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EU Risk Management Plan (Version 11)

Global Patient Safety
Signatory information is available on request.
Initial Risk Management Plan Approved by Lilly: 19 December 2007
Revised Risk Management Plan (Version 1.4) Approved: 17 December 2008
Revised Risk Management Plan (Version 2) Approved: 19 April 2010
Revised Risk Management Plan (Version 3) Approved: 19 October 2010
Revised Risk Management Plan (Version 4) Approved: 18 April 2011
Revised Risk Management Plan (Version 5) Approved: 19 October 2011
Revised Risk Management Plan (Version 6) Approved: 29 October 2012
Revised Risk Management Plan (Version 7) Approved: 22 April 2013
Revised Risk Management Plan (Version 8) Approved: 20 August 2013
Revised Risk Management Plan (Version 9) Approved: 25 October 2013
Revised Risk Management Plan (Version 8.1) Approved: 04 November 2013
Revised Risk Management Plan (Version 9.1) Approved: 31 January 2014
Revised Risk Management Plan (Version 10) Approved: 29 April 2014

Revised Risk Management Plan (Version 11) Approved by Lilly on date provided below.

Approval Date: 30-Apr-2015 GMT

Active Substance(s) (INN or common name):	prasugrel hydrochloride (INN prasugrel)
Pharmaco-therapeutic group (ATC Code):	Prasugrel B01AC22
Name of Marketing Authorisation Holder or Applicant:	Eli Lilly Nederland B.V.
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name[s]):	EFIENT

Data lock point for this RMP	25 February 2015
Version number:	11
Date of final sign off:	See cover page of this document

Part I: Product Overview

Administrative Information on the RMP

Part	Module/Annex	Date last updated for submission (final sign-off date)	Version number of each part/module when last submitted/or Not Applicable
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	29 Apr 2014	10
--	**SII** Non-clinical part of the safety specification	29 Apr 2014	10
--	**SIII** Clinical trial exposure	29 Apr 2014	10
--	**SIV** Populations not studied in clinical trials	29 Apr 2014	10
--	**SV** Post-authorisation experience	29 Apr 2014	10
--	**SVI** Additional EU requirements for the safety specification	29 Apr 2014	10
--	**SVII** Identified and potential risks	29 Apr 2014	10
--	**SVIII** Summary of the safety concerns	29 Apr 2014	10
Part III Pharmacovigilance Plan	--	29 Apr 2014	10
Part IV Plan for post-authorisation efficacy studies	--	29 Apr 2014	10
Part V Risk minimisation measures	--	29 Apr 2014	10
Part VI Summary of RMP	--	29 Apr 2014	10
Part VII Annexes	**Annex 1** EudraVigilance Interface	29 Apr 2014	10
	Annex 2 SmPC and Package Leaflet	29 Apr 2014	10
	Annex 3 Worldwide Marketing Status by Country (including EEA)	29 Apr 2014	10
	Annex 4 Synopsis of Ongoing and Completed EU Clinical Trial Programme	29 Apr 2014	10
	Annex 5 Synopsis of Ongoing and Completed EU Pharmacoepidemiological Study Programme	29 Apr 2014	10
	Annex 6 Protocols for Proposed and Ongoing Studies in Categories 1-3 of the Section "Summary Table of Additional Pharmacovigilance Activities" in RMP Part III	29 Apr 2014	10
	Annex 7 Specific adverse event follow-up forms	29 Apr 2014	10
	Annex 8 Protocols for Proposed and Ongoing Studies in RMP Part IV	29 Apr 2014	10

Part	Module/Annex	Date last updated for submission (final sign-off date)	Version number of each part/module when last submitted/or Not Applicable
Part VII Annexes	**Annex 9** Newly available study reports for RMP Parts III & IV	29 Apr 2014	10
	Annex 10 Details of Proposed Additional Risk Minimisation Measures (if applicable)	29 Apr 2014	10
	Annex 11 Mock-up of Proposed Additional EU Risk Minimisation Measures (if applicable)	29 Apr 2014	10
	Annex 12 Other Supporting Data (including Referenced Material)	Not applicable	Not applicable

QPPV name and signature on file

Contact person for this RMP: Please refer to the accompanying cover letter for contact information for this RMP.

Overview of Versions:

Version number of last RMP:	10
Version number	11
Agreed within	RMP ver 10 agreed within PRAC review of PSUR 10, September 2014.

Current RMP Versions under Evaluation:

Not applicable. There are no other versions currently submitted for evaluation.

Invented name(s) in the European Economic Area (EAA)	EFIENT
Authorisation procedure	Centralised
Brief description of the product including: • Chemical class	Thienopyridine
• Summary of mode of action	Prasugrel hydrochloride is an inhibitor of platelet activation and aggregation mediated by the platelet $P2Y_{12}$ ADP receptor.
• Important information about its composition (e.g., origin of active substance biological, relevant adjuvants or residues for vaccines)	Not applicable

Indications 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).
Posology and route of administration in the EEA Current	Given orally as follows: • 60-mg loading dose • 10-mg daily (maintenance dose) • 5-mg daily (maintenance dose) recommended for subjects <60 kg or subjects ≥75 years
Pharmaceutical form(s) and strengths Current	Film coated tablets; 5 mg and 10 mg

Country and date of first authorisation worldwide	European Union	25 Feb 2009
Country and date of first launch worldwide	United Kingdom	27 Mar 2009
Country and date of first authorisation in the EEA	United Kingdom	25 Feb 2009
Is the product subject to additional monitoring in the EU?	No	

Part II: Safety Specification

Module SI. Epidemiology of the Indication(s) and Target Population

Active Substance	prasugrel hydrochloride (INN prasugrel)
Product(s) concerned (brand name[s])	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

Acute Coronary Syndrome (ACS)

EFIENT

SI.1. Epidemiology of the Disease

SI.1.1. Acute Coronary Syndrome

SI.1.1.1. Incidence and Prevalence of Target Indication

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; Papathanasiou et al. 2004; Tousek et al. 2014). 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). 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). 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). 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).

In the UK, France, Germany, Italy, and Spain combined, there were more than 1 million ACS events reported in 2005 (Sanofi-Aventis 2006 [WWW]). 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). 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).

SI.1.1.2. Risk Factors for the Disease

A multicentre study (INTERHEART) from 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America, and South America found that the most important modifiable risk factors for MI were abnormal lipid levels, smoking, hypertension, diabetes, and abdominal obesity (Yusuf et al. 2004).

SI.1.1.3. 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). 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). 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). In an Italian study of 2046 ACS patients, the in-hospital mortality rate was found to be 5.7% (Vagnarelli et al. 2015). 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). 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).

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).

SI.1.1.4. 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). In a prospective study in Finland, the mean age was 65.6 years, and 30.1% were female (Allonen et al. 2012). In a French study of ACS patients, 65.4% were males (Béjot et al. 2011). 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).

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).

SI.1.1.5. 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), but the CLopidogrel ASpirin Stent International Cooperative (CLASSICS) study demonstrated better tolerability of clopidogrel over ticlopidine (Bertrand et al. 2000). 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).

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).

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).

SI.2. 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). 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).

SI.3. 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). A study in Greece (n=418) found the prevalence of hypertension to be 67.9% at baseline (Andrikopoulos et al. 2012). In Spain (n=824), the prevalence of hypertension at baseline was 65.78% (Camprubi et al. 2012). In a cohort in Finland (n=1945), the prevalence of hypertension at baseline was 65.6% (Allonen et al 2012). In a French study (n=525,419), prevalence of hypertension at baseline was 38.1% (Béjot et al. 2011). 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).

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). 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). 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).

In a US study (n=46,086 total patients), prevalence of hypertension at baseline was 76% (Yeh et al. 2010). 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). 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). 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).

Dyslipidaemia: An observational study in Greece (n=418) found the prevalence of dyslipidaemia to be 57.4% at baseline (Andrikopoulos et al. 2012). In a study in Spain (824 patients), the prevalence of dyslipidaemia was 58.13% at baseline (Camprubi et al. 2012). In a cohort of consecutive ACS patients in Finland (n=1945), prevalence of dyslipidaemia at baseline was 71.1% (Allonen et al 2012). In a UK study (n=155,818), prevalence of dyslipidaemia was 33.8% (Zaman et al. 2014). In an international study of 27 countries (n=15,871), prevalence of hypercholesterolemia was 72.39% at baseline (Schwartz et al. 2012). 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). 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). In a US study (n=46,086 total patients), prevalence of dyslipidaemia at baseline was 80% (Yeh et al. 2010). 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).

***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). 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). In a study in Spain (n=824), prevalence of diabetes at baseline was 33.86% (Camprubi et al. 2012). In a cohort of consecutive ACS patients in Finland (n=1945), prevalence of diabetes mellitus at baseline was 22.8% (Allonen et al 2012). In a French study of ACS patients (n=525,419), prevalence of diabetes mellitus at baseline was 19.5% (Béjot et al. 2011). 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).

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). 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). 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). In a US study (n=1321), prevalence of diabetes was 38.8% (Milani et al. 2012). 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).

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).

***Previous Myocardial Infarction*:** In Europe, prevalence of previous MI was 20.4% in Finland (n=1945) (Allonen et al. 2012), 22.4% in Sweden (n=119,786), and 18.3% in the UK (n=391,077) (Chung et al. 2014). In an international study of 27 countries (n=15,871), prevalence of previous MI was 15.58% at baseline (Schwartz et al. 2012). 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). 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).

***Congestive Heart Failure*:** In a study in Spain (n=824), prevalence of heart failure at baseline was 4.13% (Camprubi et al. 2012). 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). In an international study of 27 countries (n=15,871), CHF was 15.46% at baseline (Schwartz et al. 2012). 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). 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).

In a US study (n=46,086 total patients), prevalence of chronic heart failure at baseline was 8% (Yeh et al. 2010). 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).

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Part II: Safety Specification

Module SII. Nonclinical Part of the Safety Specification

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

Table SII.1. Key Safety Findings from Nonclinical Studies and Relevance to Humans

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
• Hepatotoxicity: In toxicology studies, liver effects were largely considered secondary to hepatic enzyme induction: increased hepatic weight, hepatocellular hypertrophy, ground glass appearance to hepatocytes upon microscopic examination, and increased smooth endoplasmic reticulum in hepatocytes. Alkaline phosphatase was also increased in the dog. Hepatic toxicity (increased alanine aminotransferase [ALT], aspartate transaminase [AST], and histopathologic changes) occurred in mice at a high dose (2000 mg/kg; >800-fold the recommended daily clinical dose, on a mg/m^2 basis), which was also lethal. • Carcinogenicity: There were no treatment-related tumours in rats, and prasugrel was not genotoxic. An increase in hepatocellular adenomas was observed at high doses (>50 times the recommended daily clinical dose based on systemic exposure to the active and inactive metabolites) in a 2-year mouse carcinogenicity study and was considered secondary to enzyme induction. The association of enzyme induction and tumour development in the rodent liver is well-documented and is not considered relevant to human risk.	• Liver effects in the toxicology studies are of little relevance to humans because: 1) cytochrome P (CYP) enzymes in rodents differ from those in humans, and induction of liver enzymes in rodents is not always reflective of liver enzyme induction in humans; in vitro studies with human hepatocytes indicated that prasugrel has a low potential for induction in humans; and 2) overt hepatic toxicity in mice occurred at lethal levels only. The association of enzyme induction and tumour development in the rodent liver is well-documented and is not considered relevant to human risk.
General safety pharmacology • Cardiovascular (including potential for QT interval prolongation) • Nervous system	No key safety findings
Mechanisms for drug interactions • No nonclinical drug-drug interaction studies were conducted.	Refer to Part II Module SVII (see Section SVII.4) of this RMP
Other toxicity-related information or data	No key safety findings

There is no need for additional nonclinical data.

SII. Conclusions on Nonclinical Data

There were no safety-related findings in nonclinical studies that would preclude the use of prasugrel to treat patients with acute coronary syndrome (ACS) who are managed by percutaneous coronary intervention (PCI).

Part II: Safety Specification

SIII. Clinical Trial Exposure

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

SIII.1. Overview of Development

Prasugrel, a thienopyridine adenosine diphosphate (ADP) receptor antagonist, is an orally administered prodrug requiring in vivo metabolism to form the active metabolite (R-138727) that irreversibly inhibits platelet activation and aggregation mediated by the P2Y12 receptor (Niitsu et al. 2005). Prasugrel is a therapeutic agent for the reduction/prevention of atherothrombotic cardiovascular events in subjects with acute coronary syndrome (ACS), including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) who are managed by percutaneous coronary intervention (PCI). This is the only currently approved indication for prasugrel.

SIII.2. Clinical Trial Exposure

The following sections present exposure data for completed, Lilly-sponsored studies. Since there have been no additional completed Lilly-sponsored studies since the previous risk management plan (RMP) update, these exposure data have not changed since that update. One non-Lilly-sponsored study, the Dual Antiplatelet Therapy Study (DAPT, Mauri et al. 2014), has completed since the previous RMP update. DAPT was a multi-centre, randomized, double-blind, placebo-controlled trial comparing dual antiplatelet therapy for 12 versus 30 months after drug-eluting stent (DES) placement. The Food and Drug Administration (FDA) requested that United States (US) stent manufacturers provide support for this study and, that P2Y12 receptor inhibitors (such as Prasugrel) be included in this study. An ongoing, Lilly-sponsored, post-approval study examining the efficacy and safety of Prasugrel plus aspirin following placement of a TAXUS Liberté stent (H7T-MC-TADN, Garratt et al. 2015), contributed a large proportion of patients to the DAPT study. Since Lilly does not currently have access to the DAPT database, Prasugrel exposure data from this study are not included in the following sections.

Table SIII.1. Duration of Exposure to Prasugrel

All Clinical Studies in Patients with ACS, Stable CAD, and Elective PCI[a]		
Duration of Exposure	**Persons**	**Person-Time (Years)**
At Least One Dose	17,164	12,708.1
≥3 Days	15,666	
≥14 Days	14,946	
≥1 month	13,177	
≥3 months	10,412	
≥6 months	9714	
≥9 months	8228	
≥12 months	6678	9788.5
≥15 months	4543	
≥18 months	1726	
≥24 months	955	
≥27 months	732	
≥30 months	243	

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

[a] This table 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

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

Table SIII.2. Exposure by Dose of Prasugrel

All Clinical Studies in Patients with ACS, Stable CAD, and Elective PCI[a]		
Dose of Exposure	**Persons**	**Person-Time (Years)**
60 mg LD / 15 mg MD	272	24.4
60 mg LD / 10 mg MD	8625	6689.2
30/30 mg LD / 10 mg MD	1103	89.4
60 mg LD / 5 mg MD	226	18.2
30/30 mg LD / 5 mg MD	241	19.0
40 mg LD / 7.5 mg MD	218	20.2
40 mg LD / 5 mg MD	19	1.5
30 mg LD / 10 mg MD	246	233.9
30 mg LD / 7.5 mg MD	122	0.6
30 mg LD / 5 mg MD	251	27.7
60 mg LD	41	0.1
30/30 mg LD	24	0.1
30 mg LD	673	1.8
10 mg MD	4318	4750.3
5 mg MD	785	831.6

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; LD = loading dose; MD = maintenance dose; PCI = percutaneous coronary intervention.

