Summary of the Risk Management Plan (RMP) for EFIENT 5 mg and EFIENT 10 mg

(INN: Prasugrel Hydrochloride)

Marketing Autorisation Holder:

SUBSTIPHARM (Centralised European Procedure - EMEA/H/C/000984)

LEMAN (National procedure 59136 01 – Efient 5mg and 59136 02 - Efient 10mg)

RMP version 13.0

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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 minimise them.

The RMP summary of EFIENT 5 and 10mg 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 médicament" 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 EFIENT in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. LEMAN is fully responsible for the accuracy and correctness of the content of the published summary RMP of EFIENT.

1. THE MEDICINE AND WHAT IT IS USED FOR

Efient, co-administered with acetylsalicylic acid (ASA), is authorised for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e., unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention. It contains prasugrel as the active substance and it is given by film-coated tablets available in 5 mg and 10 mg strength.

Further information about the evaluation of EFIENT's benefits can be found in EFIENT'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/efient.

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

Important risks of Efient together with measures to minimise such risks and the proposed studies for learning more about Efient'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 the case of EFIENT, these measures are supplemented with a targeted follow-up form regarding the risk of cancer in order to better characterize the potential important risk of colorectal cancer.

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.

2.1 List of Important Risks and Missing Information

Important risks of Efient are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Efient. 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 1. List of Important Risks and Missing Information

Summary of Safety Concerns (from Part II: Module SVIII)	
Important Identified Risks	• None
Important Potential Risks	• Colorectal Cancer
Important Missing Information	• None

2.2 Summary of Important Risks

Table 2. 2 Important identified risk with corresponding risk minimization activities: **Colorectal cancer**

Colorectal cancer	
Evidence for linking the risk to the medicine	Colorectal cancer was included as an “important potential risk” from the prasugrel Risk Management Plan (RMP) V6, approved on 29-Oct-2012, at the CHMP’s request based upon the numerical imbalance in colorectal cancers between treatment groups seen in the pivotal trial TRITON TIMI-38 (H7T-MC-TAAL), with the majority of colorectal cancer cases detected during the investigation of bleeding or anaemia. The PV activity to address this potential risk was the data collection and analysis from the post-authorisation measure study TRILOGY ACS (H7T-MC-TABY – FUM 008), a large phase 3 study in ACS patients medically managed without revascularization. As reported to the CHMP with FUM 8 submitted in October 2012 (CHMP outcome 29 January 2013; EMA/54704/2013), in TABY study, there were no significant treatment differences in the incidence of subjects with new, non-benign neoplasms (prasugrel, 82/4554 [1.80%] versus clopidogrel, 78/4551 [1.71%]; p=0.786). As was seen in TAAL study, in TABY study, there were numerically more colorectal cancers in the prasugrel group (14 versus 6), and investigation of gastrointestinal (GI) bleeding or anaemia led to the discovery of the majority of these cases (15 of 20). As reported with FUM 8 study, the colorectal cancers diagnosed in the prasugrel subjects in TABY tended to occur in younger patients and were less likely to be metastatic at the

	time of diagnosis than those diagnosed in clopidogrel subjects (14% vs. 67%) suggesting earlier detection of cancer. Furthermore, independent of the colorectal cancers detected, there were higher rates of gastrointestinal (GI) bleeding and anaemia among the prasugrel group during the study (gastrointestinal haemorrhagic disorders - prasugrel 4.82%, clopidogrel 2.73%, $p<0.001$; anaemia - prasugrel 2.57%, clopidogrel 1.82%, $p=0.013$). It was concluded that the higher rate of colorectal cancer seen in the prasugrel group was largely attributed to a higher detection rate due to the investigation of GI bleeding or anaemia, with a greater number of malignancies detected at an earlier stage in the prasugrel-treated group compared with the clopidogrel-treated group. The MAH concluded that although the preponderance of the data support that prasugrel is not a specific tumour promoter and offer support for the detection bias hypothesis, colorectal cancer remains an important potential risk in the RMP (as concurred by the CHMP following assessment of FUM 8: “The study confirmed the previous important potential risk of colorectal cancer. The majority of these cancers were discovered during the investigation of GI bleedings.” However, the CHMP acknowledged that the TRILOGY ACS trial was not powered to address this safety signal, and therefore cannot be considered to be conclusive. Then, Lilly submitted an updated RMP version 7.0, in order to address the CHMP’s assessments issues following RMP version 6.0 assessment (29 January 2013; EMA/54806/2013): “The MAH should clarify how they would further assess the issue of colorectal cancers. In addition, the MAH should explain how they will investigate the ascertainment bias associated with colorectal cancers.” To reach this issue, Lilly addressed a briefing document entitled “feasibility of using additional data sources to gain further insuight into the potential risk of colorectal cancer in patients treated with prasugrel, and the ascertainment bias associated with colorectal cancer” Two potential approaches were analysed – prospective randomised clinical trials (RCT) and a retrospective database study design and Lilly concluded that neither prospective clinical trials nor retrospective observational methods were able to meaningfully further understanding of any association

	between prasugrel and colorectal cancer, including the issue of detection bias. Lilly has also addressed the CHMP/PRAC's request to further investigate the ascertainment bias associated with colorectal cancer. Based on results of this investigation (i.e. review of the literature identifying detection bias issues with anticoagulant medications, and a new database study finding an increased association with cancer and clopidogrel and warfarin, despite no known association of cancer), the MAH concluded that the evidence was consistent with detection bias related to an increased risk of GI bleeding with prasugrel rather than to any causal or promotional effect of prasugrel on colorectal cancer. It was concluded that despite this conclusion, with regard the CHMP request, colorectal cancer will remain an important potential risk and will continue to be monitored.
Risk factors and risk groups	Risk factors for colorectal cancer include >50 years of age; African-Americans; personal or family history of colorectal cancer or polyps; inflammatory intestinal conditions such as ulcerative colitis and Crohn's disease; inherited syndrome may include familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer also known as Lynch syndrome; sedentary lifestyle; obesity; and diabetics, smokers, heavy alcohol users and radiation therapy directed at the abdomen may have an increased risk. There are no known patient characteristics relevant to the risk of colorectal cancer with prasugrel treatment
Risk minimisation measures	Specific follow-up form for colorectal cancer
Additional pharmacovigilance activities	None

2.3 Post-Authorisation Development Plan

2.3.1 Studies Which Are Conditions of the Marketing Authorization

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

2.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Efient.

REFERENCES

None.