EU Risk Management Plan for Clopidogrel Zentiva

(clopidogrel hydrogen sulphate)

No 74/25

RMP version to be assessed as part of this application:

RMP Version number:	V 1.0	
Data lock point for this RMP:	30 June 2025	
Date of final sign off:	21 July 2025	
Rationale for submitting an updated RMP:	Final initial version.	
Summary of significant changes in this RMP:	Not applicable.	
Other RMP versions under evaluation:	RMP version number:	Not applicable.
	Submitted on:	Not applicable.
	Procedure number:	Not applicable.
Details of the currently approved RMP:	RMP version number:	Not applicable.
	Approved with procedure:	Not applicable.
	Date of approval (opinion date):	Not applicable.
QPPV name:	Ludmila FILIPOVÁ, MD	
QPPV (or delegate) signature:		

ZENTIVA

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List of Abbreviations

ADP	Adenosine diphosphate
ASA	Acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical classification
DAPT	Dual Antiplatelet Therapy
EMA	European Medicines Agency
EU	European Union
EEA	European Economic Area
eCTD	Electronic Common Technical Document
ICH	lntracranial Hemorrhage
INN	International Nonproprietary Name
IS	Ischemic Stroke
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
mIS	Minor Ischemic Stroke
PCI	Percutaneous coronary intervention
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
QPPV	Qualified Person for Pharmacovigilance
SmPC	Summary of Product Characteristics
TIA	Transient Ischemic Attack

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	clopidogrel hydrogen sulphate (also known and used as clopidogrel bisulphate) and herein after referred to as clopidogrel
Pharmacotherapeutic group(s) (ATC Code)	Platelet aggregation inhibitors excl. heparin ATC Code: B01AC04
Marketing Authorisation Holder/Applicant	ZENTIVA, K.S.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Clopidogrel Zentiva 75 mg film coated tablets Clopidogrel Zentiva 300 mg film coated tablets
Marketing authorisation procedure	Centralised EMEA/H/C/000975
Brief description of the product	Chemical class: Clopidogrel is a platelet aggregation inhibitor. It is a P2Y12 ADP receptor antagonist of the thienopyridine derivative class. IUPAC Name: methyl (2S)-2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate;sulfuric acid
	Summary of mode of action: It selectively inhibits the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex together with the binding of fibrinogen to this receptor, thereby inhibiting platelet aggregation.
	Important information about its composition: None
Hyperlink to the Product Information	Please refer to section 1.3.1 in eCTD.
Indication(s) in the EEA	Current: Secondary prevention of atherothrombotic events Clopidogrel is indicated in: • Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. • Adult patients suffering from acute coronary syndrome: - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA). - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

	<u>In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)</u> Clopidogrel in combination with ASA is indicated in: • Adult patients with moderate to high-risk TIA (ABCD2[1] score ≥4) or minor IS (NIHSS[2] ≤3) within 24 hours of either the TIA or IS event. <u>Prevention of atherothrombotic and thromboembolic events in atrial fibrillation</u> 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.
	<u>Proposed:</u> <u>Secondary prevention of atherothrombotic events</u> 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. <u>In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)</u> Clopidogrel in combination with ASA is indicated in: • Adult patients with moderate to high-risk TIA (ABCD2[1] score ≥4) or minor IS (NIHSS[2] ≤3) within 24 hours of either the TIA or IS event. <u>Prevention of atherothrombotic and thromboembolic events in atrial fibrillation</u> 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

[1] Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnosis
[2] National Institutes of Health Stroke Scale

	indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.
Dosage in the EEA	Current: *Adults and elderly* *Clopidogrel Zentiva 75 mg film-coated tablets* Clopidogrel should be given as a single daily dose of 75 mg. *Clopidogrel Zentiva 300 mg film-coated tablets* This 300 mg tablet of clopidogrel is intended for use as a loading dose. In patients suffering from acute coronary syndrome: • Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg or 600 mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended. Clopidogrel treatment should be continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months. • ST segment elevation acute myocardial infarction: 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. 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. If a dose is missed:

	• Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time. • For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose. <u>Method of administration</u> For oral use It may be given with or without food.
	<u>Proposed:</u> *Adults and elderly* <u>*Clopidogrel Zentiva 75 mg film-coated tablets*</u> Clopidogrel should be given as a single daily dose of 75 mg. <u>*Clopidogrel Zentiva 300 mg film-coated tablets*</u> This 300 mg tablet of clopidogrel is intended for use as a loading dose. In patients suffering from acute coronary syndrome: • Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg or 600 mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended. Clopidogrel treatment should be continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months. • ST segment elevation acute myocardial infarction: - For medically treated patients eligible for thrombolytic/fibrinolytic therapy clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics. For medically treated patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting. - When percutaneous coronary intervention (PCI) is intended: ▪ 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. ▪ Clopidogrel 300 mg loading dose should be given in patients undergoing PCI within 24 hours of receiving fibrinolytic therapy. Clopidogrel treatment should be continued at 75 mg once a day with ASA 75 mg – 100 mg daily. Combined therapy should be started as early as possible after symptoms start and continued up to 12 months. Adult patients with moderate to high-risk TIA or minor IS: Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg - 100 mg once daily). Treatment with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy. In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel. If a dose is missed: • Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time. • For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose. <u>Method of administration</u> For oral use It may be given with or without food.
Pharmaceutical form(s) and strengths	<u>Current:</u> 75 mg and 300 mg film-coated tablets
	<u>Proposed (if applicable):</u> Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes
Not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Safety concerns are harmonised with reference medicinal product **Plavix** (https://www.ema.europa.eu/en/medicines/human/EPAR/plavix, Last updated: 16/04/2025).

