# EU RISK MANAGEMENT PLAN

# CLOPIDOGREL

| **RMP version to be assessed as part of this application** | |
|---|---|
| RMP version number | 5.1 |
| Data lock point for this RMP | 31 December 2023 |
| Date of final sign off | 26 January 2024 |
| Rationale for submitting an updated RMP | RMP document prepared:<br>• to align the indication and posology sections following the 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).;<br>• to include "major bleeding" as an important identified risk and accompanying follow-up questionnaire in line with the published RMP of the reference product, Plavix (published on EMA EPAR website). |

| **QPPV Details** | |
|---|---|
| QPPV name: | Iva Novak |
| QPPV oversight declaration: | The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy. |
| QPPV/deputy signature: | The signature is available on file. |

**Table 1: Summary of Significant Changes in This RMP Version**

| RMP part/module | Part/module version number and date of approval (opinion date) | High level description of major changes |
|---|---|---|
| **Part I**<br>Product(s) overview | 4.1<br>(19 September 2019) | Updated to align the indication and posology sections following the 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). |
| **Part II - Module SI**<br>Epidemiology of the indication(s) and target population(s) | Not applicable. | Not applicable. |
| **Part II - Module SII**<br>Non-clinical part of the safety specification | Not applicable. | Not applicable. |
| **Part II - Module SIII**<br>Clinical trial exposure | Not applicable. | Not applicable. |
| **Part II - Module SIV**<br>Populations not studied in clinical trials | Not applicable. | Not applicable. |
| **Part II - Module SV**<br>Post-authorisation experience | Not applicable. | Not applicable. |
| **Part II - Module SVI**<br>Additional EU requirements for the safety specification | Not applicable. | Not applicable. |
| **Part II - Module SVII**<br>Identified and potential risks | 4.1<br>(19 September 2019) | Updated to reflect changes introduced to the list of safety concerns. |
| **Part II - Module SVIII**<br>Summary of the safety concerns | 4.1<br>(19 September 2019) | The list of safety concerns is aligned with list of safety concerns of originator product Plavix published in EMA EPAR website. |

| | | |
|---|---|---|
| **Part III**<br>Pharmacovigilance plan (including post-authorisation safety studies) | 4.1<br>(19 September 2019) | Updated to introduce follow-up questionnaire for important identified risk 'Major bleeding (including ICH)', in line with the published RMP of the reference product, Plavix (published on EMA EPAR website). |
| **Part IV**<br>Plans for post-authorisation efficacy studies | Not applicable. | Not applicable. |
| **Part V**<br>Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) | Not applicable. | Not applicable. |
| **Part VI**<br>Summary of the risk management plan | 4.1<br>(19 September 2019) | Updated to reflect changes introduced to the list of safety concerns. |
| **Part VII**<br>Annexes | 4.1<br>(19 September 2019) | Annex 4 updated to reflect introduction of follow-up questionnaire for important identified risk 'Major bleeding (including ICH)'.<br>Annex 8 updated to reflect changes introduced in RMP v5.1. |

| **Other RMP versions under evaluation** | |
|---|---|
| RMP Version number | Not applicable. |
| Submitted on | Not applicable. |
| Procedure number | Not applicable. |

| **Details of the currently approved RMP** | |
|---|---|
| Version number | 4.1 |
| Approved with procedure | EMAE/H/C/004006 |
| Date of approval (opinion date) | 19 September 2019 |

# TABLE OF CONTENTS

## LIST OF TABLES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ADP** | Adenosine diphosphate |
| **ASA** | Acetylsalicylic acid |
| **ATC** | Anatomical Therapeutic Chemical |
| **CTD** | Common Technical Document |
| **CYP** | Cytochrome |
| **DAPT** | Dual Antiplatelet Therapy |
| **EEA** | European Economic Area |
| **e.g.** | example given |
| **EMA** | European medicines agency |
| **EPAR** | European Public Assessment Report |
| **EU** | European Union |
| **GP** | Glycoprotein |
| **ICH** | Intracranial Haemorrhage |
| **INN** | International Non-proprietary Name |
| **IS** | Ischemic Stroke |
| **NIHSS** | National Institutes of Health Stroke Score |
| **PCI** | Percutaneous Coronary Intervention |
| **QPPV** | Qualified Person for Pharmacovigilance |
| **RMP** | Risk Management Plan |
| **SPC, SmPC** | Summary Of Product Characteristics |
| **TIA** | Transient Ischemic Attack |
| **VKA** | Vitamin K Antagonists |

