT	Patient with recent STEMI	Clopi group: Mean age: 57.7 y; Clopi 300 mg LD then 75 mg MD once daily, 150-325 mg aspirin (fibrinolytic) on first day and then 75-162 mg daily (n=1752). Placebo group: Mean age: 57.2 y; Placebo LD then daily placebo MD, 150-325 mg aspirin (fibrinolytic) on first day and then 75-162 mg daily (n=1739)	Significant reduction in the incidence of primary end points (TIMI flow grade 0 or 1, death and recurrent MI) (15.0% with Clopi pre-treatment versus 21.7% with placebo, OR: 0.64; 95% CI: 0.53-0.76; p<0.001)
Sabatine, 2005 (CLARITY PCI STUDY) - Prespecified subgroup analysis of CLARITY study	Multiple countries (23)	Double-blind RCT	Patient with recent STEMI undergoing PCI	Clopi group: Mean age: 57.7 y; Clopi 300 mg LD then 75 mg MD, 150-325 mg aspirin (fibrinolytic) on first day and then 75-162 mg daily (n=933). Placebo group: Mean age: 56.9 y; Placebo LD then daily placebo MD, 150-325 mg aspirin (fibrinolytic) on first day and then 75-162 mg daily (n=930)	Significant reduction in the incidence of cardiovascular death, recurrent MI or stroke following PCI (3.6% with Clopi pre-treatment versus 6.2% with placebo, OR: 0.54; 95% CI: 0.35-0.85; p=0.008) Highly significant reduction in the incidence of cardiovascular death, MI or stroke through 30 days after PCI (7.5% with Clopi pre-treatment versus 12.0% with placebo, OR: 0.59; 95% CI: 0.43-0.81; p=0.001)

The CLARITY-Thrombolysis in Myocardial Infarction (TIMI) 28 was a randomized, double blind, placebo-controlled trial of clopidogrel in patients receiving fibrinolytics for STEMI. The purpose of the study was to determine if the addition of clopidogrel was beneficial in patients who have STEMI and who are receiving a standard fibrinolytic regimen, including aspirin. The study involved 3491 patients with STEMI randomized to either clopidogrel 300 mg LD (n=1752) or placebo (n = 1739). All patients received aspirin (150 to 325 mg) on first day and then 75 to 162 mg daily.

The PCI-CLARITY was a prospectively planned analysis of CLARITY TIMI 28. This analysis was conducted to determine if clopidogrel pre-treatment before PCI in patients with recent STEMI was superior to clopidogrel treatment initiated at the time of PCI in preventing MACE. The analysis involved 1863 patients undergoing PCI, randomized to either clopidogrel 300 mg LD (n=933) or placebo (n = 930). All patients received aspirin (150 to 325 mg) on first day and then 75 to 162 mg daily. Patients receiving 300 mg LD of clopidogrel had

a significant reduction in incidence of cardiovascular death, MI or stroke following PCI compared to those receiving placebo (3.6% with clopidogrel pre-treatment versus 6.2% with placebo, p=0.008). Also, the patients receiving 300 mg LD of clopidogrel had a significant reduction in incidence of cardiovascular death, MI or stroke through 30 days following PCI compared to those receiving placebo (7.5% with clopidogrel pre-treatment versus 12.0% with placebo, p=0.001). 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). The findings of this analysis support the early use of clopidogrel in STEMI and the strategy of routine clopidogrel pre-treatment in patients undergoing PCI.

Studies showing the efficacy of a loading dose of 600 mg of clopidogrel are shown in Table 3.

Table 3 – Overview of studies analysing a loading dose of 600 mg of clopidogrel

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Studies with significant efficacy of clopidogrel 600 mg (N = 5 distinct studies, but 6 publications)						
Mehta, 2010 (CURRENT OASIS-7 main trial)*	Multiple countries (39)	Double-blind RCT	Patient with acute coronary syndrome undergoing PCI (NSTEMI / STEMI)	Mean age: 61 y; N=25,086 Double dose Clopi group: Clopi 600 mg LD on D1, 150 mg on D2 to D7, and 75 mg on D8 to D30 + ASA ≥300 mg LD on D1, followed by 75-100 mg or 300-325 mg/day on D2 to D30 (n=12,520) Standard dose Clopi group: Clopi 300 mg LD on D1, 75 mg on D2 to D7, and 75 mg on D8 to D30 + ASA ≥300 mg LD on D1, followed by 75-100 mg or 300-325 mg/ day on D2 to D30 (n=12,566)	Similar occurrence of cardiovascular death, myocardial infarction, or stroke (4.2% with Clopi 600/150/75 mg versus 4.4% with Clopi 300/75/75 mg, HR: 0.94; 95% CI: 0.83-1.06; p=0.30) Significant reduction of stent thrombosis among 17,263 patients undergoing PCI (1.6% with 600 mg versus 2.3% with 300 mg; HR: 0.68; 95% CI: 0.55-0.85; p=0.001)	Significantly more major bleeding with Clopi 600/150/75 mg (2.5%) versus Clopi 300/75/75 mg (2.0%), HR: 1.24; 95% CI: 1.05-1.46; p=0.01.

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Patti, 2011 (ARMYDA-6 MI trial)	Europe	Blinded RCT	STEMI patients receiving PCI	Mean: 62-65 y according to the group (N=201) Clopi 600 mg LD and 75 mg/day during 1 year (n=103) Clopi 300 mg LD and 75 mg/day during 1 year (n=98)	Significantly less infarct size with 600 mg (CK-MB myocardial band 2070 ng/mL (IQR: 815-2847 ng/mL) versus 3049 ng/mL [IQR: 1050-7031 ng/mL]) than the 300 mg group, p=0.0001; troponin-I 255 ng/mL (IQR: 130-461 ng/mL) versus 380 ng/mL (IQR: 134-1406 ng/mL), p<0.0001. Less frequent thrombolysis in MI flow Grade<3 after PCI in 600 mg LD (5.8% versus 16.3%, p=0.031). Improved LVEF at discharge (52.1 ±9.5% versus 48.8 ±11.3%, p=0.026) and 30-day major adverse cardiovascular events were fewer (5.8% versus 15%, p=0.049)	No increase in bleeding or entry-site complications (secondary endpoints at Day 30): Two cases of major bleeding in each group Eight and six cases of minor bleed in 600 mg LD and 300 mg LD groups, respectively. No increase in entry-site complications (hematoma >10 cm, pseudo-aneurysm, or arteriovenous fistula); 3 cases in each group

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Dangas, 2009 (HORIZONs-AMI study)	Europe/ USA	Post-hoc analysis of RCT (randomized, prospective, open-label, 2x2 factorial design multicenter study)	STEMI undergoing primary PCI	Mean age 60 y (patients randomized into bivalirudin or unfractionated heparin and glycoprotein IIb/IIIa inhibitor, but stratified according to Clopi LD) Clopi 600 mg, then 75 mg for at least 6 months (n=2158) Clopi 300 mg, then 75 mg for at least 6 months (n=1153)	Significantly lower 30-day unadjusted rates of mortality with 600 mg compared with 300 mg (1.9% versus 3.1%, p=0.03); reinfarction (1.3% versus 2.3%, p=0.02); and definite or probable stent thrombosis (1.7% versus 2.8%, p=0.04) 600 mg LD was an independent predictor of lower rates of 30-day major adverse cardiac events (HR: 0.72 [95% CI: 0.53-0.98], p=0.04)	No increase in bleeding rates. Major bleed (non-CABG related): 6.1% in the 600 mg group and 9.4% in the 300 mg group. Incidence of acquired thrombo-cytopenia was similar in both the groups.
Mangiacapra, 2010	Belgium	Registry study (no randomi-zation)	STEMI with occluded artery undergoing PCI <12 h after symptom onsets	Mean: 64-65 years according to the group (N=255) Clopi 600 mg (n=157) Clopi 300 mg (n=98)	Clopi 600 mg dose showed a significantly lower incidence of post-PCI myocardial blush Grade 0 or 1 (OR: 0.64, 95% CI: 0.43-0.96, p=0.03) and significantly less common no-reflow phenomenon (OR: 0.38, 95% CI: 0.15-0.98, p=0.04) Significantly higher survival, free of MACE in the 600 mg group compared with the 300 mg group (HR: 0.57, 95% CI: 0.33-0.98, p=0.04)	Not reported

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Jung, 2009	Korea	Retrospective cohort study	Patients with acute STEMI who underwent PCI	Mean: 59-60 years according to the group (N=171) Clopi 600 mg (n=73) Clopi 300 mg (n=98)	Primary composite endpoint in hospital and during 30 days' follow-up occurred in 1.4% (1 of 73) of patients in the Clopi 600 mg group versus 11.2% (11 of 98) in the Clopi 300 mg group (p=0.013) Death, recurrent MI, urgent revascularization, and stroke were lower in the Clopi 600 mg versus the Clopi 300 mg group	Similar major bleedings in the two groups: Two patients (2.7%) versus one patient (1%) in the 600 mg LD and the 300 mg LD groups respectively, all during the GPIIb/IIIa receptor-inhibitor infusion (p=0.671)

* Study conducted by Sanofi.

Abbreviations: ASA: Acetylsalicylic acid; CABG: Coronary artery bypass grafting; CI: Confidence interval; CK-MB: Creatinine-kinase MB; Clopi: Clopidogrel; D: Day; GP: Glycoprotein; h: Hours; HR: Hazard ratio; IQR: Interquartile range; LD: Loading dose; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; NSTEMI: Non-ST Elevation Myocardial Infarction; OR: Odds ratio; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; STEMI: ST Elevation Myocardial Infarction; y: Years.

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Mehta, 2010 (CURRENT-OASIS -7 prespecified sub-analysis)*	Multiple countries (39)	Analysis in a sub-population of patients	Patient with acute coronary syndrome undergoing PCI (NSTEMI / STEMI)	Mean age: 61 y; sub population of patients who had undergone PCI Double dose Clopi group: Clopi 600 mg LD on D1, 150 mg on D2 to D7, and 75 mg on D8 to D30 + ASA ≥300 mg LD on D1, then 75-100 mg or 300-325 mg/day on D2 to D30 (n=8560) Standard dose Clopi group: Clopi 300 mg LD on D1, 75 mg on D2 to D7, and 75 mg on D8 to D30 + ASA ≥300 mg LD on D1, then 75-100 mg or 300-325 mg/ day on D2 to D30 (n=8703)	Compared with Clopi 300/75/75 mg, Clopi 600/150/75 mg significantly reduced the rate of primary outcome (cardiovascular death, myocardial infarction, or stroke from randomization to D30; 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). High-dose and low-dose aspirin did not differ for the primary outcome (356 [4.1%] versus 366 [4.2%]; 0.98, 0.84-1.13, p=0.76).	Major bleeding was more common with Clopi 600/75/75 mg than with Clopi 300/150/75 mg (139 [1.6%] versus 99 [1.1%]; 1.41, 1.09-1.83, p=0.009) and did not differ between high-dose and low-dose aspirin (128 [1.5%] versus 110 [1.3%]; 1.18, 0.92-1.53, p=0.20).

The CURRENT-OASIS-7 trial was undertaken to assess whether doubling of the loading and maintenance doses of clopidogrel was superior to the standard dose regimen and whether higher dose aspirin (300 to 325 mg/day) was superior to lower-dose aspirin (75 to 100 mg/day) in patients with ACS (NSTEMI or STEMI) referred for an early invasive strategy. A total of 25,086 patients were enrolled in the trial, of whom 24,835 underwent coronary angiography and 17,263 underwent PCI. The trial had a 2x2 factorial design, and the enrolled patients were randomized in a double-blinded fashion to a double-dose clopidogrel regimen or to the standard-dose regimen. In the second component of the factorial design, patients were randomized in an open-label fashion to either a high- or low-dose aspirin. Post-randomization and before coronary angiography, patients assigned to double-dose clopidogrel received a LD of 600 mg on Day 1, followed by 150 mg once daily from Day 2 through Day 7. Patients assigned to the standard-dose clopidogrel received a LD of 300 mg on Day 1, followed by 75 mg once daily from Day 2 through Day 7. On Day 8 through Day 30, both the trial groups received 75 mg of clopidogrel once daily. From Day 2 through Day 30, patients randomly assigned to lower-dose aspirin received 75 to 100 mg/day, whereas patients assigned to higher-dose aspirin received 300 to 325 mg/day. The key inference drawn from the trial was that there was no significant difference

between a 7-day double-dose regimen of clopidogrel and standard-dose clopidogrel with respect to the primary outcomes of cardiovascular death, MI, stroke (4.2% versus 4.4%; hazard ratio [HR]: 0.94; 95% confidence interval [CI]: 0.83-1.06; p=0.30), or death (2.3% versus 2.4%; HR: 0.96; 95% CI: 0.82-1.13; p=0.61) at 30 days. The increased incidence of the major and severe bleeding was accounted for mainly by a higher rate of red blood cell transfusion among patients in the double-dose group, which may be attributed to a double MD of 150 mg. There was a significantly reduced incidence of the secondary endpoint of stent thrombosis, including angiographically confirmed definite stent thrombosis, in the subgroup of patients who underwent PCI with double-dose clopidogrel compared with the standard treatment (1.6% versus 2.3%; HR: 0.68; 95% CI: 0.55-0.85; p=0.001).

A pre-specified subgroup analysis assessed the effects of various clopidogrel and aspirin regimens in the prevention of major cardiovascular events and stent thrombosis in patients undergoing PCI (NSTEMI or STEMI). The composite primary outcome of cardiovascular death, MI, or stroke was significantly lower in the double-dose group when compared to the standard group (3.9% versus 4.5%; adjusted HR: 0.86; 95% CI: 0.74-0.99; p=0.039) at 30 days. The primary composite outcome, recurrent ischemia, individual components of the composite outcomes, and stent thrombosis was significantly lower in the double-dose than in the standard-dose clopidogrel group (4.2% versus 5.0%; adjusted HR: 0.85, 95% CI: 0.74-0.98; p=0.025). Furthermore, the rate of definite stent thrombosis was lower with double-dose compared to standard-dose clopidogrel on Day 2 (0.2% versus 0.4%; HR: 0.49, 95% CI: 0.27-0.89, p=0.018), and from Day 3 through Day 10 (0.4% versus 0.6%; 0.58, 0.37-0.90, p=0.016). CURRENT-defined major bleeding overall was more common with double-dose clopidogrel compared with the standard dose (1.6% versus 1.1%; adjusted HR: 1.41, 95% CI 1.09-1.83, p=0.009). Similarly, a statistically significant increase of major bleeding was reported in the clopidogrel 600 mg LD group (1.5% [130/8560 patients]) compared to the clopidogrel 300 mg LD group (1.1% [95/8703 patients]) inpatients after PCI (p=0.0141). The analysis concluded that a 7-day, 600 mg LD regimen of clopidogrel (600 mg LD followed by a MD [150 mg for 7 days]) is more effective than the standard-dose regimen in reducing ischemic events and stent thrombosis in patients undergoing PCI for ACS.

The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty - Myocardial Infarction (ARMYDA-6 MI) trial was conducted to evaluate the efficacy and safety of pre-treatment with a 600 mg versus 300 mg clopidogrel LD in the setting of urgent PCI for STEMI. This randomized, prospective, international, multicenter trial involved 201 patients with acute MI randomized to either a 600 mg (n=103) or 300 mg LD (n=98) of clopidogrel at the time of first medical contact at the trial center performing the primary angioplasty followed by intervention as per standard technique. Patients receiving a 600 mg LD of clopidogrel had a significantly reduced infarct size compared to those receiving a 300 mg LD (median CK-MB=2070 ng/mL [interquartile range {IQR}: 815 to 2847 ng/mL versus median CK-MB=3049 ng/mL {IQR: 1050 to 7031 ng/mL}] p=0.0001); (troponin-I, 255 ng/mL [IQR: 130 to 461 ng/mL] versus 380 ng/mL [IQR: 134 to 1406 ng/mL]; p<0.0001). The TIMI flow Grade <3 after the intervention was found to be significantly lower for the 600 mg LD group compared with the 300 mg LD group (5.8%, versus 16.3%; p=0.031). Left ventricular ejection fraction at discharge was found to be higher in the 600 mg LD group compared with 300 mg LD group (52.1 ±9.5% versus 48.8±11.3%; p=0.026). The 30-day MACE incidence was found to be reduced in the 600 mg LD group compared with the 300 mg group (5.8% versus 15.0%; p=0.049). There was no difference observed between the 2 groups

with respect to safety: major bleeding at 1 month occurred in 1.9% in the 600 mg LD group as against 2.0% in the 300 mg LD group (p=0.65). Non-entry–site minor bleeding was 7.8% and 6.1% for the 600 mg LD and 300 mg LD groups, respectively (p=0.86).
Entry-site complications were observed in 2.9% and 3.1% of patients in the 600 mg LD and 300 mg LD groups, respectively.

This post-hoc analysis of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial was conducted to evaluate whether a 600 mg LD provided faster and greater inhibition of platelet activation. The analysis examined the impact of a LD of 600 mg compared with 300 mg on 30-day clinical outcomes in 3311 patients from the main trial (n=1153; 300 mg LD group; n=2158; 600 mg LD group) before cardiac catheterization followed by 75 mg/day dose for ≥6 months post-discharge. The results showed significantly lower 30-day unadjusted rates of mortality (1.9% versus 3.1%, p=0.03), reinfarction (1.3% versus 2.3%, p=0.02), and definite or probable stent thrombosis (1.7% versus 2.8%, p=0.04) with the 600 mg LD. In addition, the 600 mg LD of clopidogrel was an independent predictor of 30-day MACE (HR: 0.72 [95% CI: 0.53-0.98]; p=0.04). Major bleeding rate (non-coronary artery bypass graft [CABG] related) was 6.1% in 600 mg LD group and 9.4% in 300 mg LD group (p=0.0005). Minor bleeding rate was 11.3% in 600 mg LD group and 13.8% in 300 mg LD group (p=0.03).
The authors identified that although the clopidogrel LD was stratified before randomization, the 300 mg versus 600 mg LD was not randomized, which resulted in an imbalance between several baseline, angiographic, and procedural characteristics.

In a registry study performed at a single center in Belgium, the authors analyzed whether a higher LD (600 mg) of clopidogrel was associated with better procedural and one-year clinical outcomes compared to a standard 300 mg LD. A total of 255 patients with STEMI who underwent primary PCI were included in the study and were divided into the 600 mg (n=157) and 300 mg (n=98) LD groups. Patients who received a 600 mg LD of clopidogrel showed a significantly lower incidence of post-PCI myocardial blush Grade 0 or 1 (OR: 0.64, 95% CI: 0.43-0.96, p=0.03) and less common no-reflow phenomenon (OR: 0.38, 95% CI: 0.15-0.98, p=0.04) when compared to patients who received a 300 mg LD of clopidogrel.
The higher-dose group also had a relatively lower occurrence rate of MACE when compared to the lower-dose group (17% versus 27%; HR: 0.62, 95% CI: 0.38-1.00, p=0.05) at 1 year.

A retrospective trial that was conducted to investigate whether 600 mg LD of clopidogrel, when compared to 300 mg dose, was more beneficial in inhibiting platelet aggregation more rapidly in acute STEMI patients. The study included 171 patients with STEMI who underwent primary PCI between January 2004 and December 2005. The patients were administered either 300 mg (n=98) or 600 mg (n=73) clopidogrel before PCI and aspirin (at least 100 mg/day) indefinitely with a maintenance clopidogrel dose of 75 mg/day for up to 9 months. The cumulative incidence of death, MI, stroke, and urgent revascularization due to myocardial ischemia within 30 days of PCI was significantly lower in the higher-dose group compared to the standard 300 mg group (1.4% versus 11.2%; p=0.013). A total of 5 urgent TVRs occurred in the 300 mg group, while none occurred in the higher-dose group. There were 2 incidences of major bleeding (2.7%) observed with 600 mg LD group and 1 incidence of major bleeding (1.0%) observed with 300 mg LD group (p=0.671).The limitations of the trial included its retrospective nature; small sample

size; and non-assessment of P-selectin, ADP-induced GP IIb/IIIa activation, inhibition of ADP-induced platelet aggregation, and clopidogrel responsiveness.

Meta-analyis that evaluated clopidogrel in STEMI patients undergoing PCI

Table 4 – Overview of meta-analysis that evaluated clopidogrel in STEMI patients undergoing PCI

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Navarese, 2011[b]	NA	Meta-analysis of RCTs	Acute coronary syndrome (NSTEMI / STEMI)	Age not reported in the meta-analysis 58,591 patients from seven RCT including 43,807 patients underwent PCI Clopidogrel 300 mg (n=29,284) New antiplatelet drugs (prasugrel or ticagrelor [n=16,475] and clopidogrel 600 mg [n=12832]).	When new ADP regimens combined (prasugrel, ticagrelor, clopi 600 mg), there was a significant reduction in mortality (2.9% versus 3.4%, OR: 0.87, 95% CI: 0.79-0.95, p=0.002), recurrent myocardial infarction (4.2% versus 5.2%, OR:0.80, 95% CI: 0.74-0.87, p<0.0001), definite in-stent thrombosis (0.9% versus 1.7%, OR: 0.52, 95% CI: 0.43-0.63, p<0.0001) compared with clopi 300 mg. No significant difference between clopi 600 mg versus clopi 300 mg regarding mortality (OR: 0.95, 95% CI: 0.81, 1.12, p=0.56), myocardial infarction (OR: 0.88, 95% CI: 0.74–1.04, p=0.14) The effects were mostly driven by prasugrel and ticagrelor.	No major bleeding complications between the combination of all new ADP-antagonist regimens as compared to clopi 300 mg (5% versus 4.7%, OR: 1.06, 95% CI: 0.96-1.17, p=0.25) Superior risk of major bleedings with clopi 600 mg compared with clopi 300 mg (OR: 1.25, 95% CI: 1.02, 1.53, p=0.03)

Long Term (12 Months) Treatment with Clopidogrel in combination with ASA in STEMI Patients after PCI

A summary of efficacy and safety of long term (12 months) treatment with clopidogrel with ASA after PCI is presented in Table 5.

Table 5 – Overview of studies analyzing long term use of clopidogrel and aspirin in STEMI patients

Publication	Country / region	Type of study	Indication	Age of patients and treatment groups	Efficacy measures	Safety measures
Steinhubl, 2002 (CREDO STUDY)	North America	Double-blind RCT	Patient undergoing elective PCI or were deemed at likelihood of undergoing PCI	Mean age: 61.5 y; Clopi 300 mg LD + aspi 325 mg (3 to 24 hours before PCI) then Clopi 75 mg/d + aspi 325 mg/d through Day 28 followed by Clopi 75 mg/d + aspi (81-325 mg/d) up to 12 months (n=1053). Mean age: 61.8 y; Placebo + aspi 325 mg (3 to 24 hours before PCI) then Clopi 75 mg/d + aspi 325 mg/d through Day 28 followed by placebo + aspi (81-325 mg/d) up to 12 months (n=1063)	Significant reduction in the combined risk of death, MI or stroke at 1 year with Clopi (26.9% relative reduction, 95% CI: 3.9%-44.4%; p=0.02; absolute reduction 3%)	No significant increase in the rate of major bleeding (8.8% with Clopi versus 6.7% with placebo, p=0.07) or minor bleeding (5.3% with Clopi versus 5.6% with placebo p=0.84 at 1 year.
Gwon, 2012 (EXCELLENT STUDY)	Korea	Open-label RCT	Patients undergoing implantation of drug-eluting stents	6-months DAPT (aspi 100-200 mg/d + clopi 75 mg/d for 6 months (thereafter aspi alone) (n=722), mean age: 63.0 y. 12-months DAPT (aspi 100-200 mg/d + clopi 75 mg/d for 12 months) (n=721); mean age: 62.4 y.	No significant difference in the incidence of target vessel failure (composite of cardiac death, MI or target vessel revasculari-zation) between 6-month and 12-month DAPT groups (HR: 1.14; 95% CI: 0.70-1.86; p=0.60)	No significant difference in the safety end point (composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between 6-month and 12-month DAPT groups (HR: 1.15; 95% CI: 0.64-2.06; p=0.64

Real world use of clopidogrel in ST-elevation myocardial infarction patients

Five studies reported on dosing of clopidogrel. Loading doses varied from 75 mg to 600 mg, while maintenance dosing was either 75 mg or 150 mg. The summary of these studies is represented in Table 6.

Author	Patients receiving Clopidogrel after	Timepoint	n	%	Loading/ Maintenance Dose	Dose in units
Bahall 2019	Thrombolysis	2011-2015	964	87.2	Loading dose	300 mg
					Maintenance dose	75 mg
Gandhi 2014	PCI/thrombolysis	2011-2013	79	10.8	Loading dose	75 mg
			319	43.6	Loading dose	300 mg
			27	44.7	Loading dose	>300 mg
Parikh 2019	PCI/thrombolysis	2016-2017	636	100.0	Loading dose	600 mg
					Maintenance dose	75 mg
Pavlides 2013	PCI	2008-2009	NR	30.0	Loading dose	600 mg
			NR	98.0	Maintenance dose	75 mg
			NR	2.0	Maintenance dose	150 mg
Zhang 2016	PCI/thrombolysis	2011-2012	494	37.7	Loading dose	300 mg
			39	3.0	Loading dose	600 mg

The real-world evidence indicates that the use of PCI has increased over time in STEMI patients. The use of thrombolytic therapy as well as fibrinolytic therapy showed decreasing trends over time. Use of clopidogrel following PCI, thrombolysis, or fibrinolysis varies, with a majority of the studies identified reporting a range between 40% to 100%. Five studies reported on dosing of clopidogrel following PCI or thrombolytic/fibrinolytic treatment. Findings from these were consistent, with 3 studies reporting a loading dose of 600 mg, one study reporting initial doses between 75 mg and>300mg, and the other study reporting a 300 mg loading dose.

2.4.1. Discussion on clinical efficacy

The literature supporting the use of clopidogrel with ASA in STEMI patients undergoing PCI includes a publication of one randomized trial (Clopidogrel as adjunctive reperfusion therapy [CLARITY]) involving 3491 patients with STEMI and the other publication containing a prespecified subgroup analysis in 1863 patients of CLARITY trial undergoing PCI (CLARITY PCI study). CLARITY PCI is the prospectively planned subgroup analysis of CLARITY trial evaluating the effect of clopidogrel LD before PCI in STEMI patients followed by MD of clopidogrel as well as ASA. CLARITY PCI showed significant reduction in efficacy outcomes (incidence of cardiovascular death, MI or stroke) at Day 30.

The methodology of literature search for use of clopidogrel 600 mg LD in STEMI patients undergoing PCI was similar to the one followed for previous variation dossier submitted on 27-Mar-2020 for clopidogrel 600 mg LD in ACS with exclusion of studies having patients with only NSTEMI indication or non-specific ACS subgroup. The included RCTs showed higher efficacy for the 600 mg LD with better or similar safety outcomes compared with the standard 300 mg LD. The efficacy profile was reflected through a significant decrease in composite as well as individual outcomes of cardiovascular death, MI, or stroke with clopidogrel after 12 months treatment. Cumulative evidence shows that the 600 mg LD is at least as effective as the 300 mg LD.

Three meta-analyses including studies published between the years 2009 and 2012 highlight the effectiveness of the higher (600 mg) clopidogrel dose compared with the standard 300 mg dose. The meta-analyses showed significant reduction in cardiovascular events and mortality in the absence of a significant effect on major bleeding episodes.

Literature supporting the effective duration of use of dual antiplatelet therapy (DAPT) of clopidogrel with ASA in STEMI patients after PCI includes two publications containing a large randomized clinical trial in each (Clopidogrel for the reduction of events during observation [CREDO] involving 2116 patients and The efficacy of Xience/Promus versus Cypher to reduce late loss after stenting [EXCELLENT] involving 1443 patients). Guidelines recommend adjunctive antithrombotic therapy with ASA and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) in primary PCI and maintained over 12 months in STEMI patients undergoing primary PCI.

2.4.2. Conclusions on the clinical efficacy

Taking into account the data shown by the MAH there is supportive evidence for inclusion, in the Product Information of new indication for clopidogrel and combination of clopidogrel with ASA (In STEMI undergoing PCI) and of posology and administration (Dosage in STEMI patients: 300 mg or 600 mg LD of clopidogrel when PCI is intended; Treatment duration: 12 months for MD).

2.5. Clinical safety

Introduction

Safety review was focused on the available literature. Among the articles identified for the use of clopidogrel in STEMI patients undergoing PCI indication, a total of 12 publications reported safety data. The main and

well-known risk of clopidogrel was bleeding (major and/or minor) and was reported either as part of safety data or as a part of study end points in all these 12 publications.
The adverse events in publications focused on bleeding and death.

Patient exposure

Not applicable

Adverse events

Safety of Clopidogrel in combination with ASA in STEMI Patients undergoing PCI

- Sabatine et al. 2005 study reported no significant difference in the rates of major or minor bleeding (3.4% with clopidogrel pre-treatment [300 mg LD] versus 2.7% with placebo, p=0.24) at Day 30.
- Sabatine et al. 2005 study reported no significant difference in the rates of major or minor bleeding between clopidogrel 300 mg LD and placebo (18 cases [2.0%] with clopidogrel pre-treatment versus 17 cases [1.9%] with placebo, p>0.99) at Day 30.

Safety of 600 mg Loading Dose of Clopidogrel in STEMI Patients Undergoing PCI

The safety of each individual study is described below:
• Abuzahra et al., 2008 study reported no significant difference between major or minor bleeding at day-30 for the 300 mg LD and 600 mg LD clopidogrel groups. For major bleeding, one case was reported in each group (1.6% with 600 mg, 2.7% with 300 mg, p=0.73). For the minor bleeding episodes, 2 and 3 cases were reported with the 600 mg (3.1%) and 300 mg (8.1%) (p=0.53) LD groups, respectively.
• Patti et al., 2011 study reported no significant increase in bleeding or entry-site complications at Day 30 of the study. A total of 2 major bleeding episodes each occurred in 300 mg LD and 600 mg LD clopidogrel groups, respectively. Furthermore, no increase in entry-site complications (hematoma >10 cm, pseudoaneurysm, or arteriovenous fistula) was observed in the 2 groups.
• Dangas et al., 2009 reported no significant increase in bleeding rates with a higher LD of clopidogrel. Major bleeding rate (non-CABG related) was 6.1% in the clopidogrel 600 mg LD group and 9.4% in the clopidogrel 300 mg LD group, respectively.

• In a retrospective study by Jung et al., 2009, bleeding data showed no significant increase in the frequency of major bleeding with 600 mg LD group as compared to 300 mg LD group. There were 2 incidences of major bleeding (2.7%) observed with 600 mg LD group and 1 incidence of major bleeding (1.0%) observed with 300 mg LD group (p=0.671). This study was considered less relevant because it was subject to multiple types of bias and particularly channeling biases.
• In a clinical trial (CURRENT-OASIS 7), the patients were not treated with the standard maintenance therapeutic dose, ie, the clopidogrel LD was followed by a high clopidogrel MD of 150 mg/day for one-week in the 600 mg LD group (n=2 publications for one study [Mehta 2010 et al.]). This study reported a statistically significant increase of major bleeding in the clopidogrel 600 mg LD group (1.5% [130/8560 patients]) compared to the clopidogrel 300 mg LD group (1.1% [95/8703 patients]) in patients after PCI (p=0.0141).

Safety of Long Term (12 Months) Treatment with Clopidogrel in combination with ASA in STEMI Patients after PCI

- Steinhubl et al., 2002 study reported no significant increase in the rate of major bleeding (8.8% with clopidogrel versus 6.7% with placebo, p=0.07) or minor bleeding (5.3% with clopidogrel versus 5.6% with placebo, p=0.84) at 1 year.
- Gwon et al., 2012 study reported no significant difference in the safety end point (composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between 6--month DAPT (receiving clopidogrel 75 mg/day for 6 months) and 12-month DAPT (receiving clopidogrel 75 mg/day for 12 months) groups (HR: 1.15; 95% CI: 0.64-2.06; p=0.64) at 1 year.

Serious adverse event/deaths/other significant events

Deaths, when reported in the publications, were part of the efficacy endpoints (either all deaths or cardiovascular deaths). For the death cases presented in the publications, there are no details on the nature of the event leading to death.
Among the studies entered in a meta-analysis, only 5 included an analysis regarding death; and the analysis concluded no significant differences in death between the 2 clopidogrel LD groups (OR: 0.82; 95% CI: 0.62-1.09; p=0.17).

Laboratory findings

Not applicable

Safety in special populations

Not reported

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable

Post marketing experience

Not applicable

2.5.1. Discussion on clinical safety

The analysis of the safety data for the use of clopidogrel in combination with ASA in STEMI patients undergoing PCI in CLARITY study and CLARITY PCI subgroup analysis showed overall no significant increase in bleeding with clopidogrel versus placebo.

The analysis of the safety data for the higher clopidogrel LD (600 mg) in comparison to the standard 300 mg LD, focused on the review of bleeding and death available in 8 publications. Among these, only 3 clinical trials were fully relevant for the safety analysis due to their study design (randomized and controlled) and also because they were conducted with the standard 75 mg/day MD after the LD. In these 3 studies, the clopidogrel 600 mg LD showed no evidence of an increase in bleeding. The result of the retrospective study showed the clopidogrel 600 mg LD to be as safe as the clopidogrel 300 mg LD while considering the bleeding. It was also identified that increasing the MD of clopidogrel (150 mg/day instead of 75 mg/day) after the clopidogrel 600 mg LD may increase the risk of major bleeding.

The analysis of the safety data for the long term (12 months) treatment with clopidogrel in combination with ASA in STEMI patients after PCI in CREDO study showed no significant increase in major or minor bleeding at 1 year whereas EXCELLENT study showed no difference in safety endpoint (composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between 6-month and 12-month DAPT.

Although deaths were analyzed as part of the efficacy endpoints of the studies, in an effort to review them, the meta-analysis by Vyas et al. 2014 was selected for its relevance and showed comparable rate of death between the 2 LD groups.

The MAH recognized that, overall, there was a lack of data regarding patients >75 years-old. The MAH presented data regarding the CURRENT OASIS 7 study that reported data in the subset of patients >75 years old. This study showed consistency in the treatment effect for each dose comparison in predefined subgroups. Consistent effects were recorded with the double-dose clopidogrel regimen in patients with STEMI and patients with non-ST-segment elevation acute coronary syndromes. There was no significant interaction for weight <60 kg or >60 kg, age below and over 75 years and previous stroke (p for interaction 0.614). In this trial, clopidogrel 600 mg loading dose has shown consistent efficacy in patients age ≥75 years of age and patients <75 years of age. Although the CURRENT OASIS 7 study has shown statistically significance in reducing cardiovascular death, MI, stroke and stent thrombosis, thus supporting the recommendation of 600 mg clopidogrel regimen for patients ≥ 75 years old, the MAH recommends that the loading dose of 600 mg clopidogrel in STEMI PCI patients may be considered based on an individual benefit/risk assessment performed by the prescribing physician (by assessing both the risk of bleeding and the risk of thrombotic event recurrence in each patient). This information was added to the labelling text in agreement with the SmPC guidance with dose recommendations in the elderly stated in separate paragraphs.

2.5.2. Conclusions on clinical safety

Overall the data presented by the MAH indicates no significant increased risk of bleeding with a loading dose of clopidogrel and a 12 months maintenance dose of 75 mg of clopidogrel.

Although the CURRENT OASIS 7 study showed statistically significance in reducing cardiovascular death,

MI, stroke and stent thrombosis, thus supporting the recommendation of 600 mg clopidogrel regimen for patients ≥ 75 years old, the loading dose of 600 mg clopidogrel in STEMI PCI patients may be considered based on an individual benefit/risk assessment performed by the prescribing physician.

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 2.6 with the following content:

Safety concerns

Summary of the safety concerns

Important identified risk	Major bleeding (including ICHa)
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.

Pharmacovigilance plan

No additional pharmacovigilance activities

Risk minimisation measures

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. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific targeted FU questionnaire form **Additional pharmacovigilance activities:** 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.

2.7. Conclusion

The CHMP considers that the risk management plan version 2.6 is acceptable.

2.8. Update of the Product information

It is now stated:

Section 4.1

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 or** medically treated patients eligible for thrombolytic**/fibrinolytic** therapy.

Section 4.2

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 (see section 5.1).
-
- **When percutaneous coronary intervention (PCI) is intended:**
  - **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 LD should be administered with caution (see section 4.4).**
  - **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 (see section 5.1).

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons:

The present application for an extension indication of clopidogrel and clopidogrel + acetylsalicylic acid in ST segment elevation acute myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI) does not bring any change to Patient Information Leaflet tested for Plavix® / Iscover film-coated tablets 75 mg and 300 mg and DuoPlavin film-coated tablet 75 mg/75 mg and 75 mg/ 100 mg.

Benefit-Risk Balance

The literature supporting the use of clopidogrel with ASA in STEMI patients undergoing PCI includes a publication of one randomized trial (Clopidogrel as adjunctive reperfusion therapy [CLARITY]) involving 3491 patients with STEMI and another publication containing a prespecified subgroup analysis in 1863 patients of the CLARITY trial undergoing PCI (CLARITY PCI study). CLARITY PCI is a prospectively planned subgroup analysis of the CLARITY trial evaluating the effect of clopidogrel LD before PCI in STEMI patients followed by MD of clopidogrel as well as ASA. CLARITY PCI showed significant reduction in efficacy outcomes (incidence of cardiovascular death, MI or stroke) at Day 30.

The methodology of literature search for use of clopidogrel 600 mg LD in STEMI patients undergoing PCI was similar to the one followed for previous variation dossier submitted on 27-Mar-2020 for clopidogrel 600 mg LD in ACS with exclusion of studies having patients with only NSTEMI or non-specific ACS. The included RCTs showed higher efficacy for the 600 mg LD with better or similar safety outcomes compared with the standard 300 mg LD. The efficacy profile was reflected through a significant decrease in composite as well as individual outcomes of cardiovascular death, MI, or stroke with clopidogrel after 12 months treatment. Cumulative evidence shows that the 600 mg LD is at least as effective as the 300 mg LD.
Three meta-analyses including studies published between the years 2009 and 2012 highlight the effectiveness of the higher (600 mg) clopidogrel dose compared with the standard 300 mg dose. The meta-analyses showed significant reduction in cardiovascular events and mortality in the absence of a significant effect on major bleeding episodes.
Literature supporting the effective duration of use of dual antiplatelet therapy (DAPT) of clopidogrel with ASA in STEMI patients after PCI includes two publications large randomized clinical trials (Clopidogrel for the reduction of events during observation [CREDO] involving 2116 patients and The efficacy of Xience/Promus versus Cypher to reduce late loss after stenting [EXCELLENT] involving 1443 patients). Guidelines recommend adjunctive antithrombotic therapy with ASA and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) in primary PCI and maintained over 12 months in STEMI patients undergoing primary PCI.

Overall the data presented by the MAH indicates no significant increased risk of bleeding with a loading dose of clopidogrel and a 12 months maintenance dose of 75 mg of clopidogrel.

Although the CURRENT OASIS 7 study showed statistically significance in reducing cardiovascular death, MI, stroke and stent thrombosis, thus supporting the recommendation of 600 mg clopidogrel regimen for patients ≥ 75 years old, the MAH recommends that the loading dose of 600 mg clopidogrel in STEMI PCI patients may be considered based on an individual benefit/risk assessment performed by the prescribing physician. This information was added to the labelling text in agreement with the SmPC guidance with dose recommendations in the elderly stated in separate paragraphs.

Taking into account the data shown by the MAH there is supportive evidence for inclusion in the Product Information of a new indication for clopidogrel and combination of clopidogrel with ASA (In STEMI undergoing PCI) and of posology and administration (Dosage in STEMI patients: 300 mg or 600 mg LD of clopidogrel when PCI is intended; Treatment duration: 12 months for MD).

2.9. Therapeutic Context

2.9.1. Disease or condition

ST elevation acute myocardial infarction is a clinical entity defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic ST elevation and subsequent release of biomarkers of myocardial necrosis. ST elevation acute myocardial infarction comprises approximately 25% to 40% of MI presentations. In STEMI patients, clinical guidelines recommend the primary PCI strategy over fibrinolysis within indicated timeframes.

This applications aims to evaluate the use of Clopidogrel for the following indication: ST segment elevation acute myocardial infarction (STEMI) in patients undergoing stent placement following a percutaneous coronary intervention (PCI). This application extends the current approved indications of Clopidogrel (Plavix®/Iscover®) in patients suffering from acute coronary syndrome. The aims of the therapy are to reduce cardiovascular death, myocardial infarction, stroke and stent thrombosis.

The benefit risk assessment will evaluate if the efficacy associated with the reduction of cardiovascular events and increased survival outweighs the risk of hemorrhage and namely of major hemorrhage,

2.9.2. Available therapies and unmet medical need

Patients of ACS (UA, STEMI or NSTEMI) following an event are either managed medically or in most instances undergo PCI with stenting. 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 the patients' baseline ischemic and bleeding risks. Ticagrelor and 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 RCTs.

The 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 a better safety profile in patients with multiple comorbidities and those who are more prone to bleeding. Also 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.

Ticagrelor 60 mg twice a day along with aspirin as a DAPT is approved for patients with CAD but no prior MI or stroke.

2.9.3. Main clinical studies

In the CLARITY-PCI sub-group analysis of the 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% vs 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% vs 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% vs 0,2% HR 0.46, 95% CI 0.18-1.22, p= 0.12) or intracranial (0.04% vs 0.05% HR 0.77, 95% CI 0.17-3.43, p=0.73), nor bleeding that was related to CABG surgery (0.1% vs 0.07% HR 1.70, 95% CI 0.62-4.69, p=0.30).

2.10. Favourable effects

The literature supporting the use of clopidogrel with ASA in STEMI patients undergoing PCI includes a publication of one randomized trial (Clopidogrel as adjunctive reperfusion therapy [CLARITY]) involving 3491 patients with STEMI and a publication containing a prespecified subgroup analysis in 1863 patients of the CLARITY trial undergoing PCI (CLARITY PCI study). CLARITY PCI is a prospectively planned subgroup analysis of the CLARITY trial evaluating the effect of clopidogrel LD before PCI in STEMI patients followed by MD of clopidogrel as well as ASA. CLARITY PCI showed significant reduction in the composite efficacy outcome (incidence of cardiovascular death, MI or stroke) at Day 30 (7.5% with clopidogrel pre-treatment versus 12% with placebo, OR 5.9; 95% CI 0.43-0.81 p=0.001).

Three meta-analyses including studies published between the years 2009 and 2012 highlight the effectiveness of the higher (600 mg) clopidogrel dose compared with the standard 300 mg dose. The meta-analyses showed significant reduction in cardiovascular events.

Literature supporting the effective duration of use of dual antiplatelet therapy (DAPT) of clopidogrel with ASA in STEMI patients after PCI includes two publications containing a large randomized clinical trial in each (Clopidogrel for the reduction of events during observation [CREDO] involving 2116 patients and The efficacy of Xience/Promus versus Cypher to reduce late loss after stenting [EXCELLENT] involving 1443 patients).

2.11. Uncertainties and limitations about favourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance.

2.12. Unfavourable effects

The analysis of the safety data for the use of clopidogrel in combination with ASA in STEMI patients undergoing PCI in the CLARITY study and the CLARITY PCI subgroup analysis showed overall no significant increase in bleeding with clopidogrel versus placebo.

The analysis of the safety data for the higher clopidogrel LD (600 mg) in comparison to the standard 300 mg LD, focused on the review of bleeding and death available in 8 publications. Among these, only 3 clinical trials were fully relevant for the safety analysis due to their study design (randomized and controlled) and also because they were conducted with the standard 75 mg/day MD after the LD. In these 3 studies, the clopidogrel 600 mg LD showed no evidence of an increase in bleeding. The result of the retrospective study showed the clopidogrel 600 mg LD to be as safe as the clopidogrel 300 mg LD while considering the bleeding. It was also identified that increasing the MD of clopidogrel (150 mg/day instead of 75 mg/day) after the clopidogrel 600 mg LD may increase the risk of major bleeding.

The analysis of the safety data for the long term (12 months) treatment with clopidogrel in combination with ASA in STEMI patients after PCI in CREDO study showed no significant increase in major or minor bleeding at 1 year whereas EXCELLENT study showed no difference in safety endpoint (composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between 6-month and 12-month DAPT.

Deaths were analyzed as part of the efficacy endpoints of the studies. In an effort to review them, the meta-analysis by Vyas et al. 2014 was selected for its relevance and showed comparable rate of death between the 2 LD groups.

There was a lack of data presented by the MAH regarding safety in individuals > 75 years-old. The MAH presented data regarding the CURRENT OASIS 7 study that reported data in the subset of patients >75 years-old. This study showed consistency in the treatment effect for each dose comparison in predefined subgroups. Consistent effects were recorded with the double-dose clopidogrel regimen in patients with STEMI and patients with non-ST-segment elevation acute coronary syndromes. There was no significant interaction for weight <60 kg or >60 kg, age below and over 75 years and previous stroke (p for interaction 0.614). In this trial, clopidogrel 600 mg loading dose has shown consistent efficacy in patients age ≥75 years of age and patients <75 years of age.

2.13. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance.

2.13.1. Importance of favourable and unfavourable effects

The literature supporting the use of clopidogrel with ASA in STEMI patients undergoing stent placement in PCI procedures showed significant reduction in cardiovascular events such as cardiovascular death, MI, stroke and stent thrombosis, thus supporting the indication proposed by the MAH. These are clinically relevant endpoints.

Overall, the data presented by the MAH indicates no significant increased risk of bleeding with a loading dose of clopidogrel and a 12 months maintenance dose of 75 mg of clopidogrel. These are the most clinically relevant safety endpoints in this context.

2.13.2. Balance of benefits and risks

The overall B/R of clopidogrel is positive regarding the use of clopidogrel in patients that undergo stent placement in the context of PCI. Also, a loading dose of 600 mg was shown to be more effective although associated in some studies with an increase overall risk of bleeding not associated with major haemorrhage. DAPT during 12 months in STEMI patients with clopidogrel 75 mg and low dose ASA was shown in a double blinded clinical trial to reduce a composite cardiovascular outcome and not to be associated to an increased risk of bleeding.

There was no specific information regarding safety in patients >75 years old. The MAH recognized that overall, there is a lack of data regarding patients >75 years-old. The MAH presented data regarding the CURRENT OASIS 7 study that reported data in the subset of patients >75 years-old. This study showed consistency in the treatment effect for each dose comparison in predefined subgroups. Consistent effects were recorded with the double-dose clopidogrel regimen in patients with STEMI and patients with non-ST-segment elevation acute coronary syndromes. There was no significant interaction for weight <60 kg or >60 kg, age below and over 75 years and previous stroke (p for interaction 0.614). In this trial, clopidogrel 600 mg loading dose has shown consistent efficacy in patients age ≥75 years of age and patients <75 years of age. Although the CURRENT OASIS 7 study has shown statistically significance in reducing cardiovascular death, MI, stroke and stent thrombosis, thus supporting the recommendation of 600 mg clopidogrel regimen for patients ≥ 75 years old, the MAH recommends that the loading dose of 600 mg clopidogrel in STEMI PCI patients may be considered based on an individual benefit/risk assessment performed by the prescribing physician (by assessing both the risk of bleeding and the risk of thrombotic event recurrence in each patient). This information was added to the labelling text in agreement with the SmPC guidance with dose recommendations in the elderly stated in separate paragraphs.

Taking this into account the B/R of clopidogrel is considered to be positive.

Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive.

2.14. Conclusions

The overall B/R of clopidogrel in combination with acetylsalicylic acid in ST segment elevation acute myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI) considered to be positive.

3. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIA

Extension of indication to include clopidogrel in combination with acetylsalicylic acid in ST segment elevation acute myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI); as a consequence section 4.1, 4.2 and 5.1 of the SmPC is updated. Version 2.6 of the RMP has also been submitted. In addition, an editorial update has been made to the labelling.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIA and to the Risk Management Plan are recommended.

4. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-WS-2150'