[a] This table 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

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

Table SIII.3. Exposure to Prasugrel by Age Group and Gender

All Clinical Studies in Patients with ACS, Stable CAD, and Elective PCI[a]				
	Male		**Female**	
Age Group	**Persons**	**Person-Time (Years)**	**Persons**	**Person-Time (Years)**
≥75 years	1527	1045.4	1174	887.4
<75 years	10,661	7813.7	3802	2961.6
Total	**12,188**	**8859.0**	**4976**	**3849.1**

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

[a] This table 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

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

Table SIII.4. Exposure to Prasugrel by Ethnicity/Racial Origin

All Clinical Studies in Patients with ACS, Stable CAD, and Elective PCI[a]		
Ethnic/Racial Origin	**Persons**	**Person-Time (Years)**
Caucasian	14,304	10,295.6
African	445	312.5
Hispanic	700	773.5
Asian	1571	1259.0
Other	93	64.3

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

[a] This table 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

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

Table SIII.5. Exposure in Special Populations

Prasugrel Subjects in Clinical Pharmacology Studies (N=898)		
	Persons	**Person-Time**
Renal impairment [a,b]	37	N/A
Hepatic impairment [a,c]	22	N/A

[a] Exposure in other special populations (e.g., pregnant/lactating women, paediatric subjects, subjects with severe cardiac impairment, subpopulations with genetic polymorphisms, or immune-compromised subjects) is not applicable.

[b] Studies in renally impaired subjects included single loading-dose studies with multiple phases for dosing and appropriate wash-out periods (5-, 10-, 30-, and 60-mg prasugrel), and no multiple-dose studies.

[c] Studies in hepatically impaired subjects included single loading dose studies with multiple phases for dosing and appropriate wash-out periods (60-mg prasugrel), and multiple-dose (maintenance dose) studies (10-mg prasugrel).

Studies include: S001, S002, S003, S004, TAAA, TAAB, TAAC, TAAE, TAAF, TAAI, TAAJ, TAAK, TAAN, TAAO, TAAP, TAAQ, TAAR, TAAS, TAAT, TAAU, TAAV, TAAW, TAAX, TAAZ, TABF, TABS, TABV, TABW, TABZ, TACF, TACG, TACJ, and TACK.

Sources: Summary of Clinical Safety from initial MAA: Section 2.7.4.7; Table APP.2.7.4.1; Table APP.2.7.4.2; Table APP.2.7.4.3.

References

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Part II: Safety Specification

SIV. Populations Not Studied in Clinical Trials

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

SIV.1. Limitations of Adverse Drug Reaction Detection Common to Clinical Trial Development Programmes

Table SIV.1. Ability to Detect Adverse Reactions (Limitation of Trial Programme)

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	The number of subjects exposed to prasugrel in the primary safety database (Study TAAL plus Study TABY) is 11,364.	The 95% CI for the rate of any undetected AE for prasugrel for all subjects exposed to any dose is 0.03% or less.
Due to prolonged exposure	In the TRITON study, patients were exposed to prasugrel for up to 15 months. In the TRILOGY and TAXUS Liberte studies, patients were exposed to prasugrel for up to 30 months. There is no long-term exposure data available for prasugrel beyond 30 months.	No AEs that appear to be due to prolonged exposure to prasugrel have been observed in patients taking prasugrel.
Due to cumulative effects	There is no evidence of cumulative effects with prasugrel.	After an estimated 2.7 million postmarketing exposures, and after 6 years on the market, there has been no evidence of any specific organ toxicity due to cumulative effects.
Which have a long latency	There is no long-term follow-up information following exposure in clinical trials.	It is unknown from clinical trial data if ADRs occurring with long latency could occur after exposure to prasugrel. However, after an estimated 2.7 million postmarketing exposures, and after 6 years on the market, there has been no signal with respect to adverse effects of long latency.

Abbreviations: ADRs = adverse drug reactions; AE = adverse events; CI = confidence interval.

SIV.2. Effect of Exclusion Criteria in the Clinical Trial Development Plan

In the prasugrel clinical development programme, 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:

- subjects with active internal bleeding
- subjects at increased risk of bleeding due to use of concomitant medications (for example, fibrin-specific fibrinolytic therapy or nonfibrin-specific fibrinolytic) or clinical conditions that are associated with an increased risk of bleeding
- subjects with clinical history of haemorrhagic or ischaemic stroke, transient ischaemic attack (TIA), intracranial neoplasm, arteriovenous malformation, or aneurysm
- subjects with International Normalisation Ratio (INR) known to be greater than 1.5, platelet count of less than 100,000/mm^3, and anaemia (haemoglobin [Hgb] below 10 g/dL)
- 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])
- subjects with severe hepatic dysfunction (Child Pugh Class C) are also excluded from clinical trials with prasugrel because the risk of bleeding in these patients could cause confounding results in the clinical trial regarding the assessment of bleeding.

Subjects with known allergy to aspirin and commercially available thienopyridines (clopidogrel and ticlopidine) are excluded from clinical trials with prasugrel, as hypersensitivity to the active substance or to any of the excipients is contraindicated. Patients with serious acute medical conditions were generally excluded from studies, as were patients with a high risk of mortality unlikely to be altered by acute or chronic thienopyridine therapy (cardiogenic shock, Class IV congestive heart failure [CHF], refractory ventricular arrhythmia, end-stage renal disease (ESRD) requiring dialysis), patients with uncontrolled hypertension, and patients with conditions associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence. Patients who were pregnant or breastfeeding were excluded.

The safety of prasugrel in populations excluded from clinical trials, such as patients who are pregnant or breastfeeding, patients with severe hepatic or renal impairment, patients <18 years old, etc., has been regularly assessed through routine surveillance and presented (if applicable) in the periodic safety update reports (PSURs) since the first prasugrel marketing authorisation in the EU (2009). No new risks or specific issues relating to these populations have been observed.

The exclusion criteria for the target population which will remain as contraindications, as was required by the Committee for Medicinal Products for Human Use (CHMP), are listed in Table SIV.2. There are no exclusion criteria that are not proposed to remain as contraindications.

Table SIV.2. 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.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Children

Prescribing information states that prasugrel is not recommended for use in infants, children, or adolescents (that is, patients below age 18) due to a lack of data on safety and efficacy.

The use of prasugrel in the paediatric population with acute coronary syndrome (ACS) is unlikely.

Any reported off-label use in paediatrics is considered an "exposure condition" according to Lilly internal procedures. Off-label use in paediatrics will be evaluated by routine pharmacovigilance activities and appropriately reported to regulatory authorities.

Lilly conducts monthly surveillance activities, and additional surveillance if warranted, for relevant special populations (such as paediatric patients) based on the likelihood of use and/or potential differences in the risk/benefit profile in such a population. If a serious safety signal is identified in a special population, Lilly will conduct further targeted assessment(s), as appropriate.

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 or Breast Feeding Women

Although pregnant and breastfeeding women are excluded from clinical trials with prasugrel, 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. There have been no case reports involving use of prasugrel during lactation/breastfeeding.

Patients with Hepatic Impairment

The effects of mild and moderate hepatic impairment were assessed in 2 clinical pharmacology studies. The pharmacokinetics (PK) of prasugrel and its pharmacodynamic (PD) effects were similar in subjects with mild to moderate hepatic impairment compared to healthy subjects. No dosage adjustment is necessary in subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B). The PK and PD of prasugrel in patients with severe hepatic disease 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.

Proposed pharmacovigilance activities for subjects with severe hepatic impairment include continuing to analyse adverse event (AE) reports in clinical trials, and periodically reviewing and analysing the safety database for any spontaneously reported case associated with severe hepatic impairment.

Patients with Moderate to Severe Renal Impairment

The effects of moderate and end-stage renal disease were assessed in 3 clinical pharmacology studies. The PK of prasugrel's 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. Prasugrel induced platelet aggregation (IPA) was also similar in patients with ESRD who required haemodialysis compared to healthy subjects, although maximum observed drug concentration (C_{max}) and the area under the concentration versus time curve (AUC) of the AM was 51% and 42% lower, respectively in ESRD patients than in healthy subjects. In TRITON-TIMI 38, no trend toward increased AM exposure with increasing serum creatinine could be discerned, regardless of sex. No dosage adjustment is necessary for patients with renal impairment, although there is limited experience in patients with ESRD.

A very small number of case 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.

Patients with renal impairment have been studied during the clinical trial development programme. Lilly will continue to perform surveillance for renal impairment.

Patients with Other Relevant Comorbidities

Subjects with ACS who have the following co-morbidities have been studied with prasugrel: hypertension, dyslipidaemia, diabetes, CHF, or previous myocardial infarction, history of atrial fibrillation, peripheral arterial disease, and history of peptic ulcer disease, and hence, are not a limitation in the prasugrel clinical development programme.

Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

Not applicable.

Sub-populations Carrying Known and Relevant 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.

Patients of Different Racial and/or Ethnic Origin

Patients of varying racial and/or ethnic origin have been studied with prasugrel. Asian subjects were studied in Study H7T-MC-TACE (TACE) and Study H7T-MC-TABY (TABY), and no safety concerns related to ethnicity were identified. In Japan Study J301 and Study J302, in which lower doses of prasugrel were used, there were also no safety concerns related to ethnicity identified.

SIV.4. Conclusions on the Populations Not-Studied and Other Limitations of the Clinical Trial Development Programme

During the clinical trial development programme of prasugrel, there have been populations not studied and other limitations, as described in previous sections. Since the first marketing authorisation for prasugrel in the EU (2009), there have been 17,164 patient exposures investigating prasugrel in patients with ACS-PCI in clinical trials (***Note:*** this exposure number does not include clinical pharmacology studies or studies conducted in Japan by Daiichi-Sankyo).

Table SIV.3. Safety Concerns due to Limitations of the Clinical Trial Program

		Outstanding Concern?
Safety Concern	**Comment**	**Yes/No**
Concomitant use with fibrinolytics, other thienopyridines, warfarin, and chronic use of NSAIDs (non-ASA)	Patients concomitantly using fibrinolytics, other thienopyridines, warfarin, or chronic use of NSAIDs (non-ASA) were excluded from prasugrel trials (see Section SIV.2).	Yes
Paediatric population	Patients <18 years of age were excluded from prasugrel trials in ACS patients (see Section SIV.2).	Yes
Pregnant/Lactating women	Pregnant or breastfeeding women were excluded from prasugrel trials (see Section SIV.2).	Yes
Subjects without clinical manifestation of ACS	In the prasugrel clinical development program, the primary population studied was patients with ACS undergoing PCI (patients with ACS not managed by PCI were studied in the TRILOGY study). Patients without clinical manifestation of ACS were not eligible.	Yes

		Outstanding Concern?
Safety Concern	**Comment**	**Yes/No**
Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory ventricular arrhythmia)	Patients with cardiogenic shock, Class IV CHF, and refractory ventricular arrhythmia were excluded from prasugrel trials (see Section SIV.2).	Yes
Subjects with severe hepatic impairment	Patients with severe hepatic impairments were excluded from prasugrel trials (see Section SIV.2).	Yes

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin); CHF = congestive heart failure; NSAIDs = non-steroidal anti-inflammatory drugs; PCI = percutaneous coronary intervention.

Part II: Safety Specification

SV. Post-Authorisation Experience

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

SV.1. Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons

Table SV.1. Detailed Description of Action(s) Taken since Last Update to this Module

Not applicable	
Background to Issue	N/A
Evidence Source	N/A
Action Taken	N/A
Countries Affected	N/A
Date(s) of Action	N/A

Abbreviations: N/A = not applicable.

Table SV.2. Rejection of Marketing Authorisation Application in Indonesia

Countries	Action Taken	Comment	Date(s)
Indonesia	Lilly received a letter from the National Committee on Drug Evaluation stating that in Indonesia, the marketing authorisation application for treatment of ACS PCI was rejected based upon an interpretation that the benefit/risk for prasugrel was inferior to that of clopidogrel. Lilly appealed this decision, but the appeal was not accepted based upon the interpretation that the benefit/risk for prasugrel was inferior to that of clopidogrel.		16 Aug 2013

Abbreviations: ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

Table SV.3. Bleeding: Additional Characterisation when Prasugrel is Administered Prior to Coronary Angiography in NSTEMI Patients

Countries	Action Taken	Comment	Date(s)
Global	Proposed labelling changes and a Direct Healthcare Professional Communication (DHPC).	The important potential risk of pretreatment, which was previously referred to as 'off-label use' was updated to an important identified risk and entitled "Bleeding associated with prasugrel use prior to coronary angiography in NSTEMI patients".	CDS updated 12 July 2013; changes to the SPC were approved in December 2013.

Abbreviations: CDS = Core Data Sheet; NSTEMI = non-ST-elevation myocardial infarction; SPC = Summary of Product Characteristics.

Table SV.4. Addition of Bleeding Data for Age (<75 years, ≥75 years) and Body Weight Subgroups (<60 kg, ≥60 kg) from the TRILOGY Study

Countries	Action Taken	Comment	Date(s)
Global	Bleeding data for age (<75 years, ≥75 years) and body weight subgroups (<60 kg, ≥60 kg) from the TRILOGY Study (Study TABY) was added to Section C.8 ("Undesirable Effects") of the CDS. (To avoid confusion, the prasugrel dose was specified for TRITON age and body weight subgroups because the prasugrel dose differed from the TRILOGY dose for these subgroups).		CDS updated 29 Oct 2012, and subsequently included in local labelling.

Abbreviations: CDS = Core Data Sheet.

Table SV.5. Hypersensitivity Including Angioedema

Countries	Action Taken	Comment	Date(s)
Global	Special Warnings and Precautions was updated to reflect hypersensitivity including angioedema in prasugrel patients, including those with a history of hypersensitivity reaction to clopidogrel, and a DHPC was disseminated in the EU.		CDS updated 04 May 2011 and subsequently included in local labelling.

Abbreviations: CDS = Core Data Sheet; DHPC = Direct Healthcare Professional Communication; EU = European Union.

Table SV.6. Thrombotic Thrombocytopenic Purpura (TTP)

Countries	Action Taken	Comment	Date(s)
Global	Thrombotic Thrombocytopenic Purpura (TTP) was classified as an important identified risk, and labelling (SPC Section 4.4 ["Special Warnings and Precaution for Use"] and Section 4.8 ["Undesirable Effects"]) was updated.		CDS updated 11 June 2010 and subsequently included in local labelling.