# Part I: Product(s) Overview

**Table 2: Product(s) Overview**

| | |
|---|---|
| **Active substance(s) (INN or common name)** | **Clopidogrel** |
| **Pharmacotherapeutic group(s) (ATC Code)** | Antithrombotic agents, platelet aggregation inhibitors excl. heparin.<br>B01AC04. |
| **Marketing Authorisation Holder/Applicant** | TEVA B.V.<br>Swensweg 5<br>2031GA Haarlem<br>The Netherlands |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | [Clopidogrel] ratiopharm 75 mg film-coated tablet |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | **Chemical class**:<br>Clopidogrel bisulfate is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. |
| | **Summary of mode of action**:<br>Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP. |
| | **Important information about its composition**:<br>Not applicable. |
| **Hyperlink to the Product Information** | Please refer to CTD Module 1.3.1. |

| | |
|---|---|
| **Indication(s) in the EEA** | **Current**:<br>**Secondary prevention of atherothrombotic events**<br>Clopidogrel is indicated in:<br>• 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.<br>• Adult patients suffering from acute coronary syndrome:<br>o 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).<br>o 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.<br>**In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)**<br>Clopidogrel in combination with ASA is indicated in:<br>• 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.<br>**Prevention of atherothrombotic and thromboembolic events in atrial fibrillation**<br>In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke. |
| | **Proposed (if applicable)**:<br>Not applicable. |

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

| | |
|---|---|
| **Dosage in the EEA** | **Current**:<br>Clopidogrel should be given as a single daily dose of 75 mg.<br>*In patients suffering from acute coronary syndrome:*<br>• 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 loading dose and then 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.<br>• ST segment elevation acute myocardial infarction:<br>o 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.<br>o When percutaneous coronary intervention (PCI) is intended:<br>▪ Clopidogrel should be initiated at a loading dose of 600 mg in patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy. In patients ≥ 75 years old the 600 mg loading dose should be administered with caution.<br>▪ Clopidogrel 300 mg loading dose should be given in patients undergoing PCI within 24 hours of receiving fibrinolytic therapy.<br>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<br>*Adult patients with moderate to high-risk TIA or minor IS:*<br>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.<br>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. |
| | **Proposed (if applicable)**:<br>Not applicable. |
| **Pharmaceutical form(s) and strengths** | **Current**:<br>75 mg film-coated tablet |
| | **Proposed (if applicable)**:<br>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

Not applicable.

## Part II: Module SVII - Identified and Potential Risks

### SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

### SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

In RMP v5.1, Major bleeding is included as important identified risk.

**Reasons for the addition to the list of safety concerns in RMP v5.1:**

The above-mentioned safety concern was added in the Clopidogrel RMP v5.1 to align with the list of safety concerns of originator Plavix RMP v2.6, published in European Medicines Agency (EMA) European public assessment report (EPAR) website on 1 December 2023.

### 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 3: Summary of Safety Concerns**

| List of important risks and missing information | |
|---|---|
| **Important identified risks** | • Major bleeding (including ICH*) |
| **Important potential risks** | • None |
| **Missing information** | • None |

The summary of safety concerns is aligned with the list of safety concerns of originator product Plavix published in EMA EPAR website (RMP v2.6, published on 1 December 2023).

* 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 questionnaires:**

**Table 4: List of Questionnaires**

| Safety concern for which the questionnaire is used | Purpose | Trigger events |
|---|---|---|
| Major bleeding (including ICH) | To follow-up and collect in more detail information to further characterise safety concerns and evaluate risk factors. | SMQ Haemorrhages, Broad scope. |

## 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

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

### 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 ratiopharm 75 mg film-coated tablet

This is a summary of the risk management plan (RMP) for Clopidogrel ratiopharm 75 mg film-coated tablet (hereinafter referred to as Clopidogrel). The RMP details important risks of Clopidogrel, how these risks can be minimised, and how more information will be obtained about Clopidogrel's risks and uncertainties (missing information).

Clopidogrel's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Clopidogrel should be used.

This summary of the RMP for Clopidogrel 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's RMP.

## I. The Medicine and What It is used for

Clopidogrel 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) including non-ST segment elevation ACS and ST segment elevation acute MI. 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 orally.

Further information about the evaluation of Clopidogrel’s benefits can be found in Clopidogrel’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-ratiopharm.

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Clopidogrel, together with measures to minimise such risks and the proposed studies for learning more about Clopidogrel'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 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 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. 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).

**Table 5: Summary of Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | • Major bleeding (including ICH*) |
| **Important potential risks** | • None |
| **Missing information** | • None |

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

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

## II.B Summary of Important Risks

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.

### II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Clopidogrel.

# Part VII: ANNEXES

**Table of contents**

# Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

**Follow-up forms**

- Clopidogrel - Intracranial/intracerebral haemorrhage (ICH) in very elderly (≥75-year-old) patient with TIA (transient ischemic attack) or minor ischemic stroke treated with dual anti-platelet therapy (DAPT) - Questionnaire v1.0

**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)**

- Targeted Follow-up Form (coversheet) -

**Follow-up to Case No.:**.....

Date of receipt (dd/mm/yyyy):.....

**PATIENT INFORMATION:**

Age:.....

Gender: ☐ M ☐ F Pregnant: ☐ Y ☐ N

Height ..... cm/ ..... in Weight ..... kg/ ..... lbs .....

**In the 'Patient Information' section of Individual Safety Information (ISI) Documentation Form and in the 'Patient' section of Unsolicited ISI Report Form, specify:**

- Age group category: ≥ 75 year-old (mandatory)

**In the 'Suspect Product(s) Information' section of ISI Documentation Form and in the 'Suspect Medication/Medical Device (MD)/Vaccine (V)' section of Unsolicited ISI Form, ensure to indicate:**

- Dates of prescriptions (start - stop) of dual antiplatelet therapy of clopidogrel + low dose aspirin (i.e. ASA or ASL) and duration of treatment.
- Dose of ASA or ASL in DAPT: to specify if ≤100 mg or [> 100mg – 325mg]
- DAPT indication: transient ischemic attack (TIA), minor ischemic stroke, or other indication (antithrombotic indication/prevention of cardiovascular event at time of ICH first symptoms).

**In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Description of the Case' section of Unsolicited ISI Report Form, ensure to indicate:**

- If ICH is:
  - spontaneous / traumatic
  - symptomatic / asymptomatic
- ICH Type (subdural hemorrhage, microvascular hemorrhage, etc. ...)
- ICH Severity
- Risk factors other than medications (i.e., cerebral aneurism, cerebral hemangioma, etc. ...)

**In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' section of Unsolicited ISI Report Form, ensure to indicate:**

- If DAPT indication is TIA, please provide ABCD2 score (if known)

- If DAPT indication is minor ischemic stroke, please provide NIHSS score (if known).
- Previous history of bleeding and diagnosis
- Previous history of ICH with details: onset date, exact diagnosis and risk factors

**In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' section of Unsolicited ISI Report Form, ensure to collect:**

IRM / Scanner

**REPORTER INFORMATION:**

☐ Physician; ☐ Patient; ☐ Other, please specify.....

Name and title:.....

Affiliation:.....

Address:.....

Phone number:..... E-mail:.....

Date of report (dd/mm/yy):.....

Signature: .....

# Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.