EU Risk Management Plan for EFIENT 5 mg and EFIENT 10 mg

(INN Prasugrel Hydrochloride)

Data lock point for this RMP	30 SEP 2023	RMP Version number	Version 13.0
Date of final sign off	22-Jan-2024		

Rationale for submitting an updated RMP:

Prasugrel was co-developed by Eli Lilly and Daiichi Sankyo. The marketing authorisation for prasugrel was transferred from Eli Lilly to Daiichi Sankyo Europe GmbH on 10 DEC 2015 (commission decision). The last RMP version maintained by Eli Lilly was Number 11 which was also used by Daiichi-Sankyo's when marketing authorisation was transferred. There was a version 12 that was RMP created by Daiichi Sankyo, however this was not approved by the EMA. DAIICHI finally cancelled this V12.0.

A new version 13 was now prepared by Substipharm, as successing the previous RMP version 12 created by Daiichi Sankyo in order:

- Update the name of the MAH as the EFIENT 5 mg and 10 mg marketing authorisations have been transferred from DAIICHI SANKYO to SUBSTIPHARM on 29-Sep-2022
- to align content and format with new requirements according to GVP Module V Rev. 2, update spontaneous data of specific sections to DLP 30 Sep 2023.
- removal of a region-specific additional risk-minimisation activity i.e. educational materials.

Summary of significant changes in this RMP:

The following paragraph describes changes from the previous Prasugrel EU RMP version 11.

- **Part II: Safety specification**. The addition of the indications for prasugrel.
- **Removal of the part II, Module SII PART II: MODULE SII-NON-CLINICAL PART OF THE SAFETY SPECIFICATION**: According to the Guidance EMA/164014/2018 Rev.2.0.1, post-authorisation, this section would only be expected to be updated when new non-clinical data impact the list of safety concerns. Safety concerns identified on the basis of non-clinical data which are no longer relevant and/or have not been confirmed when sufficient relevant post-marketing experience and evidence are gathered, can be removed from the list of safety concerns. As there were no new non-clinical data since RMP V11.0 that would affect the list of safety concerns, this part is not expected for the RMP V13.0.

- **Removal of the part II**, **MODULE SIII: CLINICAL TRIAL EXPOSURE:** According to the Guidance EMA/164014/2018 Rev.2.0.1, in the absence of new significant clinical trial exposure data, this section does not need to be updated. As there were no new clinical data since RMP V11.0, this section is not applicable.
- **Restructuration of the part II, MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS** in order to comply with the EMA RMP guidance EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2
- **Removal of the part II**, **MODULE SV: PART II: MODULE SV POST-AUTHORISATION EXPERIENCE:** According to the Guidance EMA/164014/2018 Rev.2.0.1, for post-marketing RMP updates, this section should be updated only when the cumulative post-marketing exposure changes to a degree where the considerations on the risk evaluation need also to be updated (e.g. population exposed in a new indication). As EFIENT exposure data do not change to this degree, this section is not applicable.
- **Removal of safety concerns and justification of changes in the PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS** in order to comply with the EMA RMP guidance EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2 and to answer to the PRAC requests presented within the procedure EMEA/H/C/PSUSA/00002499/201702 assessment report and within the procedure EMEA/H/C/PSUSA/00002499/202102.
- **UPDATE OF PART II. MODULE SVIII SUMMARY of the Safety Concerns** in order to comply with the EMA RMP guidance EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.
- **UPDATE OF PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES):** withdrawal of the specific follow-up forms except for cancer.
- **UPDATE OF PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)** according to the new list of safety concerns and removal of additional risk minimisation activities
- **UPDATE OF SUMMARY OF THE RISK MANAGEMENT PLAN** according to the new list of safety concerns, removal of specific follow-up forms except for cancer and removal of aditional risk minimisation activities
- **UPDATE OF THE APPENDICES:**
  - Annex III: There are no ongoing studies at present and thus table has been deleted.
  - Annex IV: Removal of the specific follow-up forms for Allergy, Angioedema, Blood and Bone Marrow Disorders, Cerebral Haemorrhage, General Bleeding, Hepatic Disorders, Photosensitivity, Procedural Bleeding and Thrombotic Disorders
  - Annex IV: Removal of the additional risk minimisation measures

Other RMP versions under evaluation: NA

Details of the currently approved RMP for Prasugrel

RMP Version number: 11.0

Approval date: 30-Apr-2015

Procedure number: EMEA/H/C/000984

Substipharm QPPV name:

Caroline NAVARRE

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV.

TABLE OF CONTENTS

LIST OF TABLES

PART I PRODUCT(S) OVERVIEW

Table Part I.1 Product Overview

Active substance(s) (INN or common name):	Prasugrel Hydrochloride (INN prasugrel)
Pharmacotherapeutic group(s) (ATC Code):	Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin Prasugrel B01AC22
Name of Marketing Authorisation Holder or Applicant:	Substipharm
Medicinal products to which this RMP refers:	2
Invented name(s) in the European Economic Area (EEA):	EFIENT 5 mg EFIENT 10 mg Both products are refered to EFIENT in the rest of the document as there are no differences in the safety profile and risk management according to the dosage
Marketing authorisation procedure :	Centralised procedure
Brief description of the product:	**Chemical class:** Thienopyridine
	Summary of mode of action: Prasugrel hydrochloride is an inhibitor of platelet activation and aggregation mediated by the platelet P2Y12 ADP receptor. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke
	Important information about its composition: (e.g. origin of active substance for biologicals, relevant adjuvants or residues for vaccines): Not applicable
Hyperlink to the Product Information:	Please refer to eCTD section 1.3.1
Indication(s) in the EEA:	Current: Efient, co-administered with acetylsalicylic acid (ASA), is indicated 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 (PCI).

Dosage in the EEA	Current: *Adults* One single 60 mg loading dose and then continued 10 mg daily. Patients taking Efient should also take ASA 75 mg or 325 mg daily.
Pharmaceutical form(s) and strengths	Current: Film-coated tablets; 5 mg and 10 mg.
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin), EEA = European Economic Area; INN = International Nonproprietary Names; mg= milligrams; NSTEMI = non-ST elevated myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina.

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indications:

Prasugrel is indicated for the prevention of atherothrombotic events in adult 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 (PCI).

SI.1 Acute Coronary Syndrome (ACS)

SI.1.1 Epidemiology of the Disease

Acute coronary syndromes (ACS) are a major cause of death and disability in the developed countries of the world. Several epidemiological studies from European countries have led to important conclusions regarding the prevalence, the type of presentation, and the treatment of ACS in western Europe. These studies also showed geographic differences and heterogeneity in the care and mortality in patients with ACS throughout Europe.

In the European Union (EU), incidence is reported as being 45.8 per 10,000 in the United Kingdom (UK), 26 per 10,000 in Spain, 26.4 per 10,000 in France, 44.3 per 10,000 in Italy, 48.4 per 10,000 in Germany, 39 per 10,000 in Greece and 21.5 per 10,000 in 2012 in the Czech Republic (Taylor et al. 2007 [30]; Papathanasiou et al. 2004 [24]; Tousek et al. 2014 [31]). In an Italian study using hospital admissions data from 7 community hospitals for the period from 01 January 2008 to December 2008 (n=2,758,872 total patients), the incidence of acute coronary syndrome (ACS) hospitalisation was 2.6% (Maggioni et al. 2013 [16]). In the southwest region of Ireland (total population n=620,525), the 2006-2007 incidence of ACS admission was 149.2 per 100,000 (Cronin et al. 2012 [8]). By comparison, in a United States (US) community-based cohort study, the incidence rate of acute myocardial infarction (MI) in 2008 was 208 per 100,000 person-years after adjusting for age and sex (Yeh et al. 2010 [**Erreur ! Source du renvoi introuvable.**]). Finally, a cohort study in Australia reported an age- and sex-adjusted incidence rate of MI in 2010 of 251 per 100,000 Person years (Wong et al. 2013 [35]).

In the UK, France, Germany, Italy, and Spain combined, there were more than 1 million ACS events reported in 2005 (Sanofi-Aventis 2006 [WWW] [26]). It is estimated that in Spain alone, in the year 2013 there will be 115,752 ACS cases (Dégano et al. 2013). In the US in 2010, there were 1.1 million cases of ACS noted in hospital discharge records (Mozaffarian et al. 2015 [22]). The proportion of ACS cases classified as having ST-segment elevation myocardial infarction (STEMI) appears to be declining over time and ranges from approximately 29% to 47% depending on the methods used to identify patients and the age of the population under consideration (Mozaffarian et al. 2015 [22]).

SI.1.2 Risk Factors for the Disease

ACS is a manifestation of CHD (coronary heart disease) and usually a result of plaque disruption in coronary arteries (atherosclerosis). The common risk factors for the disease are smoking, hypertension, diabetes, hyperlipidemia, male sex, physical inactivity, family obesity, and poor nutritional practices. Cocaine abuse can also lead to vasospasm. A family history of early myocardial infarction (55 years of age) is also a high-risk factor (Singh A et al 2021 [28]).

SI.1.3 Mortality and Morbidity in Target Indication

In a European study, the mortality rate of ACS ranged from 4.0 to 4.9 per 100 (Mandelzweig et al. 2006 [18]). In Spain, 824 patients admitted to a hospital for ACS between 2009 and 2010 with an average age of 65.84 years of age and who were predominantly male (73.5%) had a mortality rate of 4.2% (37 of 824 patients). Most deaths occurred within 48 hours of the patients being admitted (19 patients), followed by 7 patient deaths between Day 2 and Day 7, and a further 9 cases after Day 7 (Camprubi et al. 2012 [6]). In a study in New Zealand, overall mortality for ACS and STEMI in 2001 to 2002 was 5.0 per 100, with significant increases as the population ages. In this study, the mortality rate was 2.5 per 100 for those under 60 years of age, 3.1 per 100 for those 61 to 74 years of age, 8.5 per 100 for those 75 to 84 years of age, and 31.6 per 100 for those over 85 years of age (Tang et al. 2006 [29]). In an Italian study of 2046 ACS patients, the in-hospital mortality rate was found to be 5.7% (Vagnarelli et al. 2015 [32]). A study of 31,689 consecutive STEMI patients from 22 Finnish hospitals reported an in-hospital mortality rate of 11.2% (Kytö et al. 2015 [14]). A more recent meta-analysis identified 12 studies with 7169 women and 21,767 men with STEMI treated with percutaneous coronary intervention (PCI) and found an unadjusted 1-year all-cause mortality of 8.8% among women and 5.5% among men (Pancholy et al. 2014 [23]). In a US study using 1999 to 2008 hospital admissions for myocardial infarction (n=46,086 total patients), 30-day mortality was 7.8% in 2008 (Yeh et al. 2010 **[Erreur ! Source du renvoi introuvable.]**).

SI.1.4 Demographic Profile of Target Population

Acute coronary syndrome occurs predominantly in males and in patients 65 years of age and older. In a Swiss study of ACS patients, mean age ranged from 65.9 to 63.5 in males and 71.3 to 71.4 in females; 72.8% of the patients in this study were males (Erne et al. 2012 [9]). In a prospective study in Finland, the mean age was 65.6 years, and 30.1% were female (Allonen et al. 2012 [1]). In a French study of ACS patients, 65.4% were males (Béjot et al. 2011 [3]). In an international study of 27 countries, 15,871 patients with ACS were enrolled from 2008 to 2010. The mean age of the group was 60.2 years, 19.34% were female, 88.36% were White, 7.76% were Asian, 2.31% were Black, and 1.56% were other races. In an Italian study of ACS patients (n=2046), the mean age was 71.6 years with 64.5% of the patient population being male (Vagnarelli et al. 2015 [32]).

In a US study using 1999 to 2008 hospital admissions for MI (n=46,086 total patients; n=4068 patients in 2008), the mean age was 69 years in 2008, and was comprised of 62% males. Race breakdown in this study was: 67% White, 12% Asian, 7% Black, 10% Hispanic, and 4% Other/Unknown (Yeh et al. 2010 **[Erreur ! Source du renvoi introuvable.]**).