Abbreviations: CDS = Core Data Sheet; SPC = Summary of Product Characteristics .

SV.2. Nonstudy Postauthorisation Exposure

SV.2.1. Method used to Calculate Exposure

The methodology for calculating prasugrel patient exposure utilises internal bulk sales data, samples distributed, IMS Midas days of therapy and standard units, IMS National Disease and Therapeutic Index data, and IMS National Prescription Audit data. A weighted average of the total possible days of therapy from the internal bulk sales data and the IMS Midas data was determined. The possible days of therapy were then factored by an average length of therapy and average courses of treatment, assumptions to determine the estimated patient exposure estimate for each country or region. Other common assumptions, such as the amount of drug not

ingested and the amount of product in inventory, were not included; thus, the resulting patient exposure estimates do not account for product that may not have reached patients.

Postmarketing Exposure by Age Group and Gender

A summary of global estimated patient exposure for prasugrel by patient age group and gender is provided in Table SV.7. These data were derived from IMS data regarding actual prescriptions. The IMS data were used to calculate the proportion of male/female patients and patients in each age group who had received a prescription for prasugrel. The overall exposure estimates in the section above were then compared to those proportions to get a patient estimate by gender and age group.

Table SV.7. Estimated Age and Gender Distributions of Global Cumulative Postmarketing Patient Exposure for Prasugrel

Age Group	Gender			
	Male	Female	Unspecified	Totals[a]
0-17 years	--	--	--	--
18-64 years	1,369,000	261,000	8,000	1,639,000
65-74 years	599,000	154,000	1,000	755,000
≥75 years	170,000	93,000	--	264,000
Unspecified	11,000	16,000	6,000	34,000
Total[a]	**2,151,000**	**526,000**	**15,000**	**2,693,000**

[a] Totals may not sum due to independent rounding.

Source: tpe_age_gender_report_EFFIENT_Core_RMP_v7_pt_exp_31JAN2015.doc.

Postmarketing Exposure by Indication

Prasugrel has only one indication: acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI).

Postmarketing Exposure by Route of Administration

There is only one route of administration for prasugrel.

Postmarketing Exposure by Dose

Data not available.

Postmarketing Exposure by Country/Region

Postmarketing exposure of prasugrel by country/region is shown in Table SV.8.

Table SV.8. Postmarketing Exposure by Country/Region

Country/Region	Total Patient Years of Exposure	Total Patient Exposure
WORLDWIDE	1,505,900	2,693,700
UNITED STATES	831,291	1,487,006
GERMANY	182,720	326,847
FRANCE	124,976	223,556
ITALY	63,893	114,291
UNITED KINGDOM	43,312	77,477
SPAIN	36,839	65,897
GREECE	25,122	44,938
NETHERLANDS	20,812	37,229
AUSTRALIA	19,111	34,186
SWITZERLAND	18,496	33,086
BRAZIL	15,027	26,881
AUSTRIA	13,778	24,647
CANADA	11,023	19,718
ISRAEL	10,897	19,492
BELGIUM	9,672	17,301
MEXICO	9,440	16,886
IRELAND	7,306	13,068
DENMARK	7,013	12,544
KOREA, REPUBLIC OF	5,183	9,271
VENEZUELA	4,915	8,791
SLOVAKIA	4,640	8,301
SWEDEN	3,611	6,459
HUNGARY	3,541	6,335
LEBANON	2,901	5,189
POLAND	2,894	5,177
SLOVENIA	2,538	4,541
ARGENTINA	2,197	3,929
HONG KONG	2,023	3,618
INDIA	1,951	3,490
FINLAND	1,898	3,395
GUATEMALA	1,892	3,385
MALAYSIA	1,772	3,169
TURKEY	1,714	3,066
CZECH REPUBLIC	1,711	3,060
PHILIPPINES	1,462	2,616
SINGAPORE	1,443	2,580
THAILAND	1,415	2,531
IRAQ	1,036	1,853

Country/Region	Total Patient Years of Exposure	Total Patient Exposure
BULGARIA	938	1,677
COLOMBIA	534	956
IRAN (ISLAMIC REPUBLIC OF)	489	874
CYPRUS	419	750
NORWAY	353	631
ROMANIA	329	588
SOUTH AFRICA	310	555
DOMINICAN REPUBLIC	200	357
PERU	147	263
NEW ZEALAND	142	254
OTHERS[a]	599	1072

[a] "Others" include aggregated estimate of countries with small estimations

Source: effient_Core_RMP_v7_pt_exp_31JAN2015

SV.3. Postauthorisation Use in Populations not Studied in Clinical Trials

Postmarketing Use in Paediatric Populations

No market research data/drug utilisation data are available in the paediatric populations. Prasugrel is not indicated for use in children.

Postmarketing Use in Elderly Populations

The marketing authorisation holder (MAH) has completed all European Union (EU) regulatory committed studies, including drug utilization studies. These studies have provided information on patterns of prasugrel use in an outpatient setting. Data are available in the very elderly population (patients ≥75 years of age) from Studies H7T-MC-B011 (B011) (Germany, the United Kingdom, and France), H7T-MC-B008 (B008) (Germany), H7T-MC-B010 (B010) (Sweden), the recently completed Study H7T-MC-B015 (B015) (Switzerland), and H7T-MC-B016 (B016) (France).

Data from all completed observational studies showed that the absolute numbers and the rates of prasugrel use in patients ≥75 years of age are lower than prasugrel use in patients <75 years of age (see country-specific data below). The studies also demonstrated that physicians were less likely to prescribe prasugrel than clopidogrel in patients ≥75 years of age. For example, Study B008 showed 6.0% prasugrel-treated patients were of ≥75 years age versus 38.8% of clopidogrel-treated patients. While prasugrel is infrequently used in patients ≥75 years of age, it appears that the 10-mg dose is being prescribed more frequently than the recommended 5-mg maintenance dose (MD), possibly due to individual prescriber medical judgment. For example, among patients ≥75 years of age, patients prescribed the 10-mg MD have a higher body weight compared to patients prescribed a 5-mg MD (see United Kingdom Study B011 data below). The hypothesis that physicians selectively prescribe the prasugrel 10-mg MD over the 5-mg MD in certain patients based on an individual benefit/risk assessment is supported by the low bleeding rates seen despite the use of the 10-mg dose, suggesting selection of patients at lower risk of bleeding based on other characteristics.

Below is a summary of the important information related to postmarketing use in the elderly population from postmarketing studies:

- France
  - In Study B011: 5.4% (57/1052) of patients treated with prasugrel were ≥75 years of age; 3.5% (2/57) of the patients ≥75 years receiving prasugrel were treated with a 5-mg dose. (The 5-mg prasugrel tablet is not marketed in France).
  - In Study B016: 28 of the 763 prasugrel-treated PCI patients (4%) were ≥75 years of age. The prasugrel dose received for these patients who were ≥75 years was not specified in the B016 report; however, the majority (approximately 98%) of the prasugrel-treated PCI patients (regardless of age) were receiving a 10-mg dose of prasugrel at the time of discharge from the hospital (the 5-mg prasugrel tablet is not marketed in France).
- United Kingdom
  - In Study B011: 10.3% (163/1580) of patients treated with prasugrel were ≥75 years of age; 44.8% (73/163) of those ≥75 years receiving prasugrel were treated with a 5-mg dose.
- Germany
  - In Study B011: 9.2% (136/1474) of patients treated with prasugrel were ≥75 years of age; 29.4% (40/136) of those ≥75 years receiving prasugrel were treated with a 5-mg dose.
  - In Study B008: for patients in the "all prasugrel and ACS clopidogrel population" (the largest population in the study, which included 2740 prasugrel-treated patients), 158 of these 2740 patients (5.8%) were ≥75 years of age. Of the very elderly patients who received a prasugrel MD, the majority (76.6%) received a prasugrel MD of 10 mg.
- Sweden
  - In Study B010: of the 2990 prasugrel-treated ACS-PCI patients, 21.7% (650/2990) were ≥75 years of age. In this study, the exact dose of prasugrel was not collected.
- Switzerland
  - In Study B015: of the 756 prasugrel-treated ACS patients, 7.5% (57/756) were ≥75 years of age. The prasugrel dose received for the patients who were ≥75 years of age was not specified in the report.

In Study B011, where body weight data were available, patients ≥75 years of age treated with the 10-mg tablet had a higher mean body weight than those prescribed a 5-mg dose.

- United Kingdom
  - Of patients ≥75 years, mean body weight was 78 kg for those receiving a 10-mg dose and was 69 kg for those receiving a 5-mg dose; body weight was unknown for only 3 of 163 patients.
- Germany
  - Of patients ≥75 years, mean body weight was 82 kg for those receiving a 10-mg dose and was 76 kg for those receiving a 5-mg dose; body weight was unknown for only 1 of 136 patients.

Postmarketing Use in Pregnant or Breast Feeding Women

No market research data/drug utilisation data are available in pregnant or lactating women. The MAH does not have safety information to suggest that there are safety issues specific to this population.

Postmarketing Use in Patients with Hepatic Impairment

No market research data/drug utilisation data are available in patients with hepatic impairment. As stated in current labelling, prasugrel should be used with caution in patients with severe hepatic impairments given their propensity to bleed.

Postmarketing Use in Patients with Renal Impairment

No market research data/drug utilisation data are available in patients with renal impairment. As stated in current labelling, prasugrel should be used with caution in patients with renal impairments given their propensity to bleed.

Other Use Postmarketing

Not applicable.

SV.4. Post-authorisation Off-Label Use

Table SV.9. Off-Label Use in European Union

Off-Label Category	Country	Source of Information	Comment[a]
Paediatrics	France	Study B011: Prasugrel Treatment Patterns in Outpatient Settings in Germany, the United Kingdom, and France	Data from outpatient database (IMS Analyzer) found 0.3% (3 out of 1052 patients with prasugrel prescription) of the study population were paediatric patients. There were no paediatric cases from Germany or the United Kingdom.
Use of prasugrel prior to coronary visualisation in NSTEMI patients[b]	Germany	Study B008: Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel and Prasugrel During the Index Hospitalisation in Germany	Data from study B008 found 52.2% (1329 of 2548 prasugrel-treated patients receiving loading dose during the index hospitalisation) of the study population had prasugrel prior to coronary visualisation.[c] (In Study B008, there was a higher percentage of pretreatment in the UA/NSTEMI [70.4%] versus the STEMI population [46.2%]).
	Sweden	Study B010: Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel or Prasugrel During the Index Hospitalisation in Sweden	Data from Study B010 found that 42.7% (1243 of 2908 prasugrel-treated ACS-PCI patients with data available) had prasugrel prior to coronary visualisation[c] (In Study B010, treatment patterns differed for prasugrel-treated patients based on ACS subtypes; UA/NSTEMI patients were less likely to receive prasugrel before PCI than STEMI patients (25.3% versus 52.3%).

Off-Label Use in European Union

Off-Label Category	Country	Source of Information	Comment[a]
Contraindication of prior TIA or stroke	Germany	Study B011: Prasugrel Treatment Patterns in Outpatient Settings in Germany, the United Kingdom, and France	Data from outpatient database (IMS Analyzer) found 1.8% (27out of 1474 patients with prasugrel prescription) of the study population had a history of TIA or stroke.
	France		Data from outpatient database (IMS Analyzer) found 0.2% (2 out of 1052 patients with prasugrel prescription) of the study population had a history of TIA or stroke.
	United Kingdom		Data from outpatient database (IMS Analyzer and GPRD) found 4.0% (63 out of 1580 patients with prasugrel prescription) of the study population had a history of TIA or stroke.
	Germany	Study B008: Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel and Prasugrel During the Index Hospitalisation in Germany	Data from study B008 found 1.5% (41 of 2689 prasugrel-treated patients receiving loading dose during the index hospitalisation) of the study population had a history of TIA or stroke.
	Switzerland	Study B015: Treatment Patterns and Bleeding Risks in ACS Patients Treated with Clopidogrel or Prasugrel During the Index Hospitalisation and Follow-Up in Switzerland" (an observational study in patients post-ACS treated with prasugrel or clopidogrel in the SPUM-ACS Cohort)	Data from Study B015 found 1.3% (10 of the 756 prasugrel-treated patients) of the study population had a history of TIA/stroke.
	France	Study B016: Treatment Patterns in Acute Myocardial Infarction Patients Initiated with Prasugrel or Clopidogrel During the Index Hospitalisation with One Year Follow-Up	Data from Study B016 found that 0.3% (2 of 763 prasugrel-treated PCI patients) had a history of TIA/stroke.

Off-Label Use in European Union

Off-Label Category	Country	Source of Information	Comment[a]
Contraindication of prior TIA or stroke (*continued*)	Summary of the MAH's interpretation of the TIA/stroke data	Not applicable	Overall, the rates do not suggest any public health concerns. The registry data suggest that in general, physicians are prescribing clopidogrel rather than prasugrel to patients with a history of TIA/stroke, and therefore are aware of the risk. While the majority of patients treated with platelet inhibitors are prescribed clopidogrel, there will necessarily be a certain percentage of physicians who, after considering the benefit/risk balance for their individual patient, will determine that prasugrel is medically indicated, and may prescribe prasugrel to a patient with a prior TIA/stroke. This would include patients who are not tolerant of clopidogrel, and who have side effects prohibiting use with ticagrelor such as dyspnea.

Abbreviations: ACS = acute coronary syndrome; GPRD = general practice research database; MAH = marketing authorisation holder; NSTEMI = Non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction; TIA = transient ischaemic attack; UA = unstable angina.

a The variability of the numbers between these countries is due to the way data is captured in the databases for each study. This causes variability of rates, which are not amenable to comparisons.

b The studies listed here evaluated pretreatment broadly. Currently, the off-label use of prasugrel prior to coronary visualisation is specific to the treatment of UA/NSTEMI patients.

c In these registry studies, "prior to coronary visualisation" was defined as the patient receiving prasugrel within 24 hours prior to PCI, which was defined as the time point that the patient entered the catheterisation laboratory. The exact timing of thienopyridine doses was not collected.

SV.5. Epidemiological Study Exposure

Epidemiological study exposure is included in Table SV.10.

