Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Clopidogrel
Pharmacotherapeutic group(s) (ATC Code)	Platelet aggregation inhibitors excl. heparin (B01AC04)
Marketing Authorisation Holder/Applicant	Pharmathen S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Grepid 75 mg film-coated tablets
Marketing authorisation procedure	Centralised ([redacted])
Brief description of the product	**Chemical class:** Platelet aggregation inhibitors excl. heparin
	Summary of mode of action: 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 P2Y12 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. Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.
	Important information about its composition: Each film-coated tablet contains 2.6 mg of lactose monohydrate
Hyperlink to the Product Information	Refer to module 1.3.1

Indication(s) in the EEA	**Current:** Secondary prevention of atherothrombotic events Clopidogrel is indicated in: • Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. • Adult patients suffering from acute coronary syndrome: - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA). - ST segment elevation acute myocardial infarction, in combination with ASA in patients undergoing percutaneous coronary intervention (including patients undergoing a stent placement) or medically treated patients eligible for thrombolytic/fibrinolytic therapy. In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS) Clopidogrel in combination with ASA is indicated in: - Adult patients with moderate to high-risk TIA (ABCD2 score ≥ 4) or minor 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.
	Proposed: N/A
Dosage in the EEA	**Current:** <u>Adults and elderly</u> Clopidogrel should be given as a single daily dose of 75 mg. 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.
	Proposed: N/A
Pharmaceutical form(s) and strengths	**Current:** 75 mg film-coated tablets
	Proposed: N/A

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

Based on the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2), this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10(1) of Directive 2001/83/EC, since there is an RMP summary of the originator product, Plavix (Sanofi Winthrop Industrie), published in EMA site.

Part II: Module SVIII - Summary of the safety concerns

Grepid 75 mg film-coated tablets is generic formulation of Plavix (Sanofi Winthrop Industrie).

The summary of safety concerns for Grepid 75 mg film-coated tablets is aligned with the originator and is presented in Table SVIII.1.

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 questionnaires for safety concern: Major bleeding

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed for Grepid 75 mg film-coated tablets.

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.

Annex 4 - Specific adverse drug reaction follow-up forms

TARGETED FOLLOW-UP QUESTIONNAIRE FOR 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)

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)

- **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 $ABCD^2$ 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