SI.1.5 Main Treatment Options

The current standard of care for patients with ACS includes dual antiplatelet therapy with either aspirin and a thienopyridine (that is, prasugrel or clopidogrel), or aspirin and ticagrelor, in both the

acute phase and chronic phase (up to 12 months) of treatment. Early studies in the setting of PCI established the superiority of dual antiplatelet therapy with aspirin and a thienopyridine over oral anticoagulation and aspirin for prevention of major adverse cardiovascular events (MACE) (Leon et al. 1998 [15]), but the CLopidogrel ASpirin Stent International Cooperative (CLASSICS) study demonstrated better tolerability of clopidogrel over ticlopidine (Bertrand et al. 2000 [4]). The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study established the benefit of clopidogrel plus aspirin versus aspirin alone for up to 1 year in subjects with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) (reducing the incidence of cardiovascular [CV] death/MI/stroke), including those who underwent PCI (Mehta et al. 2001 [**Erreur ! Source du renvoi introuvable.**]). The Phase 3 TRITON-TIMI 38 (TRITON) study compared prasugrel with clopidogrel, both coadministered with acetylsalicylic acid (ASA) and other standard therapy in patients who had ACS with moderate- to high-risk UA, NSTEMI, or STEMI and were managed with PCI. Results from TRITON demonstrated that treatment with prasugrel in patients across the full spectrum of ACS with planned PCI, compared with clopidogrel used at the standard approved dose, resulted in a statistically significant reduction in the rate of the primary composite efficacy endpoint (CV death, nonfatal MI, or nonfatal stroke) (Wiviott et al. 2007 [34]). Ticagrelor, coadministered with ASA, is also indicated for the prevention of atherothrombotic events in adult patients with ACS (UA/NSTEMI or STEMI), including patients managed medically, and those who are managed with PCI or coronary artery bypass graft (CABG).

Ticagrelor, in the PLATO study of 18,264 patients with ACS, has been shown to reduce the rate of a combined endpoint of CV death, MI, or stroke compared to clopidogrel, and to reduce the rate of death from vascular causes and the rate of death from any cause compared with clopidogrel (Wallentin et al 2009 [33]).

SI.1.6 Concomitant Medication(s) in the Target Population

Medications taken by patients with ACS who also experience MI include aspirin, warfarin, thienopyridine, heparin, GPIIb/IIIa inhibitors, angiotensin-converting-enzyme (ACE) inhibitors, β-blockers, digoxin, diuretic, inotrope, morphine, lidocaine, amiodarone, nitrate, statin, and fibrate (Hasdai et al. 2002 [13]). Among the medications taken by patients with ACS and congestive heart failure (CHF) are ACE inhibitors, angiotensin receptor blockers, β-adrenergic blocking agents, aldosterone antagonists, lipid-lowering agents, antiplatelet agents, anticoagulant agents, and calcium channel blockers (Gheorghiade et al. 2006 [11]).

SI.1.7 Important Comorbidities Found in the Target Population

Hypertension: Rates of hypertension are mostly consistent across Europe. In a Swiss study (n=33,306), prevalence of hypertension was 65.4% (Erne et al. 2012 [9]). A study in Greece (n=418) found the prevalence of hypertension to be 67.9% at baseline (Andrikopoulos et al. 2012 [2]). In Spain (n=824), the prevalence of hypertension at baseline was 65.78% (Camprubi et al. 2012 [6]). In a cohort in Finland (n=1945), the prevalence of hypertension at baseline was 65.6% (Allonen et al. 2012 [1]). In a French study (n=525,419), prevalence of hypertension at baseline was 38.1% (Béjot et al. 2011 [3]). In Sweden (n=119,786) and the UK (n=391,077), prevalence of hypertension was 45.2% and 47.3%, respectively (Chung et al. 2014 [7]).

In a European study, the relative risk of mortality in subjects with acute MI (hypertension vs. no hypertension) was 1.1 (95% confidence interval [CI]: 1.0, 1.2) (Gustafsson et al. 1998 [12]).

Globally and in North America, mortality rates are similar to those in Europe. In an international study of 27 countries, (n=15,871) prevalence of hypertension was 67.77% at baseline (Schwartz et al. 2012 **[Erreur ! Source du renvoi introuvable.]**). A large international study (GRACE) using data from 14 countries of ACS patients (n=58,767) found the prevalence of hypertension at baseline to be 61.9% (McManus et al. 2012 [19]). In a US study (n=46,086 total patients), prevalence of hypertension at baseline was 76% (Yeh et al. 2010 **[Erreur ! Source du renvoi introuvable.]**). In Canada, prevalence of hypertension among ACS patients >18 years (n=7609) was 60.8% for males and 72.7% for females (Poon et al. 2012 [25]). A more recent international study (IMPROVE-IT) of STEMI (n=5192) and NSTEMI (n=12,952) patients enrolled from October 2005 to July 2010 from 7 regions worldwide (including the US, Canada, Western Europe, Eastern Europe, Malaysia/Singapore/Hong Kong, South America, and Australia/New Zealand) reported the baseline prevalence of hypertension among STEMI patients vs. NSTEMI patients as 48% vs. 67% (overall 61%) (Blazing et al. 2014 [5]). In a US study (n=981), the relative risk of 6-month mortality in all ACS patients (hypertension vs. no hypertension) was 1.1 (95% CI: 0.7, 1.9) (Majahalme et al. 2003 [17]).

Dyslipidaemia: An observational study in Greece (n=418) found the prevalence of dyslipidaemia to be 57.4% at baseline (Andrikopoulos et al. 2012 [2]). In a study in Spain (824 patients), the prevalence of dyslipidaemia was 58.13% at baseline (Camprubi et al. 2012 [6]). In a cohort of consecutive ACS patients in Finland (n=1945), prevalence of dyslipidaemia at baseline was 71.1% (Allonen et al. 2012 [1]). In a UK study (n=155,818), prevalence of dyslipidaemia was 33.8% (Zaman et al. 2014 [37]). In an international study of 27 countries (n=15,871), prevalence of hypercholesterolemia was 72.39% at baseline (Schwartz et al. 2012 **[Erreur ! Source du renvoi introuvable.]**). Another large international study (GRACE) using data from 14 countries of ACS patients (n=58,767) found the prevalence of dyslipidaemia at baseline to be 48.3% (McManus et al. 2012 [19]). Still another large international study of 9406 non-ST-segment elevation ACS patients from 29 countries enrolled in the EARLY-ACS trial reported a baseline prevalence of 57.9% for dyslipidaemia (Mehta et al. 2014 **[Erreur ! Source du renvoi introuvable.]**). In a US study (n=46,086 total patients), prevalence of dyslipidaemia at baseline was 80% (Yeh et al. 2010 **[Erreur ! Source du renvoi introuvable.]**). In Canada, prevalence of dyslipidaemia among ACS patients >18 years of age at baseline was 59.3% for males and was 54.5% for females (Poon et al. 2012 [25]).

***Diabetes*:** Prevalence of diabetes in Europe ranges from 22% to 34%. In a Swiss study (n=33,306), prevalence of diabetes was 22.5%; 22.0% of these patients were obese (Erne et al. 2012 [9]). In a study in Greece (n=418), prevalence of diabetes mellitus was 27.5% at baseline (Type 1: 1.9% and Type 2: 25.6%) (Andrikopoulos et al. 2012 [2]). In a study in Spain (n=824), prevalence of diabetes at baseline was 33.86% (Camprubi et al. 2012 [6]). In a cohort of consecutive ACS patients in Finland (n=1945), prevalence of diabetes mellitus at baseline was 22.8% (Allonen et al. 2012 [1]). In a French study of ACS patients (n=525,419), prevalence of diabetes mellitus at baseline was 19.5% (Béjot et al. 2011 [3]). In Sweden (n=119,786) and the UK (n=391,077), prevalence of diabetes was 22.7% and 17.6%, respectively (Chung et al. 2014 [7]).

Globally and in North America, rates of diabetes in ACS patients are similar to those in Europe. In an international study of 27 countries (n=15,871), prevalence of diabetes was 24.46% at baseline (Schwartz et al. 2012 **[Erreur ! Source du renvoi introuvable.]**). The GRACE trial, a large, international study using data from ACS patients in 14 countries (n=58,767) found the prevalence

of diabetes at baseline to be 25.1% (McManus et al. 2012 [19]). In another more recent international study (IMPROVE-IT) of STEMI (n=5192) and NSTEMI (n=12,952), patients enrolled from October 2005 to July 2010 from 7 regions worldwide (including the US, Canada, Western Europe, Eastern Europe, Malaysia/Singapore/Hong Kong, South America, and Australia/New Zealand) and reported the baseline prevalence of diabetes among STEMI patients vs. NSTEMI patients as 19% vs. 30% (overall 27%) (Blazing et al. 2014 [5]). In a US study (n=1321), prevalence of diabetes was 38.8% (Milani et al. 2012 [21]). In Canada, prevalence of diabetes among ACS patients >18 years (n=7609) was 28.5% for males and 31.4% for females (Poon et al. 2012 [25]). In a global study including 14 countries, frequency of death was 11.7% in diabetics with STEMI (n=1141) compared with 6.4% in non-diabetics with STEMI (n=262) and 6.3% in diabetics with NSTEMI (n=1271) compared with 5.1% in non-diabetics with NSTEMI (n=3454); among patients with unstable angina (UA) (non-diabetic patients = 4499; diabetic patients = 1489), mortality was 3.9% in diabetics compared with 2.9% in non-diabetics (Franklin et al. 2004 [10]).

***Previous Myocardial Infarction*:** In Europe, prevalence of previous MI was 20.4% in Finland (n=1945) (Allonen et al. 2012 [1]), 22.4% in Sweden (n=119,786), and 18.3% in the UK (n=391,077) (Chung et al. 2014 [7]). In an international study of 27 countries (n=15,871), prevalence of previous MI was 15.58% at baseline (Schwartz et al. 2012 [**Erreur ! Source du renvoi introuvable.**]). In a global study including 25 countries and 10,484 patients with a discharge diagnosis of ACS, prevalence of previous MI was 22% in those with STEMI, and was 36% in those with NSTEMI (Hasdai et al. 2002 [13]). A more recent international study including 7 regions (US, Canada, Western Europe, Eastern Europe, Malaysia/Singapore/Hong Kong, South America, and Australia/New Zealand) reported the prevalence of previous MI among STEMI patients vs. NSTEMI patients as 9% vs. 26% (overall 21%) (Blazing et al. 2014 [5]).

***Congestive Heart Failure*:** In a study in Spain (n=824), prevalence of heart failure at baseline was 4.13% (Camprubi et al. 2012 [6]). In Sweden (n=119,786) and the UK (n=391,077), prevalence of heart failure was 9.7% and 5.3%, respectively (Chung et al. 2014 [7]). In an international study of 27 countries (n=15,871), CHF was 15.46% at baseline (Schwartz et al. 2012 [**Erreur ! Source du renvoi introuvable.**]). Another large international study (GRACE) using data from ACS patients >18 years in 14 countries between the years 2000 and 2007 (n=58,767) found the prevalence of CHF at baseline to be 10.0% (McManus et al. 2012 [19]). Still another international study of 9406 non-ST-segment elevation ACS patients from 29 countries enrolled in the EARLY-ACS trial reported a baseline prevalence of 12.2% for heart failure (Mehta et al. 2014 [**Erreur ! Source du renvoi introuvable.**]). In a US study (n=46,086 total patients), prevalence of chronic heart failure at baseline was 8% (Yeh et al. 2010 [**Erreur ! Source du renvoi introuvable.**]). In Canada, among ACS patients >18 years of age (n=7,609), prevalence of heart failure at baseline was 9.5% for males and was 13.7% for females (Poon et al. 2012 [25]).