Table SV.10. EU Epidemiological Studies

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Study is published
Study B008, "Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel and Prasugrel During the Index Hospitalisation in Germany" A prospective, non-interventional cohort study	To compare the incidence rates of any non-CABG related bleeding (requiring any blood transfusion of whole blood or red blood cell concentrates [RBCs]) and/or intracranial haemorrhage (ICH) between prasugrel and clopidogrel patients treated for ACS-PCI (the indicated population for prasugrel) during the index hospitalisation. To compare the incidence rates of any bleeding (requiring any blood transfusion of whole blood or RBCs) and/or ICH in all prasugrel initiators and all clopidogrel initiators, and in identified subgroups of patients at increased risk for bleeding. To describe incidence rates of any bleeding in all prasugrel and clopidogrel initiators quantified by receiving any transfusion or not and by number of units transfused, and by bleeding location. To describe the number, percentage, patient characteristics, and outcomes (for example, bleeding or death) in all prasugrel initiators who: are not indicated (elective PCI, non-ACS), are contraindicated (history of TIA/stroke), are treated with prasugrel and do not undergo angiography, receive loading dose prior to coronary visualisation, are treated with a 5-mg dose or any other maintenance dose, are very elderly (≥75 years), have a low body weight (<60 kg).	Patients Treated with Clopidogrel and Prasugrel During the Index Hospitalisation in Germany	During the index hospitalisation	Total # of patients: 11,201	Final study report completed in August 2013; submitted alongside RMP version 8.

EU Epidemiological Studies

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Study is published
Study B010, "Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel or Prasugrel During the Index Hospitalisation in Sweden" (report based on cumulative data collected in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), which includes all the angio/PCI patients in Sweden) A retrospective, non-interventional cohort study	To compare the incidence rates of SCAAR-defined major or minor bleeding between only-prasugrel-treated plus prasugrel/clopidogrel-treated patients and only-clopidogrel-treated patients with ACS undergoing PCI (the indicated population for prasugrel) during the index hospitalisation. To compare the incidence rates of SCAAR-defined major or minor bleeding in the following only-prasugrel-treated plus prasugrel/clopidogrel-treated ACS-PCI patients and only-clopidogrel treated ACS-PCI patients during the index hospitalisation: identified subgroups of patients at increased risk for bleeding (e.g., age ≥75 years, body weight <60 kg). To describe incidence rates of bleeding in only-prasugrel-treated plus prasugrel/clopidogrel-treated patients, only-prasugrel-treated plus prasugrel/clopidogrel-treated ACS patients, only prasugrel-treated plus prasugrel/clopidogrel-treated ACS-PCI patients, and only-clopidogrel treated ACS-PCI patients: by any bleeding, by SCAAR-defined major or minor, by need for blood transfusion.	Patients post-ACS treated with clopidogrel and prasugrel during the index hospitalisation using the SCAAR registry in Sweden.	During the index hospitalisation	Total # of Patients: N=43,321 *Prasugrel*: N=4248; *Clopidogrel*: N=39,073 (***Note:*** some patients received both prasugrel **and** clopidogrel)	The results of the first annual study report were reported along with the submission of PSUR 5, and the results of the second annual study report were reported along with the submission of PSUR 7. The final study report was submitted with PSUR 9.

EU Epidemiological Studies

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Study is published
Study B010 ***(continued)***	To describe treatment patterns and outcomes (for example, bleeding or death) in only-prasugrel-treated plus prasugrel/clopidogrel-treated patients based on: indications (i.e., non-ACS receiving an elective PCI), receiving loading dose prior to coronary visualisation, age (≥75 years versus <75 years), body weight (≥60 kg versus <60 kg).				
Study B011, "Prasugrel Treatment Patterns in Outpatient Setting in Germany, the United Kingdom, and France" A retrospective, non-interventional cohort study	To describe the treatment patterns of prasugrel in outpatient practices in Germany and France using the IMS Disease Analyzer, and in the United Kingdom (UK) using the IMS Disease Analyzer and the General Practitioner Research Database (GPRD).	Prasugrel outpatients in Germany, the United Kingdom, and France	Retrospective database; all data reported are cumulative over a total of 3 years	UK: N=1580; Germany: N=1474; France: N=1052	The final study report for Study B011 (which included the third and final reports for the UK and France, as well as the final report for Germany that was included with the B011 interim report) was submitted with PSUR 8.

EU Epidemiological StudiesStudy Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Study is published
Study B015, "Treatment Patterns and Bleeding Risks in ACS Patients Treated with Clopidogrel or Prasugrel During the Index Hospitalisation and Follow-up in Switzerland" (an observational study in patients post-ACS treated with prasugrel or clopidogrel in the SPUM-ACS cohort) A retrospective, non-interventional cohort study	To describe the incidence rates of bleeding in prasugrel- and clopidogrel treated ACS-PCI patients during the index hospitalisation, 30-day follow up and 12-month follow up by: TIMI major or minor; GUSTO severe or life-threatening, moderate, or mild bleeding; Bleeding Academic Research Consortium (BARC) types; bleeding location; identified subgroups of patients at increased risk for bleeding (for example, age ≥75 years, body weight <60 kg). To describe the incidence rates of bleeding in all ACS patients treated with prasugrel or clopidogrel during the index hospitalisation, 30-day follow up, and 12-month follow up by: TIMI major/minor; GUSTO severe or life-threatening, moderate, or mild bleeding; BARC types; bleeding location; identified subgroups of patients at increased risk for bleeding. To describe the incidence rates of bleeding in the core cohort of ACS-PCI patients (with age <75 years, body weight ≥60 kg, and no history of TIA/stroke) treated with prasugrel or clopidogrel during the index hospitalisation, 30-day follow up, and 12-month follow up by: TIMI major/minor; GUSTO severe or life-threatening, moderate, or mild bleeding; BARC types; bleeding location.	Patients post-ACS treated with prasugrel or clopidogrel in SPUM-ACS cohort of patients recruited at the Swiss university hospitals of Geneva, Lausanne, Bern, and Zurich.	During the index hospitalisation, and 30 days and 1-year follow-up	Total # of Patients: N=2360	The results of the first annual study report were reported along with the submission of PSUR 7. The 30-day follow-up report was submitted in Oct 2013 with PSUR 9. Final study report (1-year follow-up) submitted with PSUR 10.

EU Epidemiological Studies

Study Title and **Study Type**	**Objective(s)**	**Population Studied**	**Duration**	**Number of Persons and Person Time**	**Study is published**
Study B015 ***(continued)***	To describe the treatment patterns in ACS patients and the major adverse cardiovascular events (MACE) such as cardiac death, myocardial infarction, stroke, urgent revascularization due to ACS, and definite stent thrombosis according to the Academic Research Consortium (ARC) during the index hospitalisation, 30-day follow up, and 12-month follow up in all prasugrel initiators who: do not receive PCI; have a contraindication for prasugrel treatment (history of TIA/stroke); receive a loading dose prior to coronary visualization; are very elderly (≥75 years); have a low body weight (<60 kg). By the 'core cohort' defined as ACS-PCI patients with age <75 years, body weight ≥60 kg, and no history of TIA/stroke.				

EU Epidemiological Studies

Study Title and **Study Type**	**Objective(s)**	**Population Studied**	**Duration**	**Number of Persons and Person Time**	**Study is published**
Study B016, "Treatment Patterns in Acute Myocardial Infarction Patients Initiated with Prasugrel or Clopidogrel During the Index Hospitalisation with One Year Follow-Up" (a retrospective analysis) A retrospective, non-interventional study	To describe prasugrel and clopidogrel routine use: characteristics of the treated population (characteristics of patients, type of ACS, revascularisation strategy), dosage, duration, interruption and modification of therapy, concomitant treatments. To describe clinical outcomes: during the index hospitalisation: ischemic complications and bleeding complications (TIMI major and minor bleeding, minimal bleeding); during the follow-up period: any event requiring a new hospitalisation and any treatment modification (medication stopped, new medication, modification of dosage, date of any change); death and reason of death during the index hospitalisation and during the follow-up period.	Subset of data contained within the French FAST-MI 2010 registry.	Initial hospitalisation and 12 months of follow-up	N=3000 (Prasugrel=360)	The results of the first annual study report were reported with PSUR 6. The results of the final study report were submitted with PSUR 9.

EU Epidemiological StudiesStudy Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Study is published
Study B021, "Assessment of the effectiveness of risk minimisation measures set up for new safety information of Efient® (Prasugrel): a multinational survey among physicians to evaluate their knowledge and consideration of the new safety warning of Prasugrel in four EU countries" A non-interventional, cross-sectional survey	Primary objective: to evaluate the proportion of targeted physicians who are knowledgeable of the new safety warning for Prasugrel. Secondary objective: to evaluate whether the physicians will consider the safety warning when prescribing Prasugrel.	The survey was conducted among physicians in 4 European countries (France, Germany, Sweden, and the Netherlands) who are current prescribers or potential prescribers of Efient® (Prasugrel). (**Note: This study evaluated prescriber knowledge of the recent DHCP letter [DHCP letter to inform prescribers of increased risk of serious bleeding in UA/NSTEMI patients undergoing PCI if prasugrel is administered prior to diagnostic coronary angiography*]).	N/A	N=389 physicians participated in the survey	The final report was approved on 05 Jan 2015 and is being submitted with the accompanying PSUR (PSUR 11)

Abbreviations: ACS = acute coronary syndrome; CABG = coronary artery bypass graft; DHCP = Dear Healthcare Professional Communication; EU = European Union; FAST-MI = French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction; GUSTO = Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries; ICH = intracranial haemorrhage; N = total number of patients; N/A = not applicable; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; PSUR = Periodic Safety Update Report; RMP = risk management plan; SPUM-ACS = - Programm Universitäre Medizin - Acute Coronary Syndrome; TIA = transient ischaemic attack; TIMI = thrombolysis in myocardial infarction; UA = unstable angina; UK = United Kingdom.

Part II: Safety Specification

Module SVI. Additional EU Requirements for the Safety Specification

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

SVI.1. 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 H7T-MC-TAAL (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 risk management plan (RMP) submission, there were no reports noted of subjects who had an overdose of prasugrel. During postmarketing, 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. If the recommended dose is exceeded, the side effects would likely be mechanism-related, such as increased risk of bleeding.

SVI.2. 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 colour mixture. The release testing for the colour 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, minimises 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.

SVI.3. 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.

SVI.4. 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 2 dose forms, each is clearly marked and different in colour.

SVI.4.1. Description of Medication Errors during the Clinical Trial Programme

Unintended medication errors in dispensing or administration during controlled clinical trials are less likely to occur, as the drug is packaged specifically by dose (by the LD or MD). Medication errors in the uncontrolled clinical setting are more likely to be reported than in controlled clinical trials. See Section SVI.4.4 for a description of medication errors with the marketed product.

SVI.4.2. Preventive Measures for the Final Product(s) being Marketed

Patients are provided with a Package Leaflet for Efient. The Package Leaflet provides information about how the product should be stored, how the product should be administered,

what to do in case of side effects or overdose, and notes the difference in appearance and colour of the 5-mg and 10-mg tablets. Additionally, in the Package Leaflet, patients are informed to let the doctor know of any other medications they may be taking, not to take more than the total daily dose in a 24-hour period, to take the medication as instructed by the doctor, not to break or crush the tablets, and not to use Efient after the expiry date, which is stated on the blister and carton.

SVI.4.3. Effect of Device Failure

Not applicable

SVI.4.4. Reports of Medication Errors with the Marketed Product(s)

Table SVI.1. Reports of Medication Errors with Marketed Product

Prasugrel				
Description of Error	**Number of Occurrences**	**Analysis of Cause**	**Steps taken to Prevent**	**Comment**
Wrong Medication	2	Drug confusion with Effizinc in one case and Eliquis in other case	Distinctive marking and colouring differences between Effient, Effizinc, and Eliquis.	N/A
Wrong dose (including strength, form, concentration, or amount)	272	Though there is considerable variability in causes for this type of error, the most common causes for this error include splitting the tablet in half, dispensing prasugrel in pharmacy bottles rather than original container, missing regularly scheduled doses, and special patient populations (less than 60 kg and 75 years and older) receiving the 10-mg dosing.	Current labelling in the SPC recommends 5-mg dosing for prasugrel in special patient populations (less than 60 kg and 75 years and older). The label also provides adequate guidance to the reader to not break tablets as well as to dispense prasugrel in the original container.	Existing current label addresses this type of medication error.
Wrong route of administration	3	Given via feeding tube	Current labelling states that prasugrel is available as an oral dosage form	N/A
Wrong patient	0	N/A	N/A	N/A

Abbreviations: N/A = not applicable; SPC = Summary of Product Characteristics.
Source: Prasugrel_Core_RMP_v7_Med_error_Routine_Surveillance_(01-Jan-1983_to_25-Feb-2015).xls.

SVI.5. Potential for Off-label Use

Potential off-label uses of prasugrel may include:

- treatment of subjects with acute coronary syndrome (ACS) for whom percutaneous coronary intervention (PCI) is not indicated (requiring urgent coronary artery bypass graft [CABG] or suitable for medical management only)
- treatment of subjects with clinical history of coronary artery disease with no symptoms of ACS
- treatment of other clinical manifestations of atherosclerotic disease such as previous myocardial infarction, peripheral arterial disease, and ischaemic stroke
- treatment of subjects with ACS who underwent PCI from populations not studied in Study TAAL
- primary prevention of cardiovascular events
- prescription of higher than the recommended dose, under the belief that higher doses may confer greater efficacy
- prescription of a lower than the recommended dose for subjects who do not require dose reduction
- treatment of subjects with prior history of transient ischaemic attack (TIA) or stroke.

SVI.6. Specific Paediatric Issues

SVI.6.1. Issues Identified in Paediatric Investigation Plans

There is no paediatric investigation plan for prasugrel for the ACS population.

SVI.6.2. Potential for Paediatric Off-label Use

The use of prasugrel in the paediatric population with ACS is unlikely. Studies of clopidogrel in paediatric subjects at risk for thrombosis and coronary disease have been conducted. There is a possibility for potential off-label use of prasugrel in treating paediatric subjects.

Any reported off-label use in paediatrics is considered an "exposure condition" according to Lilly internal procedures. Off-label use in paediatrics will be evaluated by routine pharmacovigilance activities and appropriately reported to regulatory authorities.

SVI.7. Conclusions

- **Potential for Harm from Overdose:** during postmarketing, there have been reports of patients receiving a dose higher than the recommended LD or MD of prasugrel; however, none of these cases were fatal due to the overdose. 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:** this is not considered to be a significant risk.
- **Potential for Medication Errors:** the potential for medication errors with prasugrel is no greater than for most oral medications. Unintended medication errors in dispensing or administration during controlled clinical trials were less likely to occur, as the drug is packaged specifically by dose (by the LD or MD).
- **Potential for Off-label Use:** potential off-label uses for prasugrel may include treatment of subjects with ACS for whom PCI is not indicated, treatment of subjects with clinical history of coronary artery disease without ACS, treatment of other clinical manifestations of atherosclerotic disease, treatment of subjects with ACS who underwent PCI (from patient populations not studied in Study TAAL), treatment for primary prevention of cardiovascular events, giving prasugrel at a dose higher or lower than the dose recommended, and/or treatment of subjects with prior history of TIA or stroke.
- **Paediatric Issues:** there is no paediatric investigation plan for prasugrel for the ACS population. The use of prasugrel in the paediatric population with ACS is unlikely.

