Summary of the Risk Management Plan (RMP) for Plavix®

Plavix® (Clopidogrel Hydrogen Sulfate)
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Plavix® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Plavix® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of Plavix®.

I. THE MEDICINE AND WHAT IT IS USED FOR

PLAVIX 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 indications). It contains clopidogrel as the active substance and it is given by oral route.

Further information about the evaluation of PLAVIX's benefits can be found in PLAVIX's (EMEA/H/C/000174) EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpages:

https://www.ema.europa.eu/en/medicines/human/EPAR/plavix

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of PLAVIX together with measures to minimize such risks and the proposed studies for learning more about PLAVIX's risks, are outlined in the next sections.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (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 PLAVIX are risks that need special risk management activities to further investigate or minimize 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 PLAVIX. 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 (eg, on the long-term use of the medicine);

Table 1 - List of important risks and missing information (PLAVIX)

Important identified risk	Major bleeding (including ICH[a])
Important potential risk	None
Missing information	None

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

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

II.B Summary of important risks

Table 2 Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important identified risk: Major bleeding (including ICH[a])

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Evidence for linking the risk to the medicine	Postmarketing experience, clinical and epidemiological data, and literature.
Risk factors and risk groups	Generally, treated patients are at risk of increased bleeding in certain clinical circumstances, such as trauma, surgery or other pathological conditions. In some indications (eg, ACS), clopidogrel may be prescribed together with other antiplatelet agents or other medicinal products acting on hemostasis, which may increase the propensity or intensity of bleeding in these circumstances. Thus, special warnings and precautions for use are necessary for co-administration of clopidogrel with ASA, GP IIb/IIIa inhibitors, thrombolytics or heparin. Concomitant use of clopidogrel with OAC (eg, warfarin) is not recommended. Concomitant use of SSRIs should be undertaken with caution, since they can increase the propensity to bleed due to their spectrum of action on platelets. Non-steroidal anti-inflammatory drugs, including COX-2 inhibitors, should also be co-administered with caution, since they may increase the propensity to bleed, especially occult gastrointestinal bleeding. Overall, patients concomitantly treated with any drugs known to cause bleeding can also be considered at risk due a potential additive effect with clopidogrel. <u>Very elderly patients:</u> **In ACTIVE A study,** in very elderly patients who are at greater risk for bleeding, as in the overall ACTIVE A population, the rate of adjudicated major bleeding was greater in the clopidogrel in combination with ASA group than in the ASA alone group (8.32% versus 5.98%); this increase was also noted for severe bleeding (6.19% versus 4.22%). Overall, the rates of major bleeding, severe bleeding, and ICH with clopidogrel in combination with ASA compared with ASA alone was independent of all relevant baseline demographic or previous

	history covariates (including bleeding risk or previous stroke, CHADS2 score, and geographic region subgroups). **In POINT and CHANCE Pool** analysis, a limited number of very elderly patient experienced ICH, reason why pooled data have been used for determining the risk of bleeding in population ≥75 years of age. No difference between treatment group regarding frequency was identified in this population. **Table 2a - Intracranial hemorrhage, CHANCE and POINT Pooled Analysis Dataset (ITT)** **Age (N Exposed patients)** / **No. of ICH in the clopidogrel + ASA group** / **No. of ICH in the ASA group** / **Total** 75-84 years (N = 1618): 4 (0.5%; 4/781) / 3 (0.4%; 3/837) / 7 (0.4; 7/1618) ≥85 years (N = 361): 1 (0.5%; 1/201) / 0 (0,0%; 0/160) / 1 (0.3; 1/361) Total (N = 10 051): 13 (0.3%; 13/5016) / 11 (0.2%;11/5035) / 24 (0.2; 24/10 051) ASA: Acetyl Salicylic Acid; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke. **Off-label use:** No clinical benefit of clopidogrel has been demonstrated outside of approved indications while patients remained at risk of bleeding.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.3, 4.4 and 4.8 of PLAVIX SmPC. PL: Labeled in sections 2, 3 and 4 of PLAVIX PL. **Additional risk minimization measures:** 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.

ACTIVE: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Event; ACS: Acute Coronary Syndrome; CHADS: Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event; COX: Cyclo-Oxygenase; DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; ITT: Intent To Treat; mIS: Minor Ischemic Stroke; OAC: Oral Anti-Coagulant; PL: Package Leaflet; POINT: Platelet-Oriented Inhibition In New Transient Ischemic Attack And Minor Ischemic Stroke; SmPC: Summary of Product Characteristics; SSRI: Selective Serotonin Reuptake Inhibitor; TIA: Transient Ischemic Attack.

II.C Post-authorization development plan

II.C.I Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of PLAVIX.

II.C.II Other studies in post-authorization development plan

There are no studies required for PLAVIX.