References

1. Allonen J, Nieminen MS, Lokki M, Parkkonen O, Vaara S, Perola M, Kiekkalinna T, Strangberg TJ, Sinisalo J. Mortality rate increases steeply with nonadherence to statin therapy in patients with acute coronary syndrome. *Clin Cardiol*. 2012;35(11):E22-27.
2. Andrikopoulos G, Tzeis S, Mantas I, Olympios C, Kitsiou A, Kartalis A, Kranidis A, Tsaknakis T, Richter D, Pras A, Pipilis A, Lampropoulos S, Oikonomou K, Gotsis A, Anastasiou-Nana M, Triposkiadis F, Goudevenos J, Theodorakis G, Vardas P. Epidemiological characteristics and in-hospital management of acute coronary syndrome patients in Greece: results from the TARGET study. *Hellenic J Cardiol*. 2012;53(1):33-40.
3. Béjot Y, Benzenine E, Lorgis L, Zeller M, Aubé H, Giroud M, Quantin C. Comparative analysis of patients with acute coronary and cerebrovascular syndromes from the national French hospitalization health care system database. *Neuroepidemiology*. 2011;37(3-4):143-152.
4. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation*. 2000;102(6):624-629.
5. Blazing MA, Giugliano RP, Cannon CP, Musliner TA, Tershakovec AM, White JA, Reist C, McCagg A, Braunwald E, Califf RM. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. *Am Heart J*. 2014;168(2):205-212.e1.
6. Camprubi M, Cabrera S, Sans J, Vidal G, Salvado T, Bardaji A. Body mass index and hospital mortality in patients with acute coronary syndrome receiving care in a university hospital. *J Obes*. 2012;287939; Epub 2012 Jul 29.
7. Chung SC, Gedeborg, Nicholas O, James S, Jeppsson A, Wolfe C, Heuschmann P, Wallentin L, Deanfield J, Timmis A, Jernberg T, Hemingway H. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet.* 2014;383:1305-1312. doi.org/10.1016/S0140-6736(13)62070-X
8. Cronin EM, Kearney PM, Kearney PP, Sullivan P, Perry IJ; Coronary Heart Attack Ireland. Registry (CHAIR) Working Group. Impact of a national smoking ban on hospital admission for acute coronary syndromes: a longitudinal study. Clin Cardiol. 2012;35(4):205-209.
9. Erne P, Gutzwiller F, Urban P, Maggiorini M, Keller PF, Radovanovic D. Characteristics and Outcome in Acute Coronary Syndrome Patients with and without Established

Modifiable Cardiovascular Risk Factors: Insights from the Nationwide AMIS Plus Registry 1997-2010. *Cardiology*. 2012;121(4):228-236.

10. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, Marre M, Steg PG, Gowda N, Gore JM, GRACE Investigators. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. *Arch Intern Med*. 2004;164(13):1457-1463.
11. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, Sadowski Z, Golba KS, Prior DL, Rouleau JL, Bonow RO. Navigating the crossroads of coronary artery disease and heart failure. *Circulation*. 2006;114(11):1202-1213.
12. Gustafsson F, Kober L, Torp-Pedersen C, Hildebrandt P, Ottesen MM, Sonne B, Carlsen J. Long-term prognosis after acute myocardial infarction in patients with a history of arterial hypertension. TRACE study group. *Eur Heart J*. 1998;19(4):588-594.
13. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, Fioretti PM, Simoons ML, Battler A. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J*. 2002;23(15):1190-1201.
14. Kytö V, Sipilä J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multihospital nationwide registry study of 31,689 patients). *Am J Cardiol*. 2015;115(3):303-306.
15. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KKL, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339(23):1665-1671.
16. Maggioni AP, Rossi E, Cinconze E, Roggeri DP, Roggeri A, Fabbri G, De Rosa M; ARNO Cardiovascular Observatory. Outcomes, health costs and use of antiplatelet agents in 7,082 patients admitted for an acute coronary syndrome occurring in a large community setting. Cardiovasc Drugs Ther. 2013;27(4):333-340.
17. Majahalme SK, Smith DE, Cooper JV, Kline-Rogers E, Mehta RH, Eagle KA, Bisognano JD. Comparison of patients with acute coronary syndrome with and without systemic hypertension. *Am J Cardiol*. 2003;92(3):258-263.
18. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G, Gitt A, Hasdai D, Hasin Y, Marrugat J, Van de Werf F, Wallentin L, Behar S, Euro Heart Study Investigators. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J*. 2006;27(19):2285-2293.
19. McManus DD, Aslam F, Goyal P, Goldberg RJ, Huang W, Gore JM. Incidence, prognosis, and factors associated with cardiac arrest in patients hospitalized with acute coronary syndromes (the Global Registry of Acute Coronary Events Registry). *Coron Artery Dis*. 2012;23(2):105-112.

20. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA, Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-533.

21. Milani RV, Lavie CJ, Dornelles AC. The impact of achieving perfect care in acute coronary syndrome: The role of computer assisted decision support. *Am Heart J*. 2012;164(1):29-34.

22. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29-e322.

23. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA Intern Med*. 2014;174(11):1822-1830.

24. Papathanasiou AI, Pappas KD, Korantzopoulos P, Leontaridis JP, Vougiouklakis TG, Kiriou M, Dimitroula V, Michalis LK, Goudevenos JA. An epidemiologic study of acute coronary syndromes in northwestern Greece. *Angiology*. 2004;55(2):187-194.

25. Poon S, Goodman SG, Yan RT, Bugiardini R, Bierman AS, Eagle KA, Johnston N, Huynh T, Grondin FR, Schenck-Gustafsson K, Yan AT. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am Heart J*. 2012;163(1):66-73.

26. Sanofi-Aventis. 2006. European commission expands indication for PLAVIX® (clopidogrel bisulfate) offering new option for patients with most severe type of heart attack. Sanofi-Aventis Press Release Sep 7, .2006. Available at: http://en.sanofiaventis.com/press/ppc_13522.asp. Accessed 13 December 2007.

27. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367(22):2089-2099.

28. Singh A, Museedi AS, Grossman SA. Acute Coronary Syndrome. Stats Pearls Publishing. July 2021. Page 1-9.

29. Tang EW, Wong CK, Restieaux NJ, Herbison P, Williams MJA, Kay P, Wilkins GT. Clinical outcome of older patients with acute coronary syndrome over the last three decades. *Age Ageing*. 2006;35(3):280-285.

30. Taylor MJ, Scuffham PA, McCollam PL, Newby DE. Acute coronary syndromes in Europe: 1-year costs and outcomes. *Curr Med Res Opin*. 2007;23(3):495-503.

31. Tousek P, Tousek F, Horak D, Cervinka P, Rokyta R, Pesl L, Jarkovsky J, Wikimsky P; CZECH-2 Investigators. The incidence and outcomes of acute coronary syndromes ina central European country: Results of the CZECH-2 registry. *Int J Cardiol*. 2014;173:204-208.

32. Vagnarelli F, Taglieri N, Ortolani P, Norscini G, Cinti L, Bacchi Reggiani ML, Marino M, Lorenzini M, Bugani G, Corsini A, Semprini F, Nanni S, Tricoci P, De Palma R, Rapezzi C, Melandri G. Long-term outcomes and causes of death after acute coronary syndrome in patients in the Bologna, Italy, area. *Am J Cardiol*. 2015;115(2):171-177.

33. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009; 361:1045-1057.

34. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Antman EM. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357(20):2001-2015.

35. Wong CX, Sun MT, Lau DH, Brooks AG, Sullivan T, worthley MI, Robers-Thompson, KC, Sanders, P. Nationwide trends in the incidence of of acute myocardial infarction in Australia, 1993-2010. *Am J Cardiol*. 2013;112 (2):169-173.

36. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362 (23):2155-2165.

37. Zaman MJ, Stirling S, Shepstone L, Ryding A, Flather M, Bachmann M, Myint PK. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: a cohort study of the Myocardial Ischaemia National Audit Project (MINAP). *Eur Heart J*. 2014; 35(23):1551-1558 doi: 10.1093/eurheartj/ehu039. Epub 2014 Mar 18.

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

According to the the Guidance EMA/164014/2018 Rev.2.0.1; post-authorisation, this section would only be expected to be updated when new non-clinical data impact the list of safety concerns. Safety concerns identified on the basis of non-clinical data which are no longer relevant and/or have not been confirmed when sufficient relevant post-marketing experience and evidence are gathered, can be removed from the list of safety concerns. As there were no new non-clinical data since RMP V11.0 that would affect the list of safety concerns, this part is not expected for the RMP V13.0.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

According to the the Guidance EMA/164014/2018 Rev.2.0.1, in the absence of new significant clinical trial exposure data, this section does not need to be updated. As there were no new clinical data since RMP V11.0, this section is not applicable.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in pivotal clinical studies within the Development Progamme

In the prasugrel clinical development program, the primary population studied was patients with acute coronary syndrome-percutaneous coronary intervention (ACS-PCI). All studies used a core set of exclusion criteria, most of which were intended to ensure safety and minimise risk in a research setting. Because the risk of bleeding is a serious concern with the use of prasugrel, the following conditions are excluded from clinical trials with prasugrel:

Exclusion criteria in pivotal clinical studies within the development programme			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Subjects with active internal bleeding.	Patients who have active pathological bleeding are at increased risk for worsened bleeding on prasugrel.	No	Prasugrel is contraindicated in patients with active clinically significant bleeding. This is described in the contraindications, Warning and Precautions and Interactions 4.3, 4.4 and 4.5 sections of the SmPC

Exclusion criteria in pivotal clinical studies within the development programme			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Subjects using concomitant medications (for example, fibrin-specific fibrinolytic therapy or non-fibrin-specific fibrinolytic).	Patients at increased risk of bleeding due to use of certain concomitant medications or conditions that are associated with increased risk of bleeding.	No	Concomitant administration of medical products may increase risk of bleeding e.g. fibrinolytics. This is described in the Warning and Precautions and interactions sections 4.4 and 4.5 of the SmPC
Subjects with clinical history of haemorrhagic or ischaemic stroke, transient ischaemic attack (TIA), intracranial neoplasm, arteriovenous malformation, or aneurysm.	Patients with a history of TIA or ischemic stroke are at increased risk of stroke on prasugrel.	No	Prasugrel is contraindicated in patients with a history of stroke or transient ischaemic attack (TIA). This is in the contraindications section 4.3 of SmPC

Subjects with International Normalisation Ratio (INR) known to be greater than 1.5, platelet count of less than 100,000/mm3, and anaemia (haemoglobin [Hgb] below 10 g/dL).	Risk of bleeding is a serious concern with the use of prasugrel.	No	Bleeding is an important identified risk with prasugrel, and anaemia due to bleeding may occur. Low platelet count may increase the risk of bleeding.
Subjects receiving or needing to receive oral anticoagulants or other antiplatelet therapy, or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs [cyclooxygenase-1 or -2 inhibitors]).	The increased bleeding risk with chronic NSAID use is well known.	No	These interactions are listed in the sections 4.4 and 4.5 of the SmPC
Subjects with severe hepatic dysfunction (Child Pugh Class C).	The risk of bleeding in these patients could cause confounding results in the clinical trial regarding the assessment of bleeding.	No	This is in the contraindications (*section 4.3*).
Subjects with known allergy to aspirin and commercially available thienopyridines (clopidogrel and ticlopidine)	Use of any thienopyridine within 5 days before enrolment was an exclusion criterion.	No	Listed in section 4.4
Patients with serious acute medical conditions, (cardiogenic shock, Class IV congestive heart failure [CHF], refractory ventricular arrhythmia, end-stage renal disease requiring dialysis), patients with uncontrolled hypertension, and patients with conditions associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence.	Patients with a high risk of mortality unlikely to be altered by acute or chronic thienopyridine therapy.	No	Not applicable.