Part II: Safety Specification

Module SVII. Important Identified and Potential Risks

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

SVII.1. Newly Identified Important Safety Concerns (Since this Module was Last Submitted)

There have been no newly identified safety concerns since this module was last submitted (RMP version 10).

Table SVII.1. Newly Determined Important Safety Concerns (since This Module was Last Submitted)

Safety Concern 1: N/A	
Details	N/A
Source	N/A
Implications for Product Literature	N/A
New studies proposed in Pharmacovigilance Plan? Yes/No	N/A
New risk minimisation actions proposed? Yes/No	N/A

Abbreviations: N/A = not applicable.

SVII.2. Recent Study Reports with Implications for Important Safety Concerns

There are no recently completed study reports with implications for important safety concerns.

SVII.3. Details of Important Identified and Potential Risks from Clinical Development and Postauthorisation Experience (including Newly Determined)

The final PRAC recommendation for PSUR08 included the requirement that the 10 mg maintenance dose (MD) be "followed up in future RMPs and PSURs". This review addresses the use of the 10 mg MD in patients ≥75 years and older.

For the current reporting period (26 February 2014 to 25 February 2015), there were a total of 1907 initial cases reporting at least one adverse drug reaction (ADR) with 221 cases reported in patients ≥75 years of age. Of these, 47 cases were reported from Japan and were excluded from further review due to differences in approved doses and the 10 mg dose not being available. Another 91 cases from blinded clinical trials were excluded due to lack of dosing information. The remaining 83 cases included 69 spontaneous cases, 5 from post-marketing studies, 4 clinical trial cases, 4 regulatory authority cases, and 1 literature case.

Dosing was provided for 69 of the 83 cases. There were 48 patients receiving 10 mg daily, 19 patients receiving 5 mg daily, and 2 patients received only a 60 mg loading dose. The 69 cases with dosing information were reported from the United States (22 cases), Brazil (17 cases), France (12 cases), and Germany (7 cases), Italy, United Kingdom (2 cases each), Australia, Israel, Korea, Netherlands, Peru, Spain, and Switzerland (1 case each).

The ages of the 48 patients receiving 10 mg daily ranged from 75 to 88 years with a mean age of 78 years and a median age of 77 years. There were 20 females and 28 males. A total of 117 events (60 nonserious, 57 serious) were reported in the 48 patients taking 10 mg daily.

Of the 48 patients receiving 10 mg daily, 19 patients (40%) reported a total of 25 bleeding events with 15 of the events (60%) reported as serious. The most commonly reported bleeding events included epistaxis (6 events), gastrointestinal haemorrhage and haematoma (4 events each), and cerebral haemorrhage, ecchymosis, gastric haemorrhage, and melaena (2 events each). The remaining events were each reported once and included arterial haemorrhage, blood blister, blood urine present, pericardial haemorrhage, periorbital haemorrhage, shock haemorrhagic, and vaginal haemorrhage.

For all cases during the current reporting interval, including cases with unknown dose, in patients <75 years old there were 254 bleeding events out of 2120 total events (12%) and for patients ≥75 years there were 64 bleeding events out of 439 total events (14.6%).

The events reported in patients ≥75 years of age receiving 10 mg MD are consistent with the known safety profile of prasugrel. The safety in patients ≥75 years of age receiving a 10 mg MD will continue to be monitored.

Table SVII.2. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Intracranial Haemorrhage

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 37 (IR=2.96 per 1000 patient-years) ; Clopidogrel - 42 (IR=3.35 per 1000 patient-years),
RR=0.89, 95% CI: 0.57-1.38 p-value 0.5899

Postmarketing Data: Events of intracranial haemorrhage are considered rarely reported (0.014%) based on an estimated patient exposure to prasugrel of 2.7 million.

Seriousness/ Outcomes

Clinical Trial Program:
The distribution of outcomes and seriousness for intracranial haemorrhage 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 = 17,164)	40 (0.23%)	16 (0.09%)	12 (0.07%)	5 (0.03%)	1 (0.01%)	4 (0.02%)	3 (0.02%)
Serious	38 (0.22%)	16 (0.09%)	11 (0.06%)	5 (0.03%)	1 (0.01%)	4 (0.02%)	2 (0.01%)
Non-Serious	2 (0.01%)	0 (0.00%)	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.01%)
Studies TAAL and TABY (N = 11364)	34 (0.30%)	14 (0.12%)	12 (0.11%)	3 (0.03%)	1 (0.01%)	3 (0.03%)	2 (0.02%)
Serious	33 (0.29%)	14 (0.12%)	11 (0.10%)	3 (0.03%)	1 (0.01%)	3 (0.03%)	2 (0.02%)
Non-Serious	1 (0.01%)	0 (0.00%)	1 (0.01%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW,
H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_hcc.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_hcc.rtf.

Postmarketing Data: All of the postmarketing events were serious. Outcomes reported in postmarketing events included fatal (31%), recovered/recovered with sequellae/recovering (25%), not recovered (7%), and unknown (37%).

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Intracranial Haemorrhage (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent intracranial haemorrhage in Studies TAAL and TABY and in all 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 = 17,164)	40 (0.23%)	3 (0.02%)	8 (0.05%)	29 (0.17%)
Studies TAAL and TABY (N = 11364)	34 (0.30%)	2 (0.02%)	7 (0.06%)	25 (0.22%)

Abbreviations: % = percentage of subjects reporting the event; 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; n = number of subjects with events.

* 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-TABY, 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.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_hcc.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_hcc.rtf.

Postmarketing Data: Data not available.

Background incidence/prevalence

The studies below provide information on the background/prevalence of the risk of intracranial haemorrhage:

a) Alexander et al. 2011: placebo arm (n=3687, 31.7% female) of a randomized double-blind ACS clinical trial (APPRAISE-2) conducted in 39 countries between 2009 and 2010. At baseline, diagnosis of ACS was 39.4% STEMI, 41.8% NSTEMI, and 18.1% unstable angina.

Intracranial haemorrhage occurred in 0.1% of the population (0.2 events per 100 patient years) with a median follow-up of 241 days.

b) James et al. 2011: ticagrelor arm (n=2601, mean age 66 years, 36.9% female) of the PLATO project which enrolled ACS patients from 43 countries between 2006 and 2008. Baseline diagnosis of ACS was 8.4% STEMI, 55.6% NSTEMI and 36% unstable angina.

Incidence of intracranial bleeding was 0.5% of the population at 12 months.

c) Mega et al. 2013: In ATLAS ACS-2-TIMI-51, there were 7,817 patients presenting with a STEMI. Rivaroxaban arm 2.5 mg (n=2566, mean age 61.5 years, 79.2% male); Rivaroxaban 5 mg twice daily (n=2,552, mean age 61.3 years, 79.0% male) and placebo arm (n=2,607, mean age 60.8 years, 78.1% male)

Incidence of Intracranial haemorrhage: in 2.5 mg Rivaroxaban arm: 0.4%; in 5 mg Rivaroxaban arm: 0.8%; in placebo arm: 0.1% through 24 months of follow-up.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Intracranial Haemorrhage (continued)	
Risk groups or risk factors	Patients with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding (such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics), are also at higher risk for bleeding.
Potential mechanisms	The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.
Preventability	Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.
Impact on individual patient	Effects of intracranial haemorrhages can manifest as paralysis, severe sudden headaches, slurred speech, and other impairments in cognitive function and could potentially be fatal (Cleveland Clinic 2013). The quality of life varies according to the nature and extent of the bleeding event.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_hcc.rtf and others **Postmarketing Data:** Lilly Safety System
MedDRA (Version 17.1) terms	SMQ haemorrhagic cerebrovascular conditions (20000064) except PTs basal ganglia stroke, brain stem stroke, cerebrovascular accident, cerebrovascular disorder, and stroke in evolution + PTs traumatic intracranial haemorrhage and purpura cerebri

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Gastrointestinal Haemorrhage

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 498 (IR=39.88 per 1000 patient-years) ; Clopidogrel - 351 (IR=27.96 per 1000 patient-years),
RR=1.43, 95% CI: 1.24-1.63; p value<0.001

Postmarketing Data: Events of gastrointestinal haemorrhage are considered rarely reported (0.025%) based on an estimated patient exposure to prasugrel of 2.7 million.

Seriousness/ Outcomes

Clinical Trial Program:

The distribution of outcomes and seriousness for gastrointestinal haemorrhage 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 = 17,164)	539 (3.14%)	8 (0.05%)	435 (2.53%)	53 (0.31%)	7 (0.04%)	48 (0.28%)	44 (0.26%)
Serious	293 (1.71%)	8 (0.05%)	241 (1.40%)	14 (0.08%)	6 (0.03%)	28 (0.16%)	19 (0.11%)
Non-Serious	267 (1.56%)	0 (0.00%)	206 (1.20%)	39 (0.23%)	1 (0.01%)	21 (0.12%)	28 (0.16%)
Studies TAAL and TABY (N = 11364)	455 (4.00%)	7 (0.06%)	380 (3.34%)	43 (0.38%)	7 (0.06%)	43 (0.38%)	28 (0.25%)
Serious	256 (2.25%)	7 (0.06%)	214 (1.88%)	12 (0.11%)	6 (0.05%)	24 (0.21%)	14 (0.12%)
Non-Serious	217 (1.91%)	0 (0.00%)	176 (1.55%)	31 (0.27%)	1 (0.01%)	20 (0.18%)	16 (0.14%)

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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW,
H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_gi.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_gi.rtf.

Postmarketing Data: Of the reported events, 93% of the postmarketing events were serious while 7% were non-serious. Outcomes reported in postmarketing events included fatal (2%), recovered/recovered with sequellae/recovering (43%), not recovered (3%), and unknown (52%).

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Gastrointestinal Haemorrhage (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent gastrointestinal haemorrhage in Studies TAAL and TABY and in all 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 = 17,164)	539 (3.14%)	205 (1.19%)	192 (1.12%)	142 (0.83%)
Studies TAAL and TABY (N = 11364)	455 (4.00%)	174 (1.53%)	164 (1.44%)	117 (1.03%)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, 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.

Source: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_gi.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_gi.rtf.

Postmarketing data: Data not available.

Background incidence/ prevalence

The study below provides information on the background/prevalence of the risk of gastrointestinal haemorrhage:

a) Nicolsky et al. 2009: Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial of 13,819 patients with moderate- and high-risk ACS, enrolled at 450 centres in 17 countries in August 2003-December 2005, and randomized to the open-label use of 1 of 3 antithrombin regimens

In this study, the incidence of gastrointestinal bleed (GIB) within 30 days after treatment occurred in 1.3% of the ACS population (1.5% for heparin plus a glycoprotein IIb/IIIa inhibitor group, 1.4% for bivalirudin plus a glycoprotein IIb/IIIa inhibitor and 0.9% for bivalirudin monotherapy). GIB was strongly associated with 30-day all-cause mortality (hazard ratio [HR]: 4.87) and 1-year all-cause mortality (HR: 3.97).

b) Serebruany et al. 2013 reviewed gastrointestinal adverse events after dual anti-platelet therapy (DAPT) in two large, multinational trials: TRITON-TIMI-38 (n=13,608 patients with moderate to high risk ACS undergoing PCI and randomized to prasugrel or clopidogrel) and PLATO (n=18,624 patients with moderate to high risk ACS undergoing coronary intervention and randomized to either ticagrelor or clopidogrel). Gastrointestinal bleeding after P2Y12 platelet receptor inhibitors were reported as follows: Clopidogrel: 2.9%; Prasugrel: 3.9%; Ticagrelor: Data not available.

Risk groups or risk factors

Patients with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding (such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics), are also at higher risk for bleeding.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Gastrointestinal Haemorrhage (continued)	
Potential mechanisms	The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.
Preventability	Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.
Impact on individual patient	Gastrointestinal haemorrhages may manifest as hematemesis, melena, and hematochezia (Medline 2013). Quality of life varies according to the nature and the extent of the bleeding event.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_gi.rtf and others **Postmarketing data:** Lilly Safety System
MedDRA (Version 17.1) terms	SMQ Gastrointestinal haemorrhage (20000108) except PTs Duodenal operation and Gastrointestinal anastomotic leak

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Intraocular Haemorrhage

Frequency with 95% CI

Clinical Trial Program:

Prasugrel - 62 (IR=4.97 per 1000 patient-years) ; Clopidogrel - 51 (IR=4.06 per 1000 patient-years),

RR=1.20, 95% CI: 0.83-1.74) , p-value 0.3315

Postmarketing Data: Events of intraocular haemorrhage are considered very rarely reported (0.002%) based on an estimated patient exposure to prasugrel of more than 2.7 million patients.

Seriousness/ Outcomes

Clinical Trial Program:

The distribution of outcomes and seriousness for intraocular haemorrhage 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 = 17,164)	68 (0.40%)	0 (0.00%)	47 (0.27%)	8 (0.05%)	0 (0.00%)	16 (0.09%)	4 (0.02%)
Serious	12 (0.07%)	0 (0.00%)	7 (0.04%)	3 (0.02%)	0 (0.00%)	3 (0.02%)	2 (0.01%)
Non-Serious	57 (0.33%)	0 (0.00%)	41 (0.24%)	5 (0.03%)	0 (0.00%)	13 (0.08%)	2 (0.01%)
Studies TAAL and TABY (N = 11364)	55 (0.48%)	0 (0.00%)	38 (0.33%)	8 (0.07%)	0 (0.00%)	12 (0.11%)	4 (0.04%)
Serious	12 (0.11%)	0 (0.00%)	7 (0.06%)	3 (0.03%)	0 (0.00%)	3 (0.03%)	2 (0.02%)
Non-Serious	44 (0.39%)	0 (0.00%)	32 (0.28%)	5 (0.04%)	0 (0.00%)	9 (0.08%)	2 (0.02%)

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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_och.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_och.rtf.

Postmarketing Data: Of the reported events, 70% of the postmarketing events were serious while 30% were non-serious. Outcomes reported in postmarketing events included recovered/recovering (45%), not recovered (14%), and unknown (41%). There were no fatalities or events recovered with sequellae reported in the postmarketing data for these events.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Intraocular Haemorrhage (continued)

Severity and nature of risk

Clinical Trial Program: Grades of severity for treatment-emergent intraocular haemorrhage in Studies TAAL and TABY and in all 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 = 17,164)	68 (0.40%)	47 (0.27%)	15 (0.09%)	6 (0.03%)
Studies TAAL and TABY (N = 11364)	55 (0.48)	34 (0.30)	15 (0.13)	6 (0.05)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_och.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_och.rtf.

Postmarketing data: Data not available.

Background incidence/ prevalence

Becker et al. 2011: A randomized, double-blind active control international phase III clinical trial in 18,624 patients with acute STEMI and NSTEMI ACS was conducted. Patients were randomized to either ticagrelor (n=9,235) or clopidogrel (n=9,186) in addition to aspirin. The incidence of intraocular haemorrhage was 0.02% vs. 0.04% in the ticagrelor arm vs. the clopidogrel arm, respectively.

The document below provides information on the background/prevalence of the risk of intraocular haemorrhage:

a) CDER 2002 [WWW]: Approval package for clopidogrel (Plavix®)
Incidence in aspirin and placebo group was 0.03%.

Risk groups or risk factors

Patients with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics are also at higher risk for bleeding.

Potential mechanisms

The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.

Preventability

Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Intraocular Haemorrhage (continued)	
Impact on individual patient	Impact on quality of life varies according to the nature and the extent of the bleeding event.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_och.rtf and others **Postmarketing data:** Lilly Safety System
MedDRA (Version 17.1) terms	HLGT Ocular haemorrhages and vascular disorders NEC + PT Vitreous haemorrhage, PTs Eye haemorrhage, Conjunctival haemorrhage, Hyphaema, Eyelid haematoma, Eyelid bleeding, Scleral haemorrhage, Ciliary body haemorrhage, Corneal bleeding, Intraocular haematoma, Iris haemorrhage, Lacrimal haemorrhage, Ocular retrobulbar haemorrhage, Optic disc haemorrhage, Optic nerve sheath haemorrhage, Periorbital haematoma, and Periorbital haemorrhage

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Epistaxis

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 693 (IR=55.50 per 1000 patient-years) ; Clopidogrel - 371 (IR=29.56 per 1000 patient-years),
RR=1.88, 95% CI: 1.66-2.13, p value <0.0001

Postmarketing Data: Events of epistaxis are considered rarely reported (0.013%) based on an estimated patient exposure to prasugrel of more than 2.7 million patients.

Seriousness/ Outcomes

Clinical Trial Program:

The distribution of outcomes and seriousness for epistaxis 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 = 17,164)	778 (4.53%)	0 (0.00%)	672 (3.92%)	97 (0.57%)	1 (0.01%)	33 (0.19%)	80 (0.47%)
Serious	42 (0.24%)	0 (0.00%)	36 (0.21%)	3 (0.02%)	0 (0.00%)	2 (0.01%)	1 (0.01%)
Non-Serious	752 (4.38%)	0 (0.00%)	649 (3.78%)	94 (0.55%)	1 (0.01%)	31 (0.18%)	79 (0.46%)
Studies TAAL and TABY (N = 11364)	602 (5.30%)	0 (0.00%)	537 (4.73%)	89 (0.78%)	1 (0.01%)	30 (0.26%)	48 (0.42%)
Serious	40 (0.35%)	0 (0.00%)	35 (0.31%)	2 (0.02%)	0 (0.00%)	2 (0.02%)	1 (0.01%)
Non-Serious	578 (5.09%)	0 (0.00%)	515 (4.53%)	87 (0.77%)	1 (0.01%)	28 (0.25%)	47 (0.41%)

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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_epi.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_epi.rtf.

Postmarketing Data: Of the reported events, 29% of the postmarketing events were serious while 71% were non-serious. Outcomes reported in postmarketing events included recovered/recovered with sequellae/recovering (42%), not recovered (8%), and unknown (50%). There were no fatalities reported in the postmarketing data for this event.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Epistaxis (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent epistaxis in Studies TAAL and TABY and in all 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 = 17,164)	778 (4.53)	612 (3.57)	147 (0.86)	18 (0.10)
Studies TAAL and TABY (N = 11364)	602 (5.30)	459 (4.04)	130 (1.14)	13 (0.11)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_epi.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_epi.rtf.

Postmarketing data: Data not available.

Background incidence/ prevalence

Becker et al. 2011: A randomized, double-blind active control international phase III clinical trial in 18,624 patients with acute STEMI and NSTEMI ACS was conducted. Patients were randomized to either ticagrelor (n=9,235) or clopidogrel (n=9,186) in addition to aspirin. The incidence of epistaxis was 1.3% vs. 0.7% in the ticagrelor arm vs. the clopidogrel arm, respectively.

Information on the background/prevalence of the risk of epistaxis:

a) Plavix® package insert, 2007
   Incidence was 2.5%.

Risk groups or risk factors

Patients with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics are also at higher risk for bleeding.

Potential mechanisms

The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Epistaxis (continued)	
Preventability	Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.
Impact on individual patient	Epistaxis has a minimal impact on the quality of life for the individual patient as the most common of epistaxis bleeds are often self-limiting (Alter 2013).
Potential public health impact of Important identified risk or important potential risk	Not applicable.
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_epi.rtf and others **Postmarketing data**: Lilly Safety System
MedDRA (Version 17.1) terms	PT Epistaxis

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

<table>
<tr><th colspan="2">Identified Risk: Bleeding -- Percutaneous coronary intervention (PCI)-related Haemorrhage</th></tr>
<tr><td>Frequency with 95% CI</td><td>No odds ratio was reported for this risk given the nature of collection.</td></tr>
<tr><td>Seriousness/ Outcomes</td><td>
Clinical Trial Program:

The distribution of outcomes and seriousness for PCI-related haemorrhage in prasugrel-treated patients in Study TAAL (the primary safety database) is shown below:

Study TAAL (6741 subjects)
Total prasugrel-treated subjects w/ ≥1 event: 264 / 6741 (3.92%)
Serious Adverse Events: 59 / 264 (22.35%)

<table>
<tr><th colspan="7">Outcomes</th></tr>
<tr><th>Recovered
n/N (%)</th><th>Recovering/ Resolving
n/N (%)</th><th>Not Recovered
n/N (%)</th><th>Recovered/ w/ Sequelae
n/N (%)</th><th>Died
n/N (%)</th><th>Unknown
n/N (%)</th><th>Missing Data
n/N (%)</th></tr>
<tr><td>222 / 264 (84.09%)</td><td>33 / 264 (12.50%)</td><td>3 / 264 (1.14%)</td><td>2 / 264 (0.76%)</td><td>1 / 264 (0.38%)</td><td>1 / 264 (0.38)</td><td>2 / 264 (0.76)</td></tr>
</table>
Abbreviations: % = percentage of subjects reporting the event; n = number of subjects with events (some subjects may have reported more than 1 event); N = total number of SAEs in Study TAAL.
Source: l0158_fqbldl11_bleed_proc; Exposure prasugrel 2009-2011.xls.

Postmarketing Data: Data not available.
</td></tr>
</table>

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Percutaneous coronary intervention (PCI)-related Haemorrhage (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent PCI-related haemorrhage in prasugrel-treated patients in Study TAAL (the primary safety database) are shown below:

Study TAAL (6741 subjects)
Total prasugrel-treated subjects w/ ≥1 event: 264 / 6741 (3.92%)
Serious Adverse Events: 59 / 264 (22.35%)

Maximum Severity		
Mild n/N (%)	**Moderate n/N (%)**	**Severe n/N (%)**
174 / 264 (65.91%)	67 / 264 (25.38%)	23 / 264 (8.71%)

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 SAEs in Study TAAL.
Source: l0158_fqbldl11_bleed_proc; Exposure prasugrel 2009-2011.xls.

Postmarketing Data: Data not available.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Percutaneous coronary intervention (PCI)-related haemorrhage (continued)	
Background incidence/prevalence	The studies below provide information on the background/prevalence of the risk of PCI-related haemorrhage: a) Nicolsky et al. 2009: Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial of 13,819 patients with moderate- and high-risk ACS, enrolled at 450 centres in 17 countries in August 2003-December 2005, and randomized to the open-label use of 1 of 3 antithrombin regimens Incidence of gastrointestinal bleed by triage strategy was 1.4% for PCI. b) In Othman et al. (2014), among 96,637 patients undergoing PCI and enrolled in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) registry, the incidence of post-PCI bleeding was as follows: overall: 2.5%; men: 1.8%; women: 3.9%. By presentation (female vs. male): STEMI: 9.4% vs. 5.1%; NSTEMI: 4.7% vs. 2.0%; unstable angina: 2.5% vs. 1.0%; stable coronary disease: 2.6% vs. 0.8%. (Note: bleeding was defined as any bleeding associated with one of the following: haemoglobin drop of ≥3 g/dL, transfusion of whole blood or packed red blood cells, or procedural intervention/surgery at the bleeding site to reverse, stop, or correct bleeding.)
Risk groups or risk factors	Patients with a high propensity for bleeding (i.e. recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics are also at higher risk for bleeding.
Potential mechanisms	The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.
Preventability	Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.
Impact on individual patient	Impact on quality of life varies according to the nature and the extent of the bleeding event.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	l0158_fqbldl11_bleed_proc; Exposure prasugrel 2009-2011.xls
MedDRA (Version 17.1) terms	Puncture site haemorrhage, vessel puncture site haematoma, retroperitoneal haemorrhage

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

<table>
<tr><th colspan="2">Identified Risk: Bleeding -- Coronary Artery Bypass Graft (CABG)-related Haemorrhage</th></tr>
<tr><td>Frequency with 95% CI</td><td>Odds ratio: 3.587; 95% CI 1.702, 7.557</td></tr>
<tr><td>Seriousness/ Outcomes</td><td>
Clinical Trial Program:

The distribution of outcomes and seriousness for CABG-related haemorrhage in prasugrel-treated patients in Study TAAL (the primary safety database) is shown below:

Study TAAL:
Total prasugrel-treated subjects w/ ≥1 event: 30 / 213 (14.08%)
Serious Adverse Events: 22 / 30 (73.33%)

<table>
<tr><th colspan="3">Outcomes</th></tr>
<tr><th>Recovered
n/N (%)</th><th>Recovering/
Resolving
n/N (%)</th><th>Not Recovered
n/N (%)</th></tr>
<tr><td>26/30 (86.67%)</td><td>1/30 (3.33%)</td><td>3/30 (10.00%)</td></tr>
</table>
Abbreviations: % = percentage of subjects reporting the event; n = number of subjects with events (some subjects may have reported more than 1 event); N = total number of SAEs in Study TAAL.
Source: Q1636; l0159_fqbldl11_bleed_cabghmami; Exposure prasugrel 2009-2011.xls.

Postmarketing Data: Data not available.
</td></tr>
</table>

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Coronary Artery Bypass Graft (CABG)-related Haemorrhage

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent CABG-related haemorrhage in prasugrel-treated patients in Study TAAL (the primary safety database) are shown below:

Study TAAL:

Total prasugrel-treated subjects w/ ≥1 event: 30 / 213 (14.08%)
Serious Adverse Events: 22 / 30 (73.33%)

Maximum Severity		
Mild n/N (%)	**Moderate n/N (%)**	**Severe n/N (%)**
2 / 30 (6.67%)	9 / 30 (30.00%)	19 / 30 (63.33%)

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 SAEs in Study TAAL.

Source: Q1636; l0159_fqbldl11_bleed_cabghmami; Exposure prasugrel 2009-2011.xls.

Postmarketing Data: Data not available.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Coronary Artery Bypass Graft (CABG)-related haemorrhage (continued)	
Background incidence/prevalence	The studies below provide information on the background/prevalence of the risk of CABG-related haemorrhage: a) Nicolsky et al. 2009: Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial of 13,819 patients with moderate- and high-risk ACS, enrolled at 450 centres in 17 countries in August 2003-December 2005, and randomized to the open-label use of 1 of 3 antithrombin regimens Incidence of gastrointestinal bleed by triage strategy was 1.8% for CABG. b) Held et al. 2011: CABG + ticagrelor arm (n=632) of the PLATO trial which enrolled ACS patients from 43 countries between 2006 and 2008 Incidence of a major CABG bleed was 81.2%. c) CDER 2011 [WWW]: Approval package for ticagrelor: In PLATO, 1,584 patients underwent CABG surgery. Among those receiving ticagrelor (n=770), 85.8% experienced a major bleed and among those receiving Clopidogrel (n=814), 86.9% experienced a major bleed. PLATO used the following bleeding categorizations: Major bleed—fatal/life-threatening: Any one of the following: fatal, intracranial, intrapericardial bleed with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 5 g/dL, transfusion of 4 or more units (whole blood or packed red blood cells for bleeding. Major bleed—other: Any one of the following: significantly disabling (e.g. intraocular with permanent vision loss), clinically overt or apparent bleeding associated with a decrease in haemoglobin of 3 g/dL, transfusion of 2-3 units (whole blood or packed red blood cells) for bleeding.
Risk groups or risk factors	Patients with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics are also at higher risk for bleeding.
Potential mechanisms	The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.
Preventability	Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.
Impact on individual patient	Impact on quality of life varies according to the extent of the bleeding event.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	Q1636; l0159_fqbldl11_bleed_cabghmami; Exposure prasugrel 2009-2011.xls
MedDRA (version 17.1) terms	Not applicable.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding associated with prasugrel use prior to coronary angiography in NSTEMI patients

Frequency with 95% CI

Clinical Trial: HR for TIMI life-threatening bleeding among all treated patients = 2.684 , 95% CI: 1.345 - 5.355, p-value: 0.004

HR for TIMI major bleeding among all-treated patients = 1.900, 95% CI: 1.193 – 3.024, p-value: 0.006

Postmarketing Data: It is difficult to assess a definitive incidence for this risk in prasugrel, as this information is not usually provided in spontaneous reports.

Seriousness/outcomes

Clinical Trial Programme:

The distribution of outcomes and seriousness for treatment-emergent bleeding associated with prasugrel use prior to coronary angiography in NSTEMI patients for all subjects treated in the prasugrel pre-treatment group in Study TADF (ACCOAST) are shown below.

Study Population	Prasugrel-treated pts w/ ≥1 event n (%)	Fatal n (%)[a]	Recovered/ Resolved n (%)	Not Recovered/ Not Resolved n (%)	Recovered/ Resolved w/ Sequelae n (%)	Recovering/ Resolving n (%)	Unknown n (%)
All treated subjects in the prasugrel pre-treatment group (N = 2037)	286 (14.04%)	2 (0.10%)[a]	242 (11.88%)	21 (1.03%)	4 (0.20%)	25 (1.23%)	4 (0.20%)
Serious	56 (2.75%)	2 (0.10%)[a]	43 (2.11%)	4 (0.20%)	0 (0.00%)	6 (0.29%)	2 (0.10%)
Non-Serious	238 (11.68%)	0 (0.00%)	206 (10.11%)	18 (0.88%)	4 (0.20%)	19 (0.93%)	2 (0.10%)

Abbreviations: % = percentage of subjects reporting the event; n = number of subjects with the event (some subjects may have reported more than 1 event); N = total number of treated subjects.

[a] There were actually 3 fatal events. One event was not included in this table because, per the TADF protocol, events leading to the clinical outcomes of death, MI, stroke, UR, GPIIb/IIIa bailout, or stent thrombosis will be included as part of the efficacy analyses for this study and will not be recorded as SAEs unless the investigator believes the event may have been caused by the study drug.

Source: lillyce/prd/ly640315/h7t_mc_tadf/final/programs_stat/tfl_output/tadf_rmp_hmrg.rtf.

Postmarketing Data: Data are not available.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

<table>
<tr><th colspan="2">Identified Risk: Bleeding associated with prasugrel use prior to coronary angiography in NSTEMI patients (continued)</th></tr>
<tr><td>Severity and nature of risk</td><td>Clinical Trial Programme:
Grades of severity for treatment-emergent bleeding associated with prasugrel use prior to coronary angiography in NSTEMI patients for all subjects treated in the prasugrel pre-treatment group in Study TADF (ACCOAST) are shown in the table below.
<table>
<tr><th>Study Population</th><th>Prasugrel-treated pts w/ ≥1 event
n (%)</th><th>Mild
n (%)</th><th>Moderate
n (%)</th><th>Severe
n (%)</th></tr>
<tr><td>Study TADF
(N = 2037)</td><td>286 (14.04%)</td><td>201 (9.87%)</td><td>58 (2.85%)</td><td>27 (1.33%)</td></tr>
</table>
Abbreviations: % = percentage of subjects with event; n = number of subjects with the event (some subjects may have reported more than 1 event); N = total number of treated subjects.
Source: lillyce/prd/ly640315/h7t_mc_tadf/final/programs_stat/tfl_output/tadf_rmp_maxsev_hmrg.rtf.
Postmarketing Data: Data not available.</td></tr>
<tr><td>Background incidence/prevalence</td><td>There are no data that reliably show the background incidence and prevalence of bleeding associated with pre-treatment in NSTEMI patients.</td></tr>
<tr><td>Risk groups or risk factors</td><td>Any patient with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal [GI] bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) is at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics are also at higher risk for bleeding. Specifically in the case of prasugrel use prior to coronary angiography, women also have a higher risk of bleeding events.</td></tr>
<tr><td>Potential mechanisms</td><td>Not applicable</td></tr>
<tr><td>Preventability</td><td>In NSTEMI patients, the loading dose should generally be given at the time of PCI.</td></tr>
<tr><td>Impact on individual patient</td><td>Impact on quality of life varies according to the extent of the bleeding event. ACCOAST results demonstrated a wide range of these events ranging from life-threatening bleeding to TIMI minor bleeding events.</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>Not applicable</td></tr>
<tr><td>Evidence source</td><td>smbld11.rtf</td></tr>
<tr><td>MedDRA (version 17.1) terms</td><td>There are no MedDRA terms that can adequately capture this risk.</td></tr>
</table>

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

<table>
<tr><th colspan="2">Identified Risk: Bleeding -- Other Procedure-related Haemorrhage</th></tr>
<tr><td>Frequency with 95% CI</td><td>No odds ratio was reported for this risk given the nature of collection.</td></tr>
<tr><td>Seriousness/ Outcomes</td><td>
Clinical Trial Program:

The distribution of outcomes and seriousness for other procedure-related haemorrhage in prasugrel-treated patients in Study TAAL (the primary safety database) is shown below:

Study TAAL (6741 subjects)
Total prasugrel-treated subjects w/ ≥1 event: 30 / 6741 (0.45%)
Serious Adverse Events: 19 / 30 (63.33%)

<table>
<tr><th colspan="4">Outcomes</th></tr>
<tr><th>Recovered
n/N (%)</th><th>Not Recovered
n/N (%)</th><th>Recovered/
w/ Sequelae
n/N (%)</th><th>Unknown
n/N (%)</th></tr>
<tr><td>28 / 30 (93.33%)</td><td>1 / 30 (3.33%)</td><td>1 / 30 (3.33%)</td><td>0 / 30 (0.00%)</td></tr>
</table>
Abbreviations: % = percentage of subjects reporting the event; n = number of subjects with events (some subjects may have reported more than 1 event); N = total number of SAEs in Study TAAL.
Source: l0170_fqbldl11_bleed_postproc; exposure prasugrel 2009-2011.xls.

Postmarketing Data: Data not available.
</td></tr>
</table>

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Other Procedure-related Haemorrhage

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent other procedure-related haemorrhage in prasugrel-treated patients in Study TAAL (the primary safety database) are shown below:

Study TAAL (6741 subjects)
Total prasugrel-treated subjects w/ ≥1 event: 30 / 6741 (0.45%)
Serious Adverse Events: 19 / 30 (63.33%)

Maximum Severity		
Mild n/N (%)	**Moderate n/N (%)**	**Severe n/N (%)**
9 / 30 (30.00%)	11 / 30 (36.67%)	10 / 30 (33.33%)

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 SAEs in Study TAAL.
Source: l0170_fqbldl11_bleed_postproc; exposure prasugrel 2009-2011.xls.

Postmarketing Data: Data not available.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Bleeding -- Other Procedure-related Haemorrhage (continued)	
Background incidence/prevalence	The document below provides information on the background/prevalence of the risk of other procedure-related haemorrhage: a) Plavix® package insert, 2007 In patients with unstable angina/NSTEMI, incidence of operative wounds was less than 1%.
Risk groups or risk factors	Patients with a high propensity for bleeding (i.e., recent trauma or surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) are at higher risk of experiencing a bleeding event. Additionally, patients weighing under 60 kg, aged 75 years and older, or taking concomitant medications that may increase bleeding such as oral anticoagulants, non-steroidal anti-inflammatory drugs, and fibrinolytics are also at higher risk for bleeding.
Potential mechanisms	The mechanism of action of prasugrel may provide a mechanism for the various bleeding events. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. This inhibition increases the likelihood of bleeding events.
Preventability	Assessing individual bleeding risk factors may be the most reliable method for preventing bleeding events with prasugrel use. As stated in the dose, route of administration section, reduced dosing is acceptable for patients <60 kg and ≥75 years of age. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery.
Impact on individual patient	Impact on quality of life varies according to the nature and the extent of the bleeding event.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	l0170_fqbldl11_bleed_postproc; exposure prasugrel 2009-2011.xls
MedDRA (version 17.1) terms	Not applicable

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Hypersensitivity (including Angioedema)

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 111 (IR = 8.89 per 1000 patient-years) ; Clopidogrel - 117 (IR = 9.32 per 1000 patient-years),
RR=0.95, 95% CI: 0.74-1.24 p-value 0.7204

Postmarketing Data: Events of hypersensitivity (including angioedema) are considered very rarely reported (0.008%) based on an estimated patient exposure to prasugrel of 2.7 million patients.

Seriousness/ Outcomes

Clinical Trial Program:

The distribution of outcomes and seriousness for hypersensitivity including angioedema 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 = 17,164)	120 (0.70%)	0 (0.00%)	84 (0.49%)	26 (0.15%)	1 (0.01%)	18 (0.10%)	15 (0.09%)
Serious	19 (0.11%)	0 (0.00%)	14 (0.08%)	2 (0.01%)	0 (0.00%)	4 (0.02%)	3 (0.02%)
Non-Serious	101 (0.59%)	0 (0.00%)	70 (0.41%)	24 (0.14%)	1 (0.01%)	14 (0.08%)	12 (0.07%)
Studies TAAL and TABY (N = 11364)	104 (0.92%)	0 (0.00%)	79 (0.70%)	21 (0.18%)	1 (0.01%)	18 (0.16%)	10 (0.09%)
Serious	15 (0.13%)	0 (0.00%)	14 (0.12%)	1 (0.01%)	0 (0.00%)	3 (0.03%)	1 (0.01%)
Non-Serious	89 (0.78%)	0 (0.00%)	65 (0.57%)	20 (0.18%)	1 (0.01%)	15 (0.13%)	9 (0.08%)

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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_hyps.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_hyps.rtf.

Postmarketing Data: Of the reported events, 46% of the postmarketing events were serious and 54% were non-serious. Outcomes reported in postmarketing events included fatal (2%), recovered/recovered with sequellae/recovering (50.5%), not recovered (6.5%), and unknown (41%).

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Hypersensitivity including Angioedema (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent hypersensitivity including angioedema in Studies TAAL and TABY and in all 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 = 17,164)	120 (0.70%)	57 (0.33%)	50 (0.29%)	13 (0.08%)
Studies TAAL and TABY (N = 11364)	104 (0.92%)	50 (0.44%)	42 (0.37%)	12 (0.11%)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_hyps.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_hyps.rtf.

Postmarketing Data: Data not available.

Background incidence/prevalence

Hypersensitivity, including angioedema (allergic reaction) has been identified as a non-haemorrhagic adverse reaction based on spontaneous case reports of hypersensitivity reactions, including angioedema, in patients treated with prasugrel, including in patients with hypersensitivity to clopidogrel.

The document and the study below provide information on the background/prevalence of the risk of hypersensitivity including angioedema:

a) CDER 2002 [WWW]: Approval package for clopidogrel (Plavix®)

Incidence of allergic reactions was 0.3%.

b) Yang et al. 2008

In patients hospitalized for anaphylaxis, mortality was 0.0001%.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Hypersensitivity including Angioedema (continued)	
Risk groups or risk factors	Important risk factors in the ACS population for the development of a hypersensitivity reaction to prasugrel are patients who have previous exposure to thienopyridines and those with a history of ticlopidine and/or clopidogrel allergies, since both of these drugs have a similar chemical structure to prasugrel. Additional risk factors for the development of drug induced hypersensitivity reactions include prior history of allergic drug reactions and recurrent drug exposure.
Potential mechanisms	Immune related
Preventability	Patients with a history of ticlopidine and/or clopidogrel allergies are at greater risk of hypersensitivity to prasugrel, and should avoid use if possible.
Impact on individual patient	The impact on the individual patient depends on the symptoms exhibited. Hypersensitivity symptoms can include itching, urticaria, angioedema, laryngeal edema or spasm, bronchospasm, hypotension, abdominal cramps, diarrhoea, anxiety, agitation or loss of consciousness. For most patients, these symptoms will be acute and will resolve without long-term sequellae, thereby minimally affecting their quality of life. If untreated, a severe case of hypersensitivity could be fatal.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_hyps.rtf and others. **Postmarketing Data:** Lilly Safety System
MedDRA (version 17.1) terms	SMQ Severe cutaneous adverse reactions (Narrow) + selected PTs from broad SMQ (acquired epidermolysis bullosa, epidermolysis, drug eruption, pemphigoid, and pemphigus), SMQ Anaphylactic reaction (Narrow) + selected PTs from broad SMQ (generalised erythema, pruritus generalised, rash generalised, and angioedema), + PTs hypersensitivity and drug hypersensitivity

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombocytopenia

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 78 (IR=6.25 per 1000 patient-years) ; Clopidogrel - 67 (IR=5.34 per 1000 patient-years),
RR=1.17, 95% CI: 0.84-1.62 p-value 0.3452

Postmarketing Data: Events of thrombocytopenia are considered very rarely reported (0.004%) based on an estimated patient exposure to prasugrel of 2.7 million.

Seriousness/ Outcomes

Clinical Trial Program:

The distribution of outcomes and seriousness for thrombocytopenia 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 = 17,164)	92 (0.54%)	0 (0.00%)	56 (0.33%)	29 (0.17%)	0 (0.00%)	10 (0.06%)	18 (0.10%)
Serious	19 (0.11%)	0 (0.00%)	13 (0.08%)	5 (0.03%)	0 (0.00%)	2 (0.01%)	2 (0.01%)
Non-Serious	75 (0.44%)	0 (0.00%)	44 (0.26%)	24 (0.14%)	0 (0.00%)	8 (0.05%)	16 (0.09%)
Studies TAAL and TABY (N = 11364)	68 (0.60%)	0 (0.00%)	45 (0.40%)	23 (0.20%)	0 (0.00%)	9 (0.08%)	11 (0.10%)
Serious	17 (0.15%)	0 (0.00%)	13 (0.11%)	5 (0.04%)	0 (0.00%)	2 (0.02%)	0 (0.00%)
Non-Serious	53 (0.47%)	0 (0.00%)	33 (0.29%)	18 (0.16%)	0 (0.00%)	7 (0.06%)	11 (0.10%)

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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_tctp.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_tctp.rtf.

Postmarketing Data: Of the reported events, 69% of the postmarketing events were serious and 31% were non-serious. Outcomes reported in postmarketing events included recovered/recovering (42%), not recovered (6%), unknown (51%) and worsened (1.0%). There were no fatalities or events recovered with sequellae reported in the postmarketing data for these events.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombocytopenia (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent thrombocytopenia in Studies TAAL and TABY and in all 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 = 17,164)	92 (0.54%)	56 (0.33%)	24 (0.14%)	12 (0.07%)
Studies TAAL and TABY (N = 11364)	68 (0.60%)	36 (0.32%)	21 (0.18%)	11 (0.10%)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_tctp.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_tctp.rtf.

Postmarketing Data: Data not available.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombocytopenia (continued)	
Background incidence/prevalence	Thrombocytopenia has been identified as a non-haemorrhagic adverse reaction based upon postmarketing reports. The studies below provide information on the background/prevalence of the risk of thrombocytopenia: a) Fahdi et al. 2004: Consecutive patients undergoing elective PCI in the US treated with abciximab Incidence of thrombocytopenia (platelet count <100,000/mm^3) was 15/100 persons. Incidence of severe thrombocytopenia (platelet count <50,000/mm^3) was 3/100 persons. b) Prandoni et al. 2005: Consecutive patients receiving low-molecular-weight heparin (LMWH) in hospital and outpatient settings in the US. Thrombocytopenia was defined as platelet drop of at least 50% in the absence of obvious explanations for thrombocytopenia. Overall incidence within the first 2 weeks of treatment was 0.80/100 persons. In patients with previous exposure to LMWH, incidence was 1.7/100 persons. In patients naïve to LMWH, incidence was 0.3/100 persons. c) Creekmore et al. 2006: Patients receiving LMWH or unfractionated heparin (UFH) for the prophylaxis of venous thromboembolism in the US. Case definition: Patients who received argatroban or lepirudin during the admission or who had a positive enzyme-linked immunosorbent assay (ELISA) for heparin-dependent antiplatelet antibodies during the admission. Overall incidence was 0.43/100 persons; incidence in those receiving LMWH was 0.84/100 persons; incidence in those receiving UFH was 0.51/100 persons. d) Warkentin et al. 2000: A study of 744 patients were studied from 3 different clinical treatment settings, as follows: UFH during or after cardiac surgery (n=100), UFH after orthopedic surgery (n=205), and LMWH after orthopedic surgery (n=439) Prevalence of thrombocytopenia in cardiac patients treated with UFH was 1/100 persons; prevalence in orthopedic patients treated with UFH was 4.9/100 persons; prevalence in orthopedic patients treated with LMWH was 0.9/100 persons. e) Stone et al. (2015) combined data from HORIZONS-AMI (3,602) patients undergoing primary PCI for STEMI and treated with bivalirudin) and EUROMAX (2218 patients randomized to bivalirudin versus heparin +/- GPI before primary PCI). Overall, there were a total of 5800 patients included in the analysis (n=2,889 receiving bivalirudin and n=2,911 receiving heparin +/- GPI). The incidence of thrombocytopenia was 1.4% vs. 2.9%, respectively between Bivalirudin vs. heparin +/- GPI. f) Vora et al. (2014) conducted a study among 7,435 non-ST-segment elevation-acute coronary syndrome patients enrolled in the SYNERGY trial which was a large, open-label, multicenter randomized comparison between unfractionated and low molecular weight heparin administered in conjunction with established therapies including aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors. The incidence of mild vs. severe thrombocytopenia as 9.1% vs. 1.9%, respectively. One-year mortality rates were 6.5%, 8.1% and 28.1% among patients with no, mild, and severe thrombocytopenia, respectively.
Risk groups or risk factors	Patients with decreased platelet function as a result of chemotherapy, radiation therapy, or viral infections such as Epstein-Barr, hepatitis C, and mumps, may be more likely to develop thrombocytopenia. Patients on heparin, quinine, quinidine, or valproic acid are also at greater risk of developing thrombocytopenia (Landaw 2013).
Potential mechanisms	There is no known mechanism for prasugrel to cause thrombocytopenia.
Preventability	Minimizing patient risk factors prior to treatment may be the most reliable method for preventing thrombocytopenia after prasugrel use
Impact on individual patient	Often patients may be asymptomatic. Symptomatic thrombocytopenia usually manifests as mucosal (i.e., epistaxis) or cutaneous (i.e., petechial) bleeding (Landaw 2013). Mild thrombocytopenia may be self-limiting and have little impact on quality of life. Severe

	thrombocytopenia will require hospitalization with platelet transfusions, and could be life-threatening.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombocytopenia (continued)	
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_tctp.rtf and others **Postmarketing Data:** Lilly Safety System
MedDRA (version 17.1) terms	SMQ Haematopoietic thrombocytopenia (Narrow)

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombotic Thrombocytopenic Purpura (TTP)

Frequency with 95% CI

Clinical Trial Program:
It is difficult to assess the incidence of TTP in prasugrel given the relatively low numbers of reported cases. There were no cases of TTP reported in prasugrel arms.

Postmarketing Data: Events of TTP in the prasugrel spontaneous database are very rarely reported (0.0009%) based on the estimated patient exposure of 2.7 million.

Seriousness/ Outcomes

Clinical Trial Program:

The distribution of outcomes and seriousness for thrombotic thrombocytopenic purpura 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 = 17,164)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Serious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-Serious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Studies TAAL and TABY (N = 11364)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Serious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-Serious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_ttp.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_ttp.rtf.

Postmarketing Data: Of the events reported, 96% of the postmarketing events were serious and 4% were non-serious. Outcomes reported in postmarketing events included fatal (12%), recovered/recovered with sequellae/recovering (24%), not recovered (4%), and unknown (60%).

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombotic Thrombocytopenic Purpura (TTP) (continued)

Severity and nature of risk

Clinical Trial Program:

Grades of severity for treatment-emergent thrombotic thrombocytopenic purpura in Studies TAAL and TABY and in all 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 = 17,164)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Studies TAAL and TABY (N = 11364)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/idb_tace_tri_tadf_tael_rmp_maxsev_ttp.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_ttp.rtf.

Postmarketing Data: Data not available.

Background incidence/prevalence

Thrombotic thrombocytopenic purpura has been identified as a non-haemorrhagic adverse reaction based upon postmarketing data.

The studies below provide information on the background/prevalence of the risk of thrombotic thrombocytopenic purpura:

a) Steinhubl et al. 1999: Retrospective analysis of patients undergoing coronary stenting at 63 centres throughout the United States and Canada (n=43,322) between 1996 and 1997

Patients on ticlopidine incidence was 0.02/100 persons.

b) Elkins et al. 1996: A review of 41 patients with TTP between 1980 and 1994

Mortality was 54% from 1980-1984, 44% from 1985-1989, and 18% from 1990-1994.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Thrombotic Thrombocytopenic Purpura (TTP) (continued)	
Risk groups or risk factors	Women experience TTP more frequently than their male counterparts. Other conditions that increase risk of developing TTP include vasculitis and other connective tissue disorders, antiphospholipid antibody syndrome, malignant hypertension, bone marrow and organ transplantation, prosthetic heart valves, and malignancy (Tsai 2003). Additionally, patients with ADAMTS13 enzyme deficiency are more likely to experience TTP.
Potential mechanisms	Though a prasugrel-specific mechanism has not been established, there are two possible mechanisms identified for other thienopyridines (ticlopidine and clopidogrel). Ticlopidine-associated TTP typically develops 2 weeks after the drug is started and may be immune mediated with antibodies to ADAMTS13, a metaloprotease involved with depolymerisation of von Willebrand factor multimers that facilitate platelet aggregation (Aster 2002). In contrast, clopidogrel-associated TTP can appear within days of starting the drug and is thought to be a result of endothelial damage (Bennett et al. 2007).
Preventability	There is no known, reliable method for preventing TTP.
Impact on individual patient	TTP is characterised by thrombocytopenia, microangiopathic hemolytic anaemia, fever, neurological changes, and renal abnormalities (Bennett 2000). If untreated, TTP is usually progressive and fatal. The fatality rate has decreased to 20% or less with intensive plasmapheresis. The severity of the disease and the relative ease/difficulty of treatment will variably affect the quality of life for individuals.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_ttp.rtf and others. **Postmarketing Data:** Lilly Safety System
MedDRA (version 17.1) terms	PTs Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, and Thrombotic microangiopathy

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Drug-Induced Hepatic Injury

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 245 (IR=19.62 per 1000 patient-years) ; Clopidogrel - 252 (IR=20.08 per 1000 patient-years),
RR=0.98, 95% CI: 0.82-1.17 p-value 0.7980

Postmarketing Data: Events of drug-induced hepatic injury are considered very rarely reported (0.003%) based on an estimated patient exposure to prasugrel of 2.7 million.

Seriousness/ Outcomes

Clinical Trial Program:
The distribution of outcomes and seriousness for drug-induced hepatic injury 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 = 17,164)	282 (1.64%)	3 (0.02%)	151 (0.88%)	116 (0.68%)	1 (0.01%)	40 (0.23%)	95 (0.55%)
Serious	15 (0.09%)	3 (0.02%)	6 (0.03%)	4 (0.02%)	1 (0.01%)	1 (0.01%)	3 (0.02%)
Non-Serious	272 (1.58%)	0 (0.00%)	146 (0.85%)	115 (0.67%)	0 (0.00%)	39 (0.23%)	92 (0.54%)
Studies TAAL and TABY (N = 11364)	231 (2.03%)	1 (0.01%)	131 (1.15%)	99 (0.87%)	0 (0.00%)	31 (0.27%)	89 (0.78%)
Serious	13 (0.11%)	1 (0.01%)	7 (0.06%)	4 (0.04%)	0 (0.00%)	1 (0.01%)	3 (0.03%)
Non-Serious	222 (1.95%)	0 (0.00%)	125 (1.10%)	98 (0.86%)	0 (0.00%)	30 (0.26%)	86 (0.76%)

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-MC-TAAL, H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TABN, H7T-MC-TABR, H7T-MC-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_pras_dili.rtf.
lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_dili.rtf.

Postmarketing Data: Of the reported events, 43% of the postmarketing events were serious and 57% were non-serious. Outcomes reported in postmarketing events included fatal (1%), recovered/recovering (31%), not recovered (13%), and unknown (55%). There were no events recovered with sequellae reported in the postmarketing data for these events.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Drug-Induced Hepatic Injury (continued)

Severity and nature of risk

Clinical Trial Program: Grades of severity for treatment-emergent drug-induced hepatic injury in Studies TAAL and TABY and in all 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 = 17,164)	282 (1.64%)	196 (1.14%)	71 (0.41%)	15 (0.09%)
Studies TAAL and TABY (N = 11364)	231 (2.03%)	156 (1.37%)	64 (0.56%)	11 (0.10%)

Abbreviations: % = percentage of subjects reporting the event; 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-TABY, H7T-MC-TACA, H7T-MC-TACE, H7T-MC-TACM, H7T-MC-TACW, H7T-MC-TACY, H7T-MC-TADF, H7T-MC-TADI, and H7T-DS-TAEL.

Sources: lillyce/prd/ly640315/integrations/idb_q22014/programs_stat/tfl_output/idb_tace_tri_tadf_tael_rmp_maxsev_dili.rtf. lillyce/prd/ly640315/h7t_mc_taby/final/programs_stat/tfl_output/taal_taby_rmp_maxsev_dili.rtf.

Postmarketing Data: Data not available.

Background incidence/prevalence

Results of nonclinical studies with prasugrel do not indicate an association between prasugrel and drug-induced hepatic injury.

The document and the studies below provide information on the background/prevalence of the risk of drug-induced hepatic injury:

a) CDER 2002 [WWW]: Approval package for clopidogrel (Plavix®)

In ACS patients taking aspirin and placebo, incidence was 0.4%.

b) Cannon et al. 2004: A US study in 4,162 patients hospitalized for ACS within the preceding 10 days

In ACS patients taking 40 mg Pravastatin, incidence was 1.1%; in those taking 80 mg Artovastatin, incidence was 3.3%.

c) de Lemos et al. 2004: International, randomized, double-blind trial of patients with ACS receiving 40 mg/d of simvastatin for 1 month followed by 80 mg/d thereafter (n=2265) compared with ACS patients receiving placebo for 4 months followed by 20 mg/d of simvastatin (n=2232), who were enrolled in phase Z of the A to Z trial between December 29, 1999, and January 6, 2003

In ACS patients taking 40/80 mg Simvastatin, incidence was 0.9%; in those taking 20 mg Simvastatin + placebo, incidence was 0.4%.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Drug-Induced Hepatic Injury (continued)	
Risk groups or risk factors	There are no known patient characteristics relevant to the risk of hepatic injury with prasugrel treatment.
Potential mechanisms	None established.
Preventability	Idiosyncratic drug-induced liver injury is unpredictable, and toxicity does not appear to be dose-related. Idiosyncratic reactions appear to reflect host factors and individual susceptibility. Whether idiosyncratic reactions are a result of genetic and/or acquired differences has not yet been established and, to date, no genetic, metabolic, or other characteristics have been found to reliably predict severe drug-induced liver injury in an individual (US HHS 2009).
Impact on individual patient	The impact on the individual patient depends on the nature of the hepatic AE that occurs. Patients with mildly elevated hepatic enzymes usually experience no signs or symptoms. Symptoms of more severe hepatic injury that could affect quality of life include chronic fatigue, nausea, loss of appetite, abdominal pain and swelling, and yellow discolouration of the skin and eyes. A serious reaction such as an acute liver failure/injury could necessitate liver transplant, leading to lifelong treatment with immunosuppressant's, which are therapies that can increase risk of infection and cancer (Ross 2007). In some cases of liver failure, the outcome could be fatal. Cases have been reported that have met the biochemical definition of definition of Hy's rule (ALT or AST >3x ULN, total bilirubin >2x ULN, alkaline phosphatase <2x ULN all at the same time). Individual case evaluation of the subjects meeting the biochemical criteria for Hy's rule did not suggest that there was evidence of drug-induced liver injury (DILI).
Potential public health impact of Important identified risk or important potential risk	Not applicable.
Evidence source	**Clinical Trial Program**: Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_dili.rtf and others. **Postmarketing Data:** Lilly Safety System
MedDRA (version 17.1) terms	SMQ Liver related investigations, signs and symptoms (20000008 Narrow and Broad), SMQ Cholestasis and jaundice of hepatic origin (20000009 Narrow and Broad), SMQ Hepatitis, non-infectious (20000010 Narrow and Broad), SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (20000013 Narrow and Broad), SMQ Liver-related coagulation and bleeding disturbances (20000015)

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Colorectal Cancer

Frequency with 95% CI

Clinical Trial Program:
Prasugrel - 19 (IR=1.52 per 1000 patient-years) ; Clopidogrel - 8 (IR=0.64 per 1000 patient-years),
RR=2.39, 95% CI: 1.05-5.45 p-value 0.0389

Postmarketing Data: Events of colorectal cancer are considered very rarely reported (0.0007%) based on an estimated patient exposure to prasugrel of 2.7 million.

Seriousness/ Outcomes

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-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, 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.

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

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Colorectal Cancer (continued)

Seriousness/ Outcomes (continued)

Clinical Trial Program (continued):

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.

Postmarketing Data: All of the postmarketing events were serious. Outcomes reported in postmarketing events included recovered/recovering (26%), not recovered (16%), and unknown (58%). There were no fatalities or events recovered with sequellae reported in the postmarketing data for these events.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Colorectal Cancer (continued)

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: % = percentage of subjects reporting the event; 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.

[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 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.

Postmarketing Data: Data not available.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk:	**Colorectal Cancer (continued)**
Background incidence/ prevalence	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: 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: 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: 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.
Risk groups or risk factors	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). There are no known patient characteristics relevant to the risk of colorectal cancer with prasugrel treatment.
Potential mechanisms	None established.
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).

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk:	**Colorectal Cancer (continued)**
Impact on individual patient	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 2013). The impact on the individual patient depends on the stage of colorectal cancer at the time of detection.
Potential public health impact of Important identified risk or important potential risk	Not applicable
Evidence source	**Clinical Trial Program:** Clinical Trial Statistics program lillyce/prd/ly640315/integrations/programs_stat/tfl_output/idb_tace_tri_rmp_py_clrtc.rtf and others **Postmarketing Data:** Lilly Safety System
MedDRA (version 17.1) terms	HLT anal canal neoplasms malignant, HLT Colorectal neoplasms malignant, HLT Colorectal and anal neoplasms malignancy unspecified

Abbreviations: % = percentage of subjects reporting the event; ACS = acute coronary syndrome; ADP = adenosine diphosphate; AE = adverse event; ALT = alanine aminotransferase; ASA = acetylsalicylic acid (aspirin); AST = aspartate aminotransferase; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CRF = Case Report Form; DAPT = dual anti-platelet therapy; DILI = drug-induced liver injury; ELISA = enzyme-linked immunosorbent assay; FDA = Food and Drug Administration; GI = gastrointestinal; GIB = gastrointestinal bleed; HLT = MedDRA high level term; HLGT = MedDRA high level group term; HR = hazard ratio; IR = incidence rate; LMWH = low-molecular-weight heparin; MedDRA = Medical Dictionary for Regulatory Activities; 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; NEC = not elsewhere classified; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PT = MedDRA preferred term; RR = relative risk; SAE = serious adverse event; SMQ = standardised MedDRA Query; STEMI = ST segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TTP = thrombotic thrombