17 July 2025
EMA/235458/2025
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Clopidogrel Zentiva

International non-proprietary name: Clopidogrel

Procedure No. EMEA/H/C/000975/II/0092

## 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

| | |
|---|---|
| CI | Confidence Interval |
| TIA | Transient Ischemic Attack |
| PCI | Percutaneous Coronary Intervention |
| MI | Myocardial infarction |
| STEMI | ST segment elevation acute myocardial infarction |
| CABG | Coronary artery bypass graft surgery |
| DAPT | Dual antiplatelet therapy |
| mg | Milligram |
| SmPC | Summary of Product Characteristics |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Zentiva k.s. submitted to the European Medicines Agency on 5 December 2024 an application for a variation.

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 IIIB |

Extension of indication to include, in combination with acetylsalicylic acid (ASA), patients with ST segment elevation acute myocardial infarction (STEMI) who are undergoing percutaneous coronary intervention (PCI) for CLOPIDOGREL ZENTIVA. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. Version 0.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, introduce minor editorial changes to the PI and bring it in line with the latest QRD template version 10.4.

### *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 MAH 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 MAH did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: N/A

| Timetable | Actual dates |
|---|---|
| Submission date | 5 December 2024 |
| Start of procedure: | 26 January 2025 |

| Timetable | Actual dates |
|---|---|
| CHMP Rapporteur Assessment Report | 22 March 2025 |
| PRAC Rapporteur Assessment Report | 22 March 2025 |
| PRAC members comments | 3 April 2025 |
| PRAC Outcome | 10 April 2025 |
| CHMP members comments | 11 April 2025 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 18 April 2025 |
| Request for supplementary information (RSI) | 25 April 2025 |
| CHMP Rapporteur Assessment Report | 30 June 2025 |
| PRAC Rapporteur Assessment Report | 27 June 2025 |
| PRAC members comments | 1 July 2025 |
| Updated PRAC Rapporteur Assessment Report | 3 July 2025 |
| PRAC Outcome | 10 July 2025 |
| CHMP members comments | 14 July 2025 |
| Updated CHMP Rapporteur Assessment Report | 17 July 2025 |
| Opinion | 24 July 2025 |

# 2. Scientific discussion

## Introduction

This is an extension of indication to include **the use of clopidogrel** in combination with acetylsalicylic acid (ASA), **in** patients with ST segment elevation acute myocardial infarction (STEMI) who are undergoing percutaneous coronary intervention (PCI) for CLOPIDOGREL ZENTIVA.

Sections 4.1, 4.2, 4.4 and 5.1 of the SmPC were updated. Version 0.1 of the RMP has also been submitted.

### 2.1.1. About the product

Clopidogrel Zentiva is an antithrombotic agents authorised in the following indications:

*Secondary prevention of atherothrombotic events*

*Clopidogrel is indicated in:*

- *adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from seven days until less than six 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 medically treated patients eligible for thrombolytic therapy.*

*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.*

## *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

An ERA report was submitted to consider the environmental risk of Clopidogrel Zentiva, 75 mg and 300mg, film-coated tablets, a variation II/C.I.6.a. This concerns an 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).

**Table 1- Summary of main study results for Clopidogrel**

| **Substance (INN/Invented Name): Clopidogrel Zentiva** | | | |
|---|---|---|---|
| **CAS-number (if available):** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | 4.15 | Potential PBT **N** |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 4.15 | **not B** |
| **PBT-statement:** | The compound is not considered as PBT nor vPvB | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surface\ water}$ | 0.375 | µg/L | > 0.01 threshold **Y** |
| Other concerns (e.g., chemical class) | | | **N** |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 106 | log Koc= 5.17 | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment Systems | OECD 308 | DT50total system = 7.5 (sediment 1) -13.5 | |

| | | | | | |
|---|---|---|---|---|---|
| | | (sediment 2) days; DT50water =7.2(sediment 1 8.1 (sediment 2) days. At the end of the study, there was no parent compound remaining in the total system (in 104 days). Day 104: Water layer: parent compound: 0.0%. | | | |
| ***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* |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 710 | µg/L | *Daphnia magna* |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD 210 | NOEC | 310 | µg/L | *Pimephales promelas* |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC | | µg/L | |

Phase I: The shake flask method (OECD test 107) was used to determine the LogKow value of 4.15, which is below the trigger value of 4.5, for further screening of persistence, bioaccumulation, and toxicity (PBT). The log Kow reaches the threshold values for assessing secondary poisoning (Log Kow $\geqslant$ 3). However, since an existing ERA was deemed satisfactory by a competent EU authority, repeating studies is not considered required, in accordance with 3Rs principle by the EMA guideline EMEA/CHMP/SWP/4447/00 Rev. 1, 2024. . In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends that if the Applicant has a letter of access, they should provide the available results from previously referenced study reports in approved products, as well as the study reports. In the absence of data sharing, the applicant should confirm that the scientific conclusions of the previous ERA remain applicable.

The estimated PECsurface water for clopidogrel is 0.375 µg/L, far above the action limit of 0.01 µg/L, as defined in the Guideline EMEA/CHMP/SWP/4447/00. Clopidogrel is degraded in the environment, has low potential for bioaccumulation (Log KOC = 5.17) and exhibits moderate chronic toxicity. The substance has a PEC/PNEC ratio of less than 1, indicating that the risk is negligible and that it poses an insignificant environmental risk.

The precautionary and safety measures taken, including the general statement in the SmPC and PL have been applied to reduce any risk to the environment.

## 2.2.2. Discussion on non-clinical aspects

According to the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use,* EMEA/CHMP/SWP/4447/00, Rev1, 2024, an Environmental Risk Assessment (ERA) should have been submitted irrespective of the legal status basis.

### 2.2.3. Conclusion on the non-clinical aspects

The MAH submitted an updated Phase II ERA following the Guideline EMEA/CHMP/SWP/4447/00 Rev.1, 2024.

The log Kow reaches the threshold values for assessing secondary poisoning (Log Kow $\geqslant$ 3). However, since an existing ERA was deemed satisfactory by a competent EU authority, repeating studies is not considered required, in accordance with 3Rs principle by the EMA guideline EMEA/CHMP/SWP/4447/00 Rev. 1, 2024. In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends that if the Applicant has a letter of access, they should provide the available results from previously referenced study reports in approved products, as well as the study reports. In the absence of data sharing, the applicant should confirm that the scientific conclusions of the previous ERA remain applicable.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH has submitted literature to support the extension of indication.

## *2.4. Clinical efficacy*

### 2.4.1. Main study(ies)

**PCI-Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study**

This was a prospectively planned analysis of the 1863 patients undergoing PCI after mandated angiography in CLARITY–Thrombolysis in Myocardial Infarction (TIMI), a randomized, double-blind, placebo-controlled trial of clopidogrel in patients receiving fibrinolytics for STEMI.

Patients received aspirin and were randomized to receive either clopidogrel (300 mg loading dose, then 75 mg once daily) or placebo, initiated with fibrinolysis, and given until coronary angiography, which was performed 2 to 8 days after initiation of the study drug. For patients undergoing coronary artery stenting, it was recommended the administration of the open-label clopidogrel (including a loading dose) after the diagnostic angiogram.

The primary efficacy outcome for this analysis was the composite of cardiovascular death, recurrent MI, or stroke from PCI to 30 days after randomization. Secondary outcomes included recurrent MI or stroke before PCI and the composite of cardiovascular death, recurrent MI, or stroke from randomization to 30 days. Clopidogrel pretreatment significantly reduced the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding.

**Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial**

This trial was designed to determine whether a doubling of the loading and initial maintenance doses of clopidogrel was superior to the standard-dose regimen and whether higher-dose aspirin (300 to 325 mg daily) was superior to lower-dose aspirin (75 to 100 mg daily) in patients with acute coronary syndromes referred for an early invasive strategy.

The primary outcome was the time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first, up to day 30. The secondary outcomes included the composite of death from cardiovascular causes, myocardial infarction, stroke, or recurrent ischemia; the individual components of the primary outcome; and death from any cause. Definite or probable stent thrombosis, as defined by the Academic Research Consortium was a prespecified secondary outcome in the subgroup of patients who underwent PCI.

A nominally significant reduction in the primary outcome was associated with the use of higher-dose clopidogrel in the subgroup of 17,263 study participants who underwent PCI after randomization (69%). Double-dose clopidogrel significantly reduced the secondary outcome of stent thrombosis, including angiographically confirmed definite stent thrombosis, in the subgroup of patients who underwent PCI.

**The Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty - Myocardial Infarction (ARMYDA-6 MI)**

The purpose of this study was to compare 600- and 300-mg clopidogrel loading doses in patients with STEMI.

A total of 201 patients undergoing primary PCI for STEMI randomly received a 600-mg (n = 103) or 300-mg (n = 98) clopidogrel loading dose before the procedure. The primary endpoint was the evaluation of the infarct size, defined as the area under the curve of cardiac markers.

The following secondary endpoints were investigated: Prevalence of Thrombolysis In Myocardial Infarction (TIMI) flow >grade 1 at the diagnostic coronary angiography before PCI and of TIMI flow grade <3 after PCI, Left ventricular ejection fraction by transthoracic echocardiography at discharge, The incidence of major adverse cardiovascular events (MACEs), Occurrence of bleeding/entry site complications.

In STEMI patients, pre-treatment with a 600-mg clopidogrel loading dose before primary PCI was associated with a reduction of the infarct size compared with a 300-mg loading dose, as well as with improvement of angiographic results, residual cardiac function, and 30-day major adverse cardiovascular events.

**Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI)**

In this trial, 3,602 patients with STEMI undergoing primary PCI were randomized to bivalirudin (n = 1,800) or unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (n = 1,802). Randomization was stratified by thienopyridine loading dose, which was determined before random assignment. The primary randomization was stratified by whether the patient was to be loaded with 300 mg of clopidogrel, 600 mg of clopidogrel, or 500 mg of ticlopidine before catheterization.

Subgroup analyses of 300 versus 600 mg of clopidogrel was performed. The aim was to determine whether a 600-mg loading dose of clopidogrel compared with 300 mg results in improved clinical outcomes in patients with STEMI undergoing PCI.

The 30-day rates of mortality, reinfarction, MACE, and non– CABG-related major bleeding were significantly lower in the 600-mg clopidogrel loading dose group compared with the 300-mg loading dose group. The incidence of acquired thrombocytopenia was similar between the 2 groups. Among patients treated with PCI and coronary stent implantation, definite or probable stent thrombosis was also significantly lower among patients in the 600-mg compared with the 300-mg loading dose group.

**Clopidogrel for the Reduction of Events During Observation (CREDO) trial**

This study was conducted to evaluate the benefit of long-term (12-month) treatment with clopidogrel after PCI and to determine the benefit of initiating clopidogrel with a pre-procedure loading dose, both in addition to aspirin therapy.

The primary 1-year outcome was the composite of death, MI, and stroke in the intent-to-treat population. Prespecified secondary analyses included the individual components of the composite end points, administration of clopidogrel less than 6 hours or at least 6 hours before PCI, and the need for target vessel revascularization or any revascularization at 1 year.

The results indicate that in patients undergoing PCI, the continuation of clopidogrel and aspirin therapy for 1 year led to a significant reduction in atherothrombotic events compared with treatment for only 4 weeks. Although a 300-mg loading dose of clopidogrel administered more than 3 hours prior to the procedure was not significantly better than administration of clopidogrel without a loading dose immediately after the procedure, the subgroup analysis of patients treated at least 6 hours prior to PCI suggested a significant reduction in periprocedural major adverse cardiac events, with or without the concomitant use of a GpIIb-IIIa antagonist.

**Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) Randomized, Multicenter Study**

This study aimed to study whether 6-month DAPT would be noninferior to 12-month DAPT after implantation of drug-eluting stents.

The primary end point was target vessel failure defined as a composite of cardiac death, myocardial infarction, or target vessel revascularization during the 12-month period after randomization. Secondary end points included the individual components of the primary endpoint; death resulting from any cause; death or myocardial infarction; stent thrombosis; major bleeding according to the Thrombolysis in Myocardial Infarction criteria; major adverse cardiocerebral events, which were a composite of death, myocardial infarction, stroke, or any revascularization; and a safety end point, which was a composite of death, myocardial infarction, stroke, stent thrombosis, or Thrombolysis in Myocardial Infarction major bleeding.

The trial showed that the rate of target vessel failure was not significantly different between the 6- and 12-month DAPT groups after PCI with drug-eluting stents and that 6-month DAPT was noninferior to 12-month DAPT in the risk of target vessel failure.

## 2.4.2. Discussion and conclusion on clinical efficacy

Clopidogrel pretreatment significantly reduced the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding.

Double-dose clopidogrel significantly reduced the secondary outcome of stent thrombosis, including angiographically confirmed definite stent thrombosis, in the subgroup of patients who underwent PCI.

In STEMI patients, pre-treatment with a 600-mg clopidogrel loading dose before primary PCI was associated with a reduction of the infarct size compared with a 300-mg loading dose, as well as with improvement of angiographic results, residual cardiac function, and 30-day major adverse cardiovascular events.

The 30-day rates of mortality, reinfarction, MACE, and non– CABG-related major bleeding were significantly lower in the 600-mg clopidogrel loading dose group compared with the 300-mg loading dose group. The incidence of acquired thrombocytopenia was similar between the 2 groups. Among patients treated with PCI and coronary stent implantation, definite or probable stent thrombosis was also significantly lower among patients in the 600-mg compared with the 300-mg loading dose group.

In patients undergoing PCI, the continuation of clopidogrel and aspirin therapy for 1 year led to a significant reduction in atherothrombotic events compared with treatment for only 4 weeks. Although a 300-mg loading dose of clopidogrel administered more than 3 hours prior to the procedure was not significantly better than administration of clopidogrel without a loading dose immediately after the procedure, the subgroup analysis of patients treated at least 6 hours prior to PCI suggested a significant reduction in periprocedural major adverse cardiac events, with or without the concomitant use of a GpIIb-IIIa antagonist.

The rate of target vessel failure was not significantly different between the 6- and 12-month DAPT groups after PCI with drug-eluting stents and that 6-month DAPT was noninferior to 12-month DAPT in the risk of target vessel failure.

No issues are raised regarding clinical efficacy.

## *2.5. Clinical safety*

In the CLARITY study, there was no significant excess in the rates of TIMI major bleeding (0.5% vs 1.1%), TIMI minor bleeding (1.4% vs 0.8%), or the combination (2.0% vs 1.9%) following PCI in those who received clopidogrel pretreatment compared with those who did not. In addition, among patients who received a GpIIb/IIIa inhibitor during PCI, the rate of TIMI major or minor bleeding was no higher in those who had received clopidogrel pretreatment (2.1% [6/283]) than in those who did not receive pretreatment (2.9% [9/307]) (P=0.36). Eligible trial participants were between 18 and 75 years old. No patients above 75 years were included.

In the CURRENT-OASIS 7 trial, major bleeding occurred in 2.5% of patients in the double-dose clopidogrel group as compared with 2.0% of patients in the standard-dose clopidogrel group (hazard ratio, 1.24;95% CI, 1.05 to 1.46; P = 0.01). The incidence of major bleeding as defined according to the TIMI criteria and the incidence of severe bleeding were also higher among patients who received double dose clopidogrel. The increased incidences of major and severe bleeding were accounted for mainly by a higher rate of red-cell transfusion among patients in the double dose group. The use of double-dose clopidogrel did not increase the incidence of fatal or intracranial bleeding, nor did it significantly increase the incidence of bleeding that was related to Coronary artery bypass graft surgery (CABG). There were no reports of neutropenia in either clopidogrel group. In this trial, 26% of patients included were older than 75 years.

In the ARMYDA-6 MI study, the safety endpoints did not differ in the 600- and 300-mg arms: major bleeding at 1 month occurred in 1.9% versus 2.0% of patients, nonentry site minor bleeding in 7.8% versus 6.1%, and entry site complications in 2.9% versus 3.1%. No patient had post-procedure thrombocytopenia with platelet count less than $70x10^9$/L. Detailed age characteristics of participants are not available in the published article.

In the HORIZONS-AMI study, the 600-mg loading dose was not associated with increased rates of major bleeding or thrombocytopenia. Overall adverse event rates were lower after a 600-mg loading dose than a 300-mg loading dose with both anticoagulation regimens. No patients above 75 years of age were included in the trial. The 30-day rates of mortality, reinfarction, MACE, and non– CABG-related major bleeding were significantly lower in the 600-mg clopidogrel loading dose group compared with the 300-mg loading dose group. The incidence of acquired thrombocytopenia was similar between the 2 groups. Among patients treated with PCI and coronary stent implantation, definite or probable stent thrombosis was also significantly lower among patient in the 600-mg compared with the 300-mg loading dose group.

In the CREDO trial, clopidogrel pretreatment at 28 days did not significantly increase major or minor bleeding. Minor bleeding increased non-significantly in patients who also received a GpIIb-IIIa antagonist

(2.8% pretreatment vs 1.0% no pretreatment; P=0.08). Importantly, there were no fatal bleeds or intracranial haemorrhages. Nearly all major bleeding events were associated with invasive procedures (either the index PCI or CABG) in both groups. Patients treated with clopidogrel for 1 year experienced a trend toward an increase in major bleeding (8.8% clopidogrel vs 6.7% placebo; P=0.07). Approximately two thirds of all major bleeds occurred in patients undergoing CABG, with all such patients experiencing a high incidence of major bleed. No patients above 75 years of age were included in the study.

In the EXCELLENT study, there was no difference in safety outcome *(*composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between the arms 6 months DAPT and 12 months DAPT. No patients above 75 years of age were included in the study.

## 2.5.1. Discussion on clinical safety

In the studies that were presented which did not include patients older than 75 years-old, the 600-mg loading dose was not associated with increased rates of major bleeding or thrombocytopenia when compared to the 300 mg loading dose.

In the CURRENT-OASIS 7 trial that included patients older than 75 years-old although there is no specific information regarding safety in this age group, major bleeding occurred in 2.5% of patients in the double-dose clopidogrel group as compared with 2.0% of patients in the standard-dose clopidogrel group (hazard ratio, 1.24;95% CI, 1.05 to 1.46; P = 0.01). The incidence of major bleeding as defined according to the TIMI criteria and the incidence of severe bleeding were also higher among patients who received double dose clopidogrel. The increased incidences of major and severe bleeding were accounted for mainly by a higher rate of red-cell transfusion among patients in the double dose group. The use of double-dose clopidogrel did not increase the incidence of fatal or intracranial bleeding, nor did it significantly increase the incidence of bleeding that was related to CABG. There were no reports of neutropenia in either clopidogrel group.

Due to the limited clinical data in patients ≥75 years old with STEMI PCI, and increased risk of bleeding, the use of clopidogrel 600 mg loading dose should be considered only after an individual assessment of the bleeding risk of the patient by the physician, The RMP includes a targeted follow-up questionnaire for intracranial/intracerebral haemorrhage in very elderly (>75-year-old) patients

## 2.5.2. Conclusions on clinical safety

In the majority of studies that were presented, the 600-mg loading dose was not associated with increased rates of major bleeding or thrombocytopenia when compared to the 300 mg loading dose. In the CURRENT – OASIS 7 trial, that included patients older than 75 years-old, although there is no specific information regarding safety in this age group, double-dose clopidogrel group was associated with an increased risk of major bleeding. Nevertheless, the use of double-dose clopidogrel did not increase the incidence of fatal or intracranial bleeding, nor did it significantly increase the incidence of bleeding that was related to CABG.

Due to the limited clinical data in patients ≥75 years old with STEMI PCI, and increased risk of bleeding, the use of clopidogrel 600 mg loading dose should be considered only after an individual assessment of the bleeding risk of the patient by the physician, The RMP includes a targeted follow-up questionnaire for intracranial/intracerebral haemorrhage in very elderly (>75-year-old) patients.

### 2.5.3. 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 0.3 with the following content:

### *Safety concerns*

The MAH submitted an RMP version with this application (version 0.1 with DLP 1 August 2024).

The MAH has provided the first version of the RMP in this variation for extension of indication.

### *Safety Specification and Safety Concerns*

Table SVIII.1: Summary of safety concerns

| **Summary of 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.*

### *Pharmacovigilance plan*

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for:

- Major bleeding (including ICH)

Additional pharmacovigilance activities: Not applicable.

### *Risk minimisation measures*

The safety information in the proposed product information is aligned to the reference medicinal product.

The MAH has proposed routine risk minimisation measures, which are in line with the reference medicinal product. This is endorsed.

## *2.7. Update of the Product information*

**Secondary prevention of atherothrombotic events**

**Section 4.1**

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 IS (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 (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.

For further information please refer to section 5.1.

4.2

In patients suffering from acute coronary syndrome:

• 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).**

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. ASA (75 100 mg daily) should be initiated and continued in combination with clopidogrel (see section 5.1).

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.

**Special populations**

**Elderly patients**

**Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):**

**• A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended (see section 4.4).**

**ST segment elevation acute myocardial infarction:**

**• For medically treated patients eligible for thrombolytic/fibrinolytic therapy: in patients over 75 years of age clopidogrel should be initiated without a loading dose.**

**For 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).**

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, introduce minor editorial changes to the PI and bring it in line with the latest QRD template version 10.4.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

## 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the current update has no impact on the product information leaflet.

# 3. Benefit-Risk Balance

Clopidogrel pretreatment significantly reduced the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding.

Double-dose clopidogrel significantly reduced the secondary outcome of stent thrombosis, including angiographically confirmed definite stent thrombosis, in the subgroup of patients who underwent PCI.

In STEMI patients, pre-treatment with a 600-mg clopidogrel loading dose before primary PCI was associated with a reduction of the infarct size compared with a 300-mg loading dose, as well as with improvement of angiographic results, residual cardiac function, and 30-day major adverse cardiovascular events.

The 30-day rates of mortality, reinfarction, MACE, and non– CABG-related major bleeding were significantly lower in the 600-mg clopidogrel loading dose group compared with the 300-mg loading dose group. The incidence of acquired thrombocytopenia was similar between the 2 groups. Among patients treated with PCI and coronary stent implantation, definite or probable stent thrombosis was also significantly lower among patients in the 600-mg compared with the 300-mg loading dose group.

In patients undergoing PCI, the continuation of clopidogrel and aspirin therapy for 1 year led to a significant reduction in atherothrombotic events compared with treatment for only 4 weeks. Although a 300-mg loading dose of clopidogrel administered more than 3 hours prior to the procedure was not significantly better than administration of clopidogrel without a loading dose immediately after the procedure, the subgroup analysis of patients treated at least 6 hours prior to PCI suggested a significant reduction in periprocedural major adverse cardiac events, with or without the concomitant use of a GpIIb-IIIa antagonist.

The rate of target vessel failure was not significantly different between the 6- and 12-month DAPT groups after PCI with drug-eluting stents and that 6-month DAPT was noninferior to 12-month DAPT in the risk of target vessel failure.

No issues are raised regarding clinical efficacy.

In the majority of studies that were presented, the 600-mg loading dose was not associated with increased rates of major bleeding or thrombocytopenia when compared to the 300 mg loading dose. In the CURRENT – OASIS 7 trial, that included patients older than 75 years-old, although there is no specific information regarding safety in this age group, double-dose clopidogrel group was associated with an increased risk of major bleeding. Nevertheless, the use of double-dose clopidogrel did not increase the incidence of fatal or intracranial bleeding, nor did it significantly increase the incidence of bleeding that was related to CABG.

Due to the limited clinical data in patients ≥75 years old with STEMI PCI, and increased risk of bleeding, the use of clopidogrel 600 mg loading dose should be considered only after an individual assessment of the bleeding risk of the patient by the physician, The RMP includes a targeted follow-up questionnaire for intracranial/intracerebral haemorrhage in very elderly (>75-year-old) patients.

## *3.1. Conclusions*

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

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 IIIB |

Extension of indication to include, in combination with acetylsalicylic acid (ASA), patients with ST segment elevation acute myocardial infarction (STEMI) who are undergoing percutaneous coronary intervention (PCI) for CLOPIDOGREL ZENTIVA. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. Version 0.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, introduce minor editorial changes to the PI and bring it in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

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

the terms of the Marketing Authorisation, concerning the following change:

| **Variation rejected** | | **Type** |
|---|---|---|
| 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 |

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important

(pharmacovigilance or risk minimisation) milestone being reached.

# 5. 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-Var.92'

# Attachments

1. SmPC Package Leaflet (changes highlighted)