CHF = congestive heart failure; INR = International Normalisation Ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; SmPC = summary of product characteristics; TIA = transient ischaemic stroke

Exclusion Criteria which will remain as Contraindications	
Criteria	**Implications for target population**
History of stroke or transient ischaemic attack (TIA)	Patients with a history of TIA or ischemic stroke are at increased risk of stroke on prasugrel.
Active pathological bleeding	Patients who have active pathological bleeding are at increased risk for worsened bleeding on prasugrel.
Hypersensitivity to the active substance or to any of the excipients	In patients known to be hypersensitive to prasugrel or who have a known allergy to other thienopyridines (clopidogrel and ticlopidine), severe allergic reactions may occur.
Severe hepatic impairment (Child Pugh Class C)	Patients with severe hepatic disease are generally at higher risk of bleeding.

SIV.2 Limitations of Adverse Drug Reaction Common to Clinical Trial Development Programs

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, where applicable by indication of use.

SIV.3 Limitations in Respect to Populations Typically Under Represented in Clinical Trial Development Program

Table Part II: Module SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Children	The safety and efficacy of prasugrel has not been established in pediatric patients (that is, patients below age 18). However, there is safety data in the paediatric population in the TADO study (2013-2015). Overall, no new safety findings were identified for prasugrel as monotherapy in this patient population.
Elderly	The elderly subpopulation (that is, patients 65 years of age and older) has been analysed in our clinical trial programme; therefore, the elderly population is not a limitation in the prasugrel clinical trial database.
Pregnant and Breastfeeding women	Case reports have been limited.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with hypertension, dylipidemia, diabetes, CHF, or previous myocardial infarction, history of atrial fibrillation, peripheral arterial disease, and history of peptic ulcer disease • Immuno-compromised patients	<u>Hepatic impairment:</u> No dose adjustment for patients with mild to moderate impaired hepatic function. Pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic impairment have not been studied. A very small number of case reports in patients with preexisting hepatic impairment have been reported during postmarketing experience. Analyses of cases in this population of patients have not identified any new safety issues. The MAH will continue to perform surveillance of spontaneously reported case associated with severe hepatic impairment. <u>Renal impairment:</u> The effects of moderate and end-stage renal disease were assessed in 3 clinical pharmacology studies. The PK of prasugrels active metabolite (AM) and its PD effects are similar in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) and subjects with normal renal function. A very small number of case

Type of special population	Exposure
	reports in patients with preexisting renal impairment have been reported during postmarketing experience. Analyses of cases in this population of patients have not identified any new safety issues, but as noted in the label, patients with renal disease have a higher risk of bleeding. Not limited to prasugrel clinical development programme.
Populations with relevant different ethnic origins	Patients of varying racial and/or ethnic origin have been studied with prasugrel. Asian subjects were studied in Studies TACE and TABY, and no safety concerns related to ethnicity were identified. In Japan Studies J301 and J302, in which lower doses of prasugrel were used, there were also no safety concerns related to ethnicity identified.
Subpopulations carrying relevant genetic polymorphisms	In healthy subjects, patients with stable atherosclerosis, and ACS patients receiving prasugrel, no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 was observed on the PK of prasugrel or its effect on PD.

ACS = Acute Coronary Syndrome; AM = Active Metabolite; CHF = congestive heart failure; CYP = cytochrome P450; MAH = Marketing Authoization Holder; PD = pharmacodynamic; PK = pharmacokinetic

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

According to the Guidance EMA/164014/2018 Rev.2.0.1, for post-marketing RMP updates, this section should be updated only when the cumulative post-marketing exposure changes to a degree where the considerations on the risk evaluation need also to be updated (e.g. population exposed in a new indication). As EFIENT exposure data do not change to this degree, this section is not applicable.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Harm from Overdose

During the clinical development of prasugrel, the highest doses tested were 80-mg loading dose (LD) and 20 mg maintenance dose (MD). During the conduct of Study TAAL, any prasugrel dose greater than the recommended LD (60 mg) and MD (10 mg) was considered an overdose.

At the time of the initial RMP submission, there were no reports noted of subjects who had an overdose of prasugrel. During post-marketing period, there have been reports of patients receiving a dose higher than the recommended LD or MD. None of these cases were fatal due to the overdose.

However, in the case *DE-SUBSTIPHV-200905626*, reported by a physician, a fatal outcome due to pulmonary embolism in a polymedicated male patient treated with EFIENT as the only suspect drug and concomitantly treated with HEPARIN and AAS for acute coronary syndrome and percutaneous coronary intervention was reported. There was no narrative in this case and there was few information regarding the overdose: Indeed, a prescribed overdose was reported in this case, but the dosage of EFIENT was not provided. In addition, there was no confirmation that an overdose was really administered to the patient. In this case, the causal relationship between EFIENT and the pulmonary embolism as evaluated by the physician was not reported ans was assessed as not related from the Company.

If the recommended dose is exceeded, the side effects would likely be mechanism-related, such as increased risk of bleeding.

Potential for Transmission of Infectious Agents

The potential for transmission of infectious agents via ingestion of prasugrel is not considered to be a significant risk. The only animal-sourced material used in the prasugrel tablet formulation is lactose monohydrate as a component of the film coating color mixture. The release testing for the color mixture includes a microbiological specification. The manufacture and packaging of prasugrel hydrochloride tablets is conducted in a manner to control the moisture content of the finished tablets. This, in conjunction with controls on the excipients, minimizes the potential for microbiological concerns with this solid oral dosage form. The water content during stability remains sufficiently low (<0.6%) that microbial growth cannot be sustained. No albumin or other human tissue derived materials are contained in or used during the manufacture of the medicinal product.

Potential for Misuse for Illegal Purposes

The potential for misuse of prasugrel for illegal purposes is not considered to be a significant risk. Prasugrel does not result in central nervous system stimulation or any other symptom that could make it suitable for illegal use.

Potential for Medication Errors

The potential for medication errors with prasugrel is no greater than for most oral medications. The proposed product is for a single indication and without any device involvement. Although there are two dose forms, each is clearly marked and different in color.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

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

The list of safety concerns as submitted within the initial RMP for EFIENT 5 mg and EFIENT 10 mg prepared by Lilly was as follows:

Important Identified Risks

- Intracranial Hemorrhage
- Gastrointestinal Hemorrhage
- Intraocular Hemorrhage
- Epistaxis
- PCI-Related Hemorrhage
- CABG-Related Hemorrhage
- Other Procedure-Related Hemorrhage
- Anemia

Important Potential Risk

- Phototoxicity (Skin or Ocular)
- Drug-Induced Hepatic Injury
- Allergic Reactions
- Thrombocytopenia
- Thrombotic Thromboctyopenic Purpura
- Neutropenia

Important Missing Information

- Concomitant use with fibrinolytics and chronic use of NSAIDs (non-ASA)
- Pediatric population
- Pregnant/Lactating women

- Subjects without clinical manifestation of ACS or with ACS not managed by PCI
- Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory ventricular arrhythmia)
- Subjects with severe hepatic impairment.

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

The list of safety concerns as submitted within the RMP V 11.0 for EFIENT approved on 30-Apr-2015 was as follows:

Important Identified Risks

- Bleeding
    - Intracranial Haemorrhage
    - Gastrointestinal Haemorrhage
    - Intraocular Haemorrhage
    - Epistaxis
    - PCI-Related Haemorrhage
    - CABG-Related Haemorrhage
    - Associated with prasugrel use prior to coronary angiography in NSTEMI patients
    - Other Procedure-Related Haemorrhage
- Hypersensitivity including Angioedema
- Thrombocytopenia
- Thrombotic Thrombocytopenic Purpura

Important Potential Risks

- Drug-Induced Hepatic Injury
- Potential off-label use in patients with prior TIA/stroke
- Colorectal Cancer

Important Missing Information

- Concomitant use with fibrinolytics, other thienopyridines, warfarin, and chronic use of NSAIDs (non-ASA)
- Paediatric population
- Pregnant/Lactating women
- Subjects without clinical manifestation of ACS
- Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory ventricular arrhythmia)
- Subjects with severe hepatic impairment

Safety concerns have to be re-assessed and reclassified as compared with the approved EU-RMP V11 in order to align content and format with new requirements according to GVP mod V rev.2 issued in Dec 2018.

In addition, there was a PRAC request within the procedure EMEA/H/C/PSUSA/00002499/201702 concerning the important potential risk of drug-induced hepatic injury:

- In the PSUSA, DAIICHI-SANKYO conducted a cumulative review of drug induced liver injury (DILI). Overall, the totality of data in this review did not suggest a causal relationship between prasugrel and DILI. The removal of DILI from the safety specification as an important potential risk was endorsed by the PRAC.

Furthermore, through the final assessment report EMEA/H/C/PSUSA/00002499/202102, the PRAC published some recommendations which have to be implemented in this updated RMP.

- PRAC noted that the current approved EU risk management plan (RMP) for Efient was not in line with GVP V rev2.
- In addition, the PRAC analysed the additional Risk Minimisation Measures (aRMM) (i.e. educational material) which contain information on the important identified risk '*Bleeding risk(s) including: intracranial, GI, intraocular, epistaxis, PCI-related, CABG-related, and other procedure-related'* implemented after the authorisation of Efient in 2009 and not updated within the 12 years of marketing experience. The PRAC assessed that the safety profile is well known to healthcare professionals and the risk minimisation measures are likely implemented in routine clinical practice. Moreover, the PRAC assessed that this aRMM does not seem to provide substantial additional information to the SmPC and both format and content seem outdated compared to current standards. Consequently, the MAH was requested to submit via an appropriate procedure an updated RMP including a discussion on the need to maintain the aRMM at the next regulatory opportunity.

Furthemore, it appears that some specific follow-up forms implemented at time of the initial RMP and along the successive updates are no more relevant:

- As described within EFIENT RMP V1.0, submitted by Lilly, Prasugrel-specifically designed follow-up forms were developed to facilitate the collection of relevant scientific/medical data in spontaneous and clinical study AEs associated with prasugrel. They were initially implemented for the risks of *bleeding, epistaxis, intraocular bleeding, anemia, photosensitivity, hepatic abnormalities, allergic reactions, thrombotic thrombocytopenic purpura, thrombocytopenia and neutropenia/leukopenia/agranulocytopenia.*
- In addition, these specific follow-up forms were based upon a list of Surveillance Terms for all Lilly drugs derived from the FDA list of Designated Medical Events subjected to additional surveillance. These terms included *Acute liver failure, Acute respiratory failure, Agranulocytosis, Anaphylaxis, Aplastic anaemia, Congenital anomalies, Hepatitis, Liver necrosis, Malignant hypertension, Seizures, Torsade de Pointes, Toxic epidermal necrosis and Ventricular fibrillation.*
- The list of specific topics monitored by Lilly has evolved along the successive RMP updates up to the RMP V7.0 approved on 22-Apr-2013. They concerned the following topics: *Cerebral Hemorrhage, General Bleeding, Procedural Bleeding, Photosensitivity, Possible Angioedema, Allergic Reaction (the form specifies to include*

relevant exposure and whether an allergist or dermatologist was consulted), Hepatic Disorders, Blood Clotting and Thrombotic Disorders, Cancer/Neoplasm, Blood and Bone Marrow Disorders.

Considering that these specific follow-up forms have initially been implemented to facilitate the collection of information; that EFIENT is approved since 2009 and considering its well-established safety profile, SUBSTIPHARM considered that these follow-up forms can be deleted except for cancer/neoplasm considering the potential risk of colorectal cancer.

Finally, it must be considered that EFIENT was first approved on 25-Feb-2009.

Considering the *Annex 2: HaRP-methodology of harmonising RMPs*, EFIENT is categorised within Domain 2 which concerns, among others, assessment of new RMPs submitted (as part of new applications for marketing authorisation or variations) of products already authorised for a long time (e.g more than 8 years).

In domain 2, an algorithm has been agreed to harmonise the list of safety concerns for such products. This algorithm implies that only those safety concerns are eligible for inclusion that either:

1. have ongoing additional pharmacovigilance activity, or
2. have ongoing additional risk minimisation measure, or
3. have essential targeted questionnaires in place.

All other safety concerns can be removed, unless there is a strong and compelling scientific argument as to why it should remain.

Altogether, these regulatory requirements highlight the need to re-assess and reclassify the safety concerns to present within EFIENT RMP.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

As compared with EFIENT RMP V11.0, the following safety concerns can be removed:

Important identified risks

- **Bleeding**
    - Intracranial Haemorrhage
    - Gastrointestinal Haemorrhage
    - Intraocular Haemorrhage
    - Epistaxis
    - PCI-Related Haemorrhage
    - CABG-Related Haemorrhage
    - Associated with prasugrel use prior to coronary angiography in NSTEMI patients
    - Other Procedure-Related Haemorrhage

As stated by the PRAC, the risk of bleeding is well-known to healthcare professionals and appropriate measures to manage the risk of bleeding are likely implemented in routine clinical practice. Moreover, the PRAC assessed that the implemented aRMM on the important

identified risk of bleeding does not seem to provide substantial additional information to the SmPC.

The additional risk minimization measures which have been implemented regarding this risk consisted in educational material to ensure that prescribers are appropriately informed about this risk through labelling including:

- A copy of SmPC
- Emphasis that:
  - Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg;
  - Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age;
  - If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5mg should be prescribed;
  - Patients weighing < 60 kg should have a reduced maintenance dose of 5mg.

In addition, regarding the bleeding Risk Associated with Prasugrel use Prior to Coronary Angiography in NSTEMI Patients, a Direct Healthcare Professional Communication (DHPC) was distributed in all EU countries where prasugrel is marketed if approved by the local National Competent Authority (NCA) (the DHPC distribution has been completed in all EU Member States).

The risk of bleeding is well addressed within EFIENT SmPC and patient's leaflet. It also contains specific information for the particular populations of patients older than 75 years-old and with a weight below 60 kgs or in case of coronary angiography.

Consequently, SUBSTIPHARM considered that the educational material related to the risk of bleeding and the different bleeding specific follow-up forms can be deleted.

- **Hypersensitivity including Angioedema**

The risk of hypersensitivity is well-known to healthcare professionals and the management care of such reactions is well implemented in routine clinical practice. The risk is addressed within EFIENT SmPC and patient's leaflet.

Consequently, SUBSTIPHARM considered that the allergy and angioedema targeted questionnaires can be deleted.

- **Thrombocytopenia**

The risk of thrombocytopenia is well-known to healthcare professionals and the management care of such reactions is well implemented in routine clinical practice. The risk is addressed within EFIENT SmPC and patient's leaflet.

- **Thrombotic Thrombocytopenic Purpura**

The risk of thrombotic thrombocytopenic purpura is well-known to healthcare professionals and the management care of such reactions is well implemented in routine clinical practice. The risk is addressed within EFIENT SmPC as it described as a serious condition required prompt treatment. It is also described within the patient's leaflet.

Important potential risks

- **Drug-Induced Hepatic Injury**

As stated by the PRAC, the cumulative review of cases presented in the PSUSA/00002499/201702 did not suggest a causal relationship between prasugrel and DILI. The removal of DILI from the safety specification as important potential risk was endorsed by the PRAC.

- **Potential off-label use in patients with prior TIA/stroke**

This potential risk was presented within previous EFIENT RMPs and PSUSAs based upon a PRAC request.

There is a contradication for these patients in the section 4.3 of EFIENT SmPC and patient's leaflet section 2.

Important Missing Information

- **Concomitant use with fibrinolytics, other thienopyridines, warfarin, and chronic use of NSAIDs (non-ASA)**

The risk of bleeding due to drug-drug interactions between PRASUGREL and other fibrinolytics, thienopyridines, warfarin and chronic use of NSAIDs is well-known to healthcare professionals and well described within sections 4.4 and 4.5 of EFIENT SmPC as well as in the section 2 of patient's leaflet where it is described to inform the physician in case of such drugs intake.

- **Pediatric population and patients with no manifestations of ACS**

This missing information are assessed as non-relevant considering the indications of EFIENT: *"Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events* ***in adult 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 (PCI)"

- **Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory ventricular arrhythmia)**

This missing information was specific to clinical trials, there is no restriction of use, nor precautions of use regarding these comorbities within EFIENT SmPC.

- **Pregnant/Lactating women**

Pregnant or breastfeeding women were excluded from prasugrel trials (see Section SIV.3). Case reports involving use of prasugrel during pregnancy have been relatively limited, and review of available information has not identified any trends or specific safety concerns.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Because animal reproduction studies are not always predictive of a human response, Efient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

It is unknown whether prasugrel is excreted in human breast milk. Animal studies have shown excretion of prasugrel in breast milk.

The use during pregnancy and breastfeeding is well addressed within EFIENT SmPC section 4.6 and patient's leaflet section 2.

- **Subjects with severe hepatic impairment**

Patients with severe hepatic impairments were excluded from prasugrel trials (see Section SIV.1). Use is contraindicated for this subpopulation as described within SmPC section 4.3 and patient's leaflet section 2.

SVII.1.2. Risk considered important for inclusion in the list of safety concerns in the RMP

Important potential risk

- **Colorectal cancer:**

Colorectal cancer was included as an "important potential risk" from the prasugrel Risk Management Plan (RMP) V6, issued 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.

In both studies TAAL and TABY, 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. 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.

In conclusion, the risk of colorectal cancer remained as an important potential risk.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

No new important identified or potential risks have been added to this RMP update since the previously approved version 11.0 (approved on 30-Apr-2015).

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
Potential mechanisms	**A cumulative literature review up to 30-Sep-2023 highlighted the following relevant articles:** **Serebruany VL. Platelet inhibition with prasugrel and increased cancer risks: potential causes and implications. Am J Med. 2009 May;122(5):407-8 [1].** In this article issued in 2009, authors aimed to analyse the results reported during the TRITON-TIMI 38 study in which it was reported a higher risk of colorectal cancer in prasugrel-treated than clopidogrel-treated patients. According to these authors, there were 3 potential mechanisms that could be responsible for the harmful association: • **Direct hazard of the experimental drug on cancer occurrence and/or progression**; • **Indirect modulation of tumor growth**: a plausible mechanism should be enhancement of tumor growth by prasugrel through a greater inhibition of platelet activity than clopidogrel. There is an established link between tumor progression and platelet activity, and it is generally agreed that increased thrombotic risks are common in cancer patients. The role of platelet activity, hypercoagulation and depressed fibrinolysis is complex, however, and often multidirectional. Tumor growth causes impaired local metabolism and extensive release of procoagulant mediators, and this thrombophilia might actually protect from external expansion and cancer dissemination. • **Enhanced metastatic dissemination due to instability of platelet-tumor cell aggregates, and/or inability to contain the disease locally due to more potent long-term platelet inhibition**. The last hypothesis has been proved for platelet factor-4, nitric oxide, P-selectin and PAR-1 thrombin receptor, suggesting that profound chronic inhibition of platelet biomarkers does affect tumor growth. They concluded that the most reasonable and likely clinical scenario by which prasugrel could cause significantly more gastrointestinal neoplasms than clopidogrel is more potent chronic platelet inhibition, causing easier dissemination of cancer cells and elevating metastasis risks. Aggressive platelet inhibition with prasugrel disintegrates benign mechanisms of platelet-tumor cell interactions to a much stronger extent than the moderate platelet inhibition seen with clopidogrel treatment and results in the significantly higher cancer rates observed in TRITON. **Kaul S, Diamond GA. Prasugrel and cancer: an uncertain association or a credible risk that meaningfully alters the benefit-risk balance. Arch Intern Med. 2010 Jun 28;170(12):1010-2 [2]** Once again, the authors of this article were interested by the results of TRITON–TIMI38 regarding the risk of colorectal cancer in prasugrel treated patients. They were interested

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	to determine whether these observations represent an incidental false-positive signal or a credible safety concern clearly meriting careful scrutiny. According to them, there were 4 potential explanations for the association: • prasugrel causes cancer: *the authors considered that given the relatively brief duration of TRITON–TIMI 38 (16 months) and the early emergence of many of the tumors, de novo tumor induction is unlikely to explain the increase in cancer signal.* • prasugrel does not cause but promotes the growth of pre-existing cancer*: they considered that Preclinical studies of prasugrel provide suggestive, but not conclusive, evidence that prasugrel is a tumor promoter. Data in mice (but not in rats) point toward a carcinogenic effect that is consistent with tumor promotion. However, they described that the negative results of tumor progression studies of prasugrel and its metabolites in human colon, lung, and prostate tumor-cell lines grown in vitro and in congenitally immunodeficient "nude" mice in vivo are inconsistent with tumor promotion. They concluded it was difficult to know which among the myriad preclinical models is the right one and even more difficult to extrapolate findings from studies in animals to humans.* • prasugrel neither causes nor promotes cancer but leads to its detection by triggering bleeding: *they analysed the bias related to increased bleeding that has been offered as the most likely explanation for the association between prasugrel and cancer. They concluded that this postulate could no statistically be confirmed and that additional analyses that might mitigate the impact of this bias include are needed.* • prasugrel is unrelated to cancer: *Besides the aforementioned drug effects, one other possible explanation for the association between prasugrel and cancer is the incidental play of chance resulting in morecancer-prone individuals ending up in the prasugreltreated group.* Furthermore, an in vitro study provided another plausible mechanism: **Kim WT, Mun JY, Baek SW, Kim MH, Yang GE, Jeong MS, Choi SY, Han JY, Kim MH, Leem SH. Secretory SERPINE1 Expression Is Increased by Antiplatelet Therapy, Inducing MMP1 Expression and Increasing Colon Cancer Metastasis. Int J Mol Sci. 2022 [3]** Context: Contrary to many reports that antiplatelet agents inhibit cancer growth and metastasis, new solid tumors have been reported in patients receiving long-term antiplatelet therapy.

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	Methods: The authors investigated the effects of these agents directly on cancer cells in the absence of platelets to mimic the effects of long-term therapy. Results: When four antiplatelet agents (aspirin, clopidogrel, prasugrel, and ticagrelor) were administered to colon cancer cells, cancer cell proliferation was inhibited similarly to a previous study. **However, surprisingly, when cells were treated with a purinergic P2Y12 inhibitor (purinergic antiplatelet agent), the motility of the cancer cells was significantly increased**. Therefore, gene expression profiles were identified to investigate the effect of P2Y12 inhibitors on cell mobility, and Serpin family 1 (SERPINE1) was identified as a common gene associated with cell migration and cell death in three groups. Conclusion: Antiplatelet treatment increased the level of SERPINE1 in cancer cells and also promoted the secretion of SERPINE1 into the medium. Increased SERPINE1 was found to induce MMP1 and, thus, increase cell motility. In addition, an increase in SERPINE1 was confirmed using the serum of patients who received these antiplatelet drugs.
Evidence source and strength of evidence:	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 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, in TABY 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, 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%,

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	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.**

Important Potential Risk: Colorectal Cancer

MedDRA (version 26.1): HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified

Characterisation of the risk:

Seriousness/Outcomes

Clinical Trial Program: Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_hyps.rtf and others.

In 17 studies including studies TAAL and TABY, the incidence rate for colorectal cancer is 0.64 and 1.52 per 1000 person-years in clopidogrel and prasugrel, respectively.

Clinical Trial Program: The distribution of outcomes and seriousness for colorectal cancer in prasugrel treated patients is shown below.

Study Population	Prasugrel-treated pts w/ ≥1 event n (%)	Fatal n (%)	Recovered/ Resolved n (%)	Not Recovered/ Not Resolved n (%)	Recovered/ Resolved w/ Sequelae n (%)	Recovering/ Resolving n (%)	Unknown n (%)
All treated patients with ACS, stable CAD, and elective PCI* (N = 12,541)[a]	**23 (0.18 %)**	**3 (0.02 %)**	**7 (0.06 %)**	**9 (0.07 %)**	**2 (0.02 %)**	**3 (0.02 %)**	**2 (0.02 %)**
Serious	**21 (0.17 %)**	**3 (0.02 %)**	**7 (0.06 %)**	**8 (0.06 %)**	**2 (0.02 %)**	**2 (0.02 %)**	**2 (0.02 %)**
Non-Serious	**2 (0.02 %)**	**0 (0.00 %)**	**0 (0.00 %)**	**1 (0.01 %)**	**0 (0.00 %)**	**1 (0.01 %)**	**0 (0.00 %)**

Abbreviations: % = percentage of subjects reporting the event; ACS = acute coronary syndrome; CAD = coronary artery disease; n = number of subjects with events (some subjects may have reported more than 1 event); N = total number of treated subjects; PCI = percutaneous coronary intervention.

**This includes the following studies: H7T-CR-TAEH, H7T-DS-TADS, H7T-DS-TAEI, H7T-EW-TAAD, H7T-MC-TAAH, H7T-MCTAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MCTACW, H7T-MC-TACY, H7T-MC-TADI, and H7T-MC-TADF, and H7T-DS-TAEL.*

a Important Note: The data for colorectal cancer were initially pooled to combine Studies TAAL and TABY. However, upon further review, it was noted that the pooling of dissimilar data was not valid, so the table was corrected in the last revision (version 5) of the Core RMP. The number of affected patients has not changed, however, and the original analysis/conclusions from the data have not changed.

Important Potential Risk: Colorectal Cancer

MedDRA (version 26.1): HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified

Source: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_clrtc.rtf.

Clinical Trial Program: Neoplasm data was a pre-defined outcome variable in Study TABY, and was collected on a specific Case Report Form (CRF) and adjudicated by an independent, blinded committee. This resulted in 14 new non-benign colorectal cases being identified out of 4623 prasugrel-treated patients. This data includes all prasugrel-treated subjects, including subjects with or without a history of malignancy at baseline.

Study Population	Prasugrel-treated pts w/ New Non-Benign Colorectal Neoplasms n (%)	Disease Status at End of Study		
		In Remission n (%)	Active Disease at End of Study n (%)*	Relapse or Disease Progression n (%)
Study TABY (N = 4623 prasugrel-treated patients)	**14 (0.30%)**	**9 (0.19%)**	**3 (0.06%)***	**1 (0.02%)**

Abbreviations: % = percentage of subjects reporting the event; n = number of subjects with treatment-emergent adverse event within severity (some subjects may have reported more than 1 event); N = total number of treated subjects.
** Note: There was one case in which the end disease state was "unknown".*
Source: 15012_m1frq101_c1.

Severity and nature of risk

Clinical Trial Program: Grades of severity for treatment-emergent colorectal cancer in prasugrel-treated patients with ACS, stable CAD, and elective PCI are shown below.

Study Population	Prasugrel-treated pts w/ ≥1 event n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
All treated patients with ACS, stable CAD, and elective PCI* (N = 12,541)	23 (0.18%)	0 (0.00%)	4 (0.03%)	19 (0.15%)

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; n = number of subjects with treatment-emergent adverse event within severity (some subjects may have reported more than 1 event); N = total number of treated subjects; PCI = percutaneous coronary intervention. *This includes the following studies: H7T-CR-TAEH, H7T-DS-TADS, H7T-DS-TAEI, H7T-EW-TAAD, H7T-MC-TAAH, H7T-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADI, H7T-MC-TADF, and H7T-DS-TAEL.

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	[a]Important Note: The data for colorectal cancer were initially pooled to combine Studies TAAL and TABY. However, upon further review, it was noted that the pooling of dissimilar data was not valid, so the table was corrected in version 5 revision of the Core RMP. The numbers of affected patients has not changed, however, and the original analysis/conclusions from the data have not changed. Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_clrtc.rtf. <u>Background incidence/ prevalence</u> There was an imbalance in colorectal cancer noted between treatment groups seen in both TRITON TIMI-38 and TRILOGY. **The higher rate of colorectal cancer detection in the prasugrel group can be largely attributed to investigation of GI bleeding or anaemia, with a greater number of malignancies detected at an earlier stage in the prasugrel-treated compared with the clopidogrel-treated group**. While the imbalance of colorectal cancers detected with prasugrel can likely be explained by the higher rates of GI bleeding and anaemia observed in the prasugrel group compared to the clopidogrel group, the clinical trial data do not allow for definitive conclusions. Investigation of gastrointestinal (GI) bleeding or anaemia led to the discovery of the majority of these cases (15 of 20). The studies below provide information on the background/prevalence of the risk of colorectal cancer: a) FDA 2009 [4]: CURE study In patients taking ASA, incidence of colorectal cancer was 1.7 per 1,000-person years, and in patients taking ASA and clopidogrel incidence was 3.4 per 1,000-person years. b) Chan et al. 2007 [5]: Patients in Hong Kong screened for colonoscopy after undergoing coronary angiography for suspected CAD during November 2004 and June 2006 (n=706) In patients with coronary artery disease, prevalence of colorectal cancer was 34.0%. This was in comparison to the two control groups: patients without CAD, 18.8% and general population, 20.8%. c) Neaton et al. 1992 [5]: A study of 350,977 men aged 35 to 57 years who had been screened for the Multiple Risk Factor Intervention Trial were followed up for an average of 12 years following a single standardized measurement of serum cholesterol level and other coronary heart disease risk factors Among men with a serum cholesterol level of 200-239, crude mortality rate for colon cancer was 2.3/10,000 person-years; among men with serum cholesterol >240, crude mortality rate for colon cancer was 2.2/10,000 person-years. **Post marketing Data:**

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	Cumulatively, up to 30-Sep-2023, considering the HLTs "Anal Canal Neoplasms Malignant ", "Colorectal Neoplasms Malignant", " Colorectal And Anal Neoplasms Malignancy Unspecified", a total of 94 cases were identified by DAIICHI SANKYO. The table SVII.3.1, presented after the characterization of this risk, provides a summary of the main information related to the risk of colorectal cancer from these cases. Analysis of the 94 cases provided the following observations: **Source and type of cases** • Sixty (60) cases came from post-marketing studies or solicited patients' programs. • Thirty-one (31) cases were spontaneously reported by healthcare professionals (26 from healtcare professionals, 2 from literature and 3 from patients). • Two (2) cases came from the clinical trial ANTARCTIC (DSJ-2014-109501 and DSJ-2014-132988). • One (1) case was from another type of study (no detailed information). **Geographic distribution** • Sixty-two (62) cases came from Japan • Twenty-one (21) cases came from United States • Four (4) cases came from Korea • Four (4) cases came from France • One (1) case came from Colombia, one (1) case came from Brazil, one (1) case from Germany Among these 94 cases, only the four (4) cases from France and the case from Germany have been recorded within SUBSTIPHARM's safety database due to the transfer of the European centrealised procedure. Among these 94 cases, only the four (4) cases from France and the case from Germany have been recorded within SUBSTIPHARM's safety database due to the transfer of the European centrealised procedure. SUBSTIPHARM became the MAH of EFIENT for the EU centralised procedure and is the global safety owner for the national procedures in Switzerland (where the local MAH is Leman) and in UK (where the local MAH is Vygoris). Consequently, only cases from these territories have been transferred within SUBSTIPHARM's safety database. In addition, as part of the commercial agreement between Susbtipharm and Daiichi, in Russia and Turkey, JSC Servier and Daiichi Sankyo İlaç Ticaret Ltd. Şti remain the local MAHs and Substipharm becomes the global safety owner as well. Despite of not having all the 94 cases in SUBSTIPHARM's safety database, it was decided to make a complete analysis of the data provided by Daiichi regarding this important potential risk:

Important Potential Risk: Colorectal Cancer

MedDRA (version 26.1): HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified

Demographic data

Gender

- Cases occurred in male patients in seventy (70) cases
- Cases occurred in female patients in twenty-one (21) cases
- Gender was not reported in three (3) cases

Age

- Precise ages were reported in eighty (80) cases [39-89]. The mean and median age from these cases were 71 and 72 years-old respectively.
- Some group of age or uncertain ages were reported in nine (9) cases: two patients were in the 70's, two patients were in the 60's, one patient was 71 or 72 years-old, one patient was older than 50 years-old, one patient was 54 or 55 years-old, one patient was 47 or 49 years-old and one patient was in the 30's or 40's.
- Age was not reported in five (5) cases.

Medical information

Type of colorectal cancer and localisations reported

- Colon cancers, with no more details, were reported in twenty-one (21) cases
- Rectal cancers, with no more details, were reported in sixteen (16) cases
- Cancer of sigmoid colon was reported in thirteen (13) cases
- Cancer of ascending colon was reported in seven (7) cases
- Cancer of descending colon was reported in two (2) cases
- Metastatic colon cancers were reported in four (4) cases
- Cancer of transverse colon was reported in four (4) cases
- Caecal cancer was reported in nine (9) cases
- Appendix cancer in one (1) case
- Large intestinal polyp was reported in one (1) case
- Right colon cancer was reported in one (1) case
- Colorectal cancer, with no more details, was reported in four (4) cases
- Large intestinal carcinoma, with no more details, was reported in eleven (11) cases

Risk factors, suggestive underlying conditions Risk factors, suggestive medical history and concurrent conditions were reported in seventy (70) cases i.e 74.4% of the cases

- Hypercholesterolemia, lack of exercise, dyslipidemia, diabetes
- Alcohol use, tobacco use.
- There was also history of haemorrhoids, gastrointestinal haemorrhages, colorectal cancers or gastrointestinal endoscopies suggestive of previous disorders.
- In five (5) cases, a familial risk factor was reported

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	No medical history and concurrent conditions were reported in nine (9) cases. **No relevant medical history or concurrent conditions was detected in fifteen (15) cases based upon the information provided.** **Suggestive concomitant/co-suspect drugs were reported in thirty-three (33) cases i.e 35% of the cases** *(mainly acetylsalicylic acid or antiplatelet drug such as clopidogrel).* **Circumstances of discovery of colorectal cancer during treatment with EFIENT were described in 42 cases i.e half of the cases**: • Bloody stools, melena, gastrointestinal haemorrhage, bleeding internally: Twenty-eight (28) cases • Anaemia: Nine (9) cases • Positive occult blood test: Three (3) cases • Anaemia and gastrointestinal haemorrhage: One (1) case • Other: shortness of breath and fatigue in one (1) case **Delay between beginning of EFIENT administration and diagnosis of colorectal cancer** This information was provided in 72 cases: • Diagnosis the day of EFIENT introduction: 1 case • Less than one month: 9 cases • Approximatively 1 month: 3 cases • Approximatively 2 months: 3 cases • Approximatively 3 months: 8 cases • Approximatively 4 months: 5 cases • Approximatively 5 months: 2 cases • Approximatively 6 months: 2 cases • Approximatively 7 months: 3 cases • Approximatively 8 months: 4 cases • Approximatively 9 months: 6 cases • Approximatively 10 months: 1 case • Approximatively 11 months: 2 cases • Approximatively 12 months: 2 cases • Approximatively 16 months: 2 cases • Approximatively 17 months: 1 case • Approximatively 19 months: 2 cases • Approximatively 20 months: 2 cases • Approximatively 21 months: 2 cases • Approximatively 23 months: 2 cases • Approximatively 24 months: 3 cases • Approximatively 25 months: 2 cases • Approximatively 28 months: 1 case • Approximatively 29 months: 1 case

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	• Approximatively 30 months: 1 case • Approximatively 36 months: 1 case • Approximatively 39 months: 1 case The mean and median delays from these data were 10 and 7.5 months respectively. **Corrective action** • Surgery in sixty-one (61) cases • Chemotherapy in two (2) cases • Surgery and chemotherapy in three (3) cases • Unknown in twenty-five (25) cases • Not applicable in three (3) fatal cases **Outcomes** • Fatal in eight (8) cases (8.5%) • Not recovered in nine (9) cases (9.6%) • Recovering in thirty-six (36) cases (38.3%) • Recovered in sixteen (16) cases (17%) • Unknown in twenty-five (25) cases (26.6%) **Relatedness from the reporter** • Unrelated in seventy-two (72) cases (76.6%) • Related in nine (9) cases (9.6%) • Unknown in thirteen (13) cases (13.8%) **Among the seventy-two (72) cases with an unrelated causal relationship as evaluated by the reporter, alternative etiologies were described in forty (40) cases:** • **Advanced age:** three (3) cases • **Patient's predisposition**: one (1) case • **Aggravation or progression of a primary disease:** ten (10) cases • **Incidental event:** nineteen (19) cases • **Dietary habits and/or lack of physical activity:** three (3) cases • **Other**: It turned out that the haemorrhoid, which the patient believed it was, was actually a colorectal tumour (1 case), treatment of the patient's primary disease (1 case), medical history related with no more details (2 cases). • **Not reported** in thirty-two (32) cases **Among the nine (9) cases with a related causal relationship as evaluated by the reporter:** • Onset temporal sequences between EFIENT introduction and colorectal diagnosis varied from less than one month to approximatively 11 months. • There were other suspect drugs in four (4) cases.

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	• There were no other suspect drugs in (5) cases: There was a suggestive medical history and concurrent conditions in two (2) out of these five cases. Medical history and concurrent conditions were not reported in the three (3) remaining cases. There was no detailed assessments for these five (5) cases. • There were no detailed assessements in six (6) cases • The detailed assessment was reported in three (3) cases: o *"The physician stated that the events were possibly related to prasugrel with an underlying cause of intercurrent new disease and were most likely related to the therapy with clopidogrel, acetyl salicylic acid, and phenprocoumon."* o *"The reporting physician assessed the events as related to the use of prasugrel, abciximab and acetylsalicylate lysine/glycine."* o *"The reporting investigator considered the colon cancer and anaemia to be related to prasugrel"* **<u>Analysis of these data as compared with the general population and colorectal cancer:</u>** • First of all, regarding the time sequence, it must be considered that the natural history of a colorectal cancer takes 10 to 15 years to develop from an adenomatous polyp to a colorectal cancer. Considering this, the review of the data provided within post-marketing cases does not suggest that colorectal cancer is related to the use of EFIENT as the onset sequences reported in the cases vary from 0 to approximatively 3 years (median delay: 7.5 months). • Furthermore, regarding the suggestive medical history and concurrent conditions, as described earlier, some relevant information were detected in three quarters of the cases. Considering the high incidence of colorectal cancer in the general population, especially in patients with risk factors (dyslipidemia, tobacco, alcohol, familial history,.), it cannot be concluded that colorectal cancer is related to the use of EFIENT. Indeed, according to the WHO, in 2020, more than 1.9 million new cases of colorectal cancer and more than 930 000 deaths due to colorectal cancer were estimated to have occurred worldwide. Several lifestyle factors contribute to the development of colorectal cancer such as a high intake of processed meats and low intake of fruits and vegetables, sedentary lifestyle, obesity, smoking, and excessive alcohol consumption *(WHO, 2023).* • In addition, the median age of 72 years-old retrieved from these cases is in line with the worldwide data on colorectal cancer. Indeed, the risk of colorectal cancer increases as people get older. The majority of colorectal cancers occur in people older than 50. For colon cancer, the average age at the time of diagnosis for men is 66 and for women is 69. For rectal cancer, it is age 62 for men and 63 for women (Cancer.net, 2023). • Furthermore, as stated from the analysis of the cases, in more than 75% of the cases, it was concluded that there was no causal relationship between EFIENT and colorectal cancer as stated by the reporters: in most of the cases, the reporters thought there was an aggravation of an underlying condition, that it

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	was an incidental event or that advanced age and way of life were the causes of cancer. • Finally, regarding the nine (9) cases with a related causal relationship between EFIENT and colorectal cancer as evaluated by the reporters, the cases were insufficiently documented to confirm the assessment and review of the cases did not bring any relevant information. **In conclusion,** medical review of these cases tends to show that there is no sufficient evidence for the time being to consider a causal relationship between PRASUGREL and colorectal cancer. **However, as described earlier, the circomstances of colorectal discovery may be related to the use of EFIENT (in association or not with another ant-platelet aggregants):** • The onset of gastrointestinal haemorrhages in 28 cases and aneamia in 9 cases have contributed to the discovery of colorectal cancer as investigations were performed to find the cause of haemorrhage or anaemia. Both events are listed for EFIENT. **Literature Data:** A retrospective cumulative literature search using Adis Insigh Safety Reports and MEDLINE® databases had been conducted to strengthen searches and find any published safety reports and studies which could be relevant to assess the potential risk of colorectal cancer with PRASUGREL up to 30-Sep-2023 with the keywords "colorectal cancer', "colon cancer" and "rectal cancer". Out of a total of seven (7) articles identified, four (4) relevant articles were selected. • Three of them are described in the potential mechanism section • The remaining article was published by Lilly: **Buckley LA, Sanbuissho A, Starling JJ, Knadler MP, Iversen PW, Jakubowski JA. Nonclinical assessment of carcinogenic risk and tumor growth enhancement potential of prasugrel, a platelet-inhibiting therapeutic agent. Int J Toxicol. 2012 Jul-Aug;31(4):317-25 [6]** Context: A comprehensive nonclinical safety assessment including genotoxicity and carcinogenicity studies supported the chronic use of prasugrel in patients with atherothrombotic disease. In addition, a special assessment of the potential for prasugrel to enhance tumor growth was undertaken to address regulatory concerns relating to increases in human cancers. Results: • Prasugrel demonstrated no evidence of genotoxicity and was not oncogenic in a 2-year rat carcinogenicity study.

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
	• In the 2-year mouse study, an increase in hepatocellular adenomas was considered secondary to enzyme induction and not relevant to human safety. Further, the absence of any increase in common background tumors at any other organ site in either rodent study indicated a lack of tumor promoting activity (apart from the CYP450 induction-related increase in mouse liver tumors). • Cell culture studies with 3 human tumor cell lines (lung, colon, prostate) demonstrated that exposure of serum-starved cells to prasugrel's active and major circulating human metabolites does not increase cell proliferation relative to starved cells stimulated to proliferate by addition of 10% FBS. • Prasugrel also did not increase tumor growth relative to vehicle controls in nude mice implanted with 3 human tumor cell lines Conclusion: It was so concluded that traditional genotoxicity and 2-year bioassays as well as specially designed tumor growth enhancement studies in human tumor cell lines and mouse xenograft models clearly demonstrated prasugrel's lack of tumorigenic potential. **Conclusion:** Finally, as described within the last EFIENT PSUSA covering a period from 26-Feb-2018 to 25-Feb-2021, the event of Colorectal Cancer, in the prasugrel spontaneous data base are very rarely reported based on the estimated patient exposure of 4 895 000 (number of patients). EFIENT has been approved since 2009 so there is more than 13 years of safety evaluation with this product and its safety profile is now well established. The cases of colorectal cancer recorded since EFIENT approval remain isolated as compared with the high patient's exposition and do not provide sufficient information to confirm a causal relationship between EFIENT and colorectal cancer. Analysis of the cases recorded since EFIENT approval does not confirm the observations from clinical trials about a possible causal relationship between EFIENT and colorectal cancer. Analysis of the literature allowed to detect some possible mechanistic explanations but they remained hypothetic and conflicting. Altogether, this information showed that occurrence of GI bleeding and anaemia, in an elderly population, may have led to deep investigations and to discovery of colorectal cancer. Considering the incidence of colorectal cancer in the general population, especially in elderly population, there is no sufficient evidence to consider a causal relationship between colorectal cancer and EFIENT. However, considering the impact of such reaction on the benefit/risk balance and based upon CHMP request, a potential risk is considered and the specific follow-up form is maintained.
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 (Mayo Clinic 2013[5]). There are no known patient characteristics relevant to the risk of colorectal cancer with prasugrel treatment.

Important Potential Risk: Colorectal Cancer **MedDRA (version 26.1):** HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified	
Preventability:	Although the occurrence of these events may not be preventable, several screening options are available. People with average risk can consider screening at age 50, while people with an increased risk, such as a family history of colon cancer, should consider screening sooner. African-Americans and American Indians may begin screening at age 45. Screening options include faecal occult blood testing, flexible sigmoidoscopy, and colonoscopy (Mayo Clinic 2013 [5]).
Impact on the risk-benefit balance of the product:	Considering the seriousness of this risk, the high rate of mortality and the impact on the benefit/risk balance, this potential risk needs to be carefully monitored and a specific follow-up form for cancer is needed in order to better characterize this potential risk of colorectal cancer.
Public health impact:	Many people experience no symptoms in the early stages of colon cancer. Symptoms of colorectal cancer will vary depending on the cancer's size and location in the large intestine and include a change in bowel habits (diarrhoea, constipation, or consistency change); rectal bleeding or blood in the stool; persistent abdominal discomfort (cramps, gas or pain); feeling that bowel doesn't empty completely; weakness or fatigue; and unexplained weight loss (Mayo Clinic 2016). The impact on the individual patient depends on the stage of colorectal cancer at the time of detection.

SVII.3.2 Presentation of the Missing Information

Not applicable

References

1 Serebruany VL. Platelet inhibition with prasugrel and increased cancer risks: potential causes and implications. Am J Med. 2009 May;122(5):407-8

2 Kaul S, Diamond GA. Prasugrel and cancer: an uncertain association or a credible risk that meaningfully alters the benefit-risk balance. Arch Intern Med. 2010 Jun 28;170(12):1010-2

3 Kim WT, Mun JY, Baek SW, Kim MH, Yang GE, Jeong MS, Choi SY, Han JY, Kim MH, Leem SH. Secretory SERPINE1 Expression Is Increased by Antiplatelet Therapy, Inducing MMP1 Expression and Increasing Colon Cancer Metastasis. Int J Mol Sci. 2022

4 FDA Deputy Director Division of Cardiovascular and Renal Products Office Drug Evaluation-I Office of New Drugs Center for Drug Evaluation and Research (CDER) U.S. Food and Drug Administration (FDA). 2009. Prasugrel For Reduction of Cardiovascular Events in Patients with Acute Coronary Syndrome (ACS). Cardiovascular and Renal Drugs Advisory Committee, Silver Spring, Maryland, 03 February 2009.

5 Mayo Clinic Staff. Colon Cancer, updated 27 July 2023: https://www.mayoclinic.org/diseases-conditions/colon-cancer/symptoms-causes/syc-20353669

6 Buckley LA, Sanbuissho A, Starling JJ, Knadler MP, Iversen PW, Jakubowski JA. Nonclinical assessment of carcinogenic risk and tumor growth enhancement potential of prasugrel, a platelet-inhibiting therapeutic agent. Int J Toxicol. 2012 Jul-Aug;31(4):317-25

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 2: Summary of Safety Concerns (Important Identified Risks, Important Potential Risks, and Important Missing Information)

Summary of Safety Concerns	
Important Identified Risks	• None
Important Potential Risks	• Colorectal Cancer
Important Missing Information	• None

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 any safety concerns:

A specific follow-up form is implemented for the important potential risk of colorectal cancer.

Implementation of the pharmacovigilance plan will allow for further elaboration of the risk profile as it relates to this important identified risk to better understand the identified risk in a naturalistic setting and in a wider spectrum of ACS subjects.

As previously described in section SVII.2, the previous specific follow-up forms implemented by the first MAH of EFIENT are no longer assessed as relevant as they were used to facilitate the collection of the information. Indeed, considering the well-established EFIENT safety profile, the specific follow-up forms for Allergy, Angioedema, Blood and Bone Marrow Disorders, Cerebral Haemorrhage, General Bleeding, Hepatic Disorders, Photosensitivity, Procedural Bleeding and Thrombotic Disorders are withdrawn with this RMP V13.0.

Other forms of routine pharmacovigilance activities for any safety concerns:

Not applicable. A review of the safety concerns will be performed at each PSUR elaboration.

III.2 Additional Pharmacovigilance Activities

Not applicable.

There are no ongoing or planned additional pharmacovigilance activities in place for Prasugrel.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

There are no ongoing or planned additional pharmacovigilance activities for Prasugrel.

Part IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable. No additional efficacy studies are required or planned.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.I Routine Risk Minimization Measures

Table Part V.3: Summary of Risk Minimization Measures since initial marketing authorisation

Description of routine risk minimization measures by safety concern.

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
None	
Important Potential Risks	
Colorectal cancer	Specific follow-up form
Important Missing Information	
None	

V. 2 Additional risk minimization measures

Routine risk minimisatiojn activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Removal of additional risk minimization activities

As stated by the PRAC, the risk of bleeding is well-known to healthcare professionals and appropriate measures to manage the risk of bleeding are likely implemented in routine clinical practice. Moreover, the PRAC assessed that the implemented aRMM on the important identified risk of bleeding does not seem to provide substantial additional information to the SmPC.

The additional risk minimization measures which have been implemented regarding this risk consisted in educational material to ensure that prescribers are appropriately informed about this risk through labelling including:

- A copy of SmPC
- Emphasis that:
  - Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg.
  - Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.
  - If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5mg should be prescribed.

- Patients weighing < 60 kg should have a reduced maintenance dose of 5mg.

In addition, regarding the bleeding Risk Associated with Prasugrel use Prior to Coronary Angiography in NSTEMI Patients, a Direct Healthcare Professional Communication (DHPC) was distributed in all EU countries where prasugrel is marketed if approved by the local National Competent Authority (NCA) (the DHPC distribution has been completed in all EU Member States).

The risk of bleeding is well addressed within EFIENT SmPC and patient's leaflet. It also contains specifc information for the particular populations of patients older than 75 years-old and with a weight below 60 kgs or in case of coronary angiography.

Consequently, SUBSTIPHARM considered that the educational material related to the risk of bleeding can be removed in this EU-RMP (V13.0).

V.3 Summary of Risk Minimisation Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks: None		
Important Potential Risks		
Colorectal cancer	• None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific follow-up form Additional pharmacovigilance activities: • None proposed
Important Missing Information: None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR EFIENT 5 MG (INN PRASUGREL)

This is a summary of the risk management plan (RMP) for Efient. The RMP details important risks of Efient, how these risks can be minimised, and how more information will be obtained about Efient's risks and uncertainties (missing information).

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

This summary of the RMP for EFIENT 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 EFIENT's RMP.

I 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.

II 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.

II.A 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).

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

II.B Summary of Important Risks

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

II.C Post-Authorisation Development Plan

II.C.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.

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

There are no studies required for Efient.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR EFIENT 10 MG (INN PRASUGREL)

This is a summary of the risk management plan (RMP) for Efient. The RMP details important risks of Efient, how these risks can be minimised, and how more information will be obtained about Efient's risks and uncertainties (missing information).

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

This summary of the RMP for EFIENT 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 EFIENT's RMP.

I 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.

II 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.

II.A 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).

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

II.B Summary of Important Risks

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, 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

II.C Post-Authorisation Development Plan

II.C.3 Studies Which Are Conditions of the Marketing Authorization

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

II.C.4 Other Studies in Post-Authorisation Development Plan

There are no studies required for Efient.

PART VII ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific Adverse Event Follow-up Form	Event(s) associated with the form
Form #1: Follow-up Form – Colorectal Cancer	Cancer/Neoplasms

SUBSTIPHARM

Spontaneous Follow-up Form – Colorectal Cancer

You have reported an adverse reaction of colorectal cancer with Efient (prasugrel). This questionnaire is being sent to you for obtaining valuable additional information about the reported case to thoroughly evaluate the relation to prasugrel's exposure. By providing as detailed information as possible, you can make a useful contribution to the safety of Efient (prasugrel).

Substipharm Case #:

Reporter

☐ Healthcare professional	☐ Patient	☐ Other, precise:
INFORMATION ABOUT THE REPORTER HEALTHCARE PROFESSIONAL (if applicable)		
Name:	Street:	
Specialty:	Postal code:	
Tel.:	City:	
E-mail:	Country:	

Patient

Patient's information:
○ Initials: ○ Date of birth: ○ Age: ○ Gender: ○ Weight: ○ Height:

Patient's historical / concomitant diseases (add as many lines as necessary):

- ☐ History of cancer
- ☐ Chemotherapy
- ☐ Radiotherapy
- ☐ Diabetes mellitus
- ☐ Alcohol use
- ☐ Tobacco use
- ☐ Obesity
- ☐ Surgery
- ☐ Familial history of cancer

*Please complete below with any other relevant history like an environmental risk which could contribute to the cancer development.

Medical history/concurrent condition	Start date (DD/MM/YYYY)	Treatment provided	Outcome	End date (if applicable) (DD/MM/YYYY)

Patient's historical / concomitant treatments (please add lines if necessary):

Treatment (drug name)	Start date (DD/MM/YYYY)	Stop date (DD/MM/YYYY)	Indication

Suspect Drug

EFIENT®	
Indication	
Start date (DD/MM/YYYY)	
Stop date (DD/MM/YYYY)	
Loading dose (in mg)	
Daily dose (in mg)	
Batch number (s)	
Treatment frequency	
Route of administration	
EFIENT® action taken	
Was Efient's treatment discontinued due to any adverse event? (please describe the event)	
If Efient's treatment was discontinued due to any adverse event, did the patient recovered from this event?	

If Efient's treatment was discontinued due to any adverse event, was the treatment restarted later?	
Did the patient experience any adverse event after the treatment was restarted?	

Other suspect drugs:			
Co-suspect medication	Start date	Stop date	Indication

COLORECTAL CANCER

Date of the cancer diagnosis (DD/MM/YYYY)	
How does the cancer was discovered? (please describe if the patient presented pain, bleeding for example, which led to a cancer investigation).	
Please specify the primary site of the cancer.	
Tumor description? (please add if one tumor, metastasis and locations if applicable)	
For malignant tumor, please provide a copy of pathology report or provide the information of Stage/Grade, Staging classification and tissue source.	
Description of the corrective treatment	
Description of surgical treatment (if applicable)	

Did the patient improved/recovered after Efient's treatment interruption?	
If treatment was restarted, did the cancer reappeared / progressed?	
Patient's outcome	
Other relevant useful information	

Case description (open text)

Laboratory data

Lab tests		
Neme of the test	Performed date	Results and units if applicable
Histopathology (please indicate stage/grade, staging classification and tissue source)		
Ultrasound		
CAT Scan		
MRI		

Others		

- Please attach copy of pathology report if available

Assessment by the reporter

Relation between adverse reaction and suspected product:

- ☐ Certain Probable
- ☐ Possible
- ☐ Doubtful
- ☐ Not related
- ☐ Not assessable
- ☐ Any other alternative etiology? _____

Source of information

- **Date:**
- **Information completed by (please enter name and title):**
- **Reporter's signature/initials:**

Please return your responses to the pharmacovigilance Department of SUBSTIPHARM

SUBSTIPHARM

Formulaire de suivi spontané – Cancer colorectal

Vous avez signalé un effet indésirable de cancer colorectal avec Efient (prasugrel). Ce questionnaire vous est envoyé pour obtenir des informations supplémentaires précieuses sur le cas signalé afin d'évaluer de manière approfondie la relation avec l'exposition

au prasugrel. En fournissant des informations aussi détaillées que possible, vous pouvez apporter une contribution utile à la sécurité d'emploi d'Efient (prasugrel).

Cas Substipharm #:

Notificateur

☐ Professionnel de santé ☐ Patient(e) ☐ Autre, précisez:	
INFORMATIONS SUR LE PROFESSIONNEL DE SANTÉ AYANT NOTIFIE LE CAS (si applicable)	
Nom :	Rue :
Spécialité :	Code Postal :
Téléphone :	Ville :
E-mail :	Pays :

Patient (e)

Informations du patient :

- Initiales :
- Date de naissance :
- Âge :
- Genre :
- Poids :
- Taille :

Antécédents / maladies concomitantes du patient (ajouter autant de lignes que nécessaire) :

- ☐ Antécédents de cancer
- ☐ Chimiothérapie

- ☐ Radiothérapie
- ☐ Diabète
- ☐ Consommation d'alcool
- ☐ Consommation de tabac
- ☐ Obésité
- ☐ Chirurgie
- ☐ Antécédents familiaux de cancer

*Veuillez compléter ci-dessous avec tout autre historique pertinent comme un risque environnemental qui pourrait contribuer au développement du cancer.

Antécédents médicaux/conditions concomitantes	Date de début (JJ/MM/AAAA)	Traitement reçu	Résultat / Evolution des conditions médicales	Date de fin (si applicable) (JJ/MM/AAAA)

Traitements antérieurs / concomitants du patient (veuillez ajouter des lignes si nécessaire) :

Traitement (nom du médicament)	Date de début (JJ/MM/AAAA)	Date de fin (le cas échéant) (JJ/MM/AAAA)	Indication

Médicaments suspects

EFIENT®	
Indication	
Date de début (JJ/MM/AAAA)	
Date de fin (JJ/MM/AAAA)	
Dose de charge (en mg)	
Dose de maintenance (en mg)	
Numéro(s) de lot	
Fréquence d'administration	
Voie d'administration	
EFIENT® action prise	
Le traitement par Efient a-t-il été interrompu en raison d'un événement	

indésirable ? (veuillez décrire l'événement)	
Si le traitement par Efient a été interrompu en raison d'un événement indésirable, le patient s'est-il rétabli de cet événement ?	
Si le traitement par Efient a été interrompu en raison d'un événement indésirable, le traitement a-t-il été repris plus tard ?	
Le patient a-t-il présenté un événement indésirable après la reprise du traitement ?	

Autres médicaments suspectés :			
Médicaments co-suspects	Date de début (JJ/MM/AAAA)	Date de fin (le cas échéant) (JJ/MM/AAAA)	Indication

CANCER COLORECTAL

Date du diagnostic du cancer (JJ/MM/AAAA)	
Comment le cancer a-t-il été découvert ? (veuillez décrire si le patient a présenté des douleurs, des saignements par exemple, qui ont conduit à une investigation d'un cancer).	
Veuillez préciser le site primaire du cancer.	
Description de la tumeur ? (veuillez ajouter s'il s'agit d'une tumeur, les métastases et les sites dans le cas échéant)	
En cas de tumeur maligne, veuillez fournir une copie du rapport d' anatomo-	

pathologie et fournir les informations sur le stade et, le grade de la maladie	
Description du traitement correcteur	
Description du traitement chirurgical (si applicable)	
La condition du patient s'est-elle améliorée suite à l'arrêt du traitement par EFIENT ?	
Si le traitement a été repris, le cancer est-il réapparu/a-t-il progressé ?	
Evolution des évènement (cancer)	
Autres informations utiles pertinentes	

Description du cas (texte ouvert)

Investigations

Tests de laboratoire		
Nom du test / examen	Date de réalisation	Résultats
Histopathologie (veuillez indiquer le stade/grade)		

Echographie		
Scanner		
IRM		
Autres		

- Veuillez joindre une copie du rapport de pathologie si disponible

Évaluation par le rapporteur

Relation entre effet indésirable et produit suspecté :

- ☐ Certain
- ☐ Probable
- ☐ Possible
- ☐ Douteux
- ☐ Sans rapport
- ☐ Non évaluable
- ☐ Toute autre étiologie alternative _____

Contact du notificateur

- **Date:**

- **Informations complétées par (veuillez inscrire votre nom et votre fonction) :**
- **Signature/initiales du notificateur :**

Merci de retourner vos réponses au Service de pharmacovigilance de SUBSTIPHARM

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

There are no proposed additional risk minization measures for this RMP.