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.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is the initial version.

SVII.3 Details of important identified risks, important potential risks, and missing information

Not applicable.

Part II: Module SVIII - Summary of the 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.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for:

- Major bleeding (including ICH)

The form is provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities:
Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

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

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Clopidogrel Zentiva (clopidogrel hydrogen sulphate)
This is a summary of the risk management plan (RMP) for Clopidogrel Zentiva. The RMP details important risks of Clopidogrel Zentiva and how more information will be obtained about Clopidogrel Zentiva's risks and uncertainties (missing information).
Clopidogrel Zentiva's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Clopidogrel Zentiva should be used.

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

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

I. The medicine and what it is used for

Clopidogrel Zentiva is indicated in adults for the secondary prevention of atherothrombotic events in recent myocardial infarction (MI), recent ischemic stroke (IS) or established peripheral arterial disease (PAD) and moderate to high-risk transient ischemic attack (TIA) or minor IS, and in acute coronary syndrome (ACS). It is also indicated for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation (AF) (see SmPC for the full indication). It contains clopidogrel as the active substance and it is given by oral route of administration.

Further information about the evaluation of Clopidogrel Zentiva's benefits can be found in Clopidogrel Zentiva's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/clopidogrel-zentiva-previously-clopidogrel-winthrop

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Clopidogrel Zentiva, together with measures to minimise such risks and the proposed studies for learning more about Clopidogrel Zentiva's risks, are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

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

II.A List of important risks and missing information

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

List of important risks and missing information	
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/mlS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.*
DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; mlS: Minor Ischemic Stroke; TIA: Transient Ischemic Attack.

II.B Summary of important risks

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

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Clopidogrel Zentiva.

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

There are no studies required for Clopidogrel Zentiva.

Annex 4 - Specific adverse drug reaction follow-up forms

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

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

ACETYLSALICYLIC ACID + CLOPIDOGREL
Specific adverse reaction/event Follow-up Form
INTRACRANIAL/INTRACEREBRAL HAEMORRHAGE IN VERY ELDERLY PATIENT (≥75-YEAR-OLD) WITH TIA (TRANSIENT ISCHEMIC ATTACK) OR MINOR ISCHEMIC STROKE TREATED WITH DUAL ANTI-PLATELET THERAPY (DAPT)

Global database ID:

Country of occurrence:

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

PATIENT INFORMATION

Date of the follow-up (XX/YY/ZZZZ):
Patient initials (first, last):
Age or Age Group:
Age group category: ≥ 75-year-old (mandatory): ☐ Yes ☐ No
Gender: Male ☐ Female ☐

SPECIFIC INFORMATION

Treatment information

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

Start Date	Stop Date	Duration of treatment

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

DAPT indication:

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

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

ZENTIVA

Adverse Event Information

ICH is:
☐ spontaneous ☐ traumatic
☐ symptomatic ☐ asymptomatic

ICH severity: _____

ICH type:
☐ Subdural hemorrhage
☐ Microvascular hemorrhage
☐ Other (specify): _____

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

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

Outcome:
☐ Recovered/Resolved
☐ Recovered/Resolved with Sequelae
☐ Not Recovered/Not Resolved
☐ Recovering/Resolving
☐ Fatal
☐ Unknown

Specify date of resolution or date of death, if applicable: _____
If patient recovered with sequelae, describe sequelae: _____
Event Relationship to Zentiva Product (Clopidogrel+ASA): ☐ Related ☐ Not Related ☐ Unknown

Medical History/Risk Factors

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

If DAPT indication is TIA, provide **ABCD^2 score** (if known):

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

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

Previous history of ICH with details:
☐ Yes - specify onset date, exact diagnosis, and risk factors: _____
☐ No
☐ Unknown

IRM / Scanner

Date (DD-MMM-YYYY) and Results:

ADDITIONAL INFORMATION

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

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

Additional requests for the reporter (if any):

Reporter Information *(person who provides the information reported on this form)*:
Name or Initials:
Qualification: ☐ Health Care Professional (HCP) ☐ non-HCP
Email address:
Phone Number:

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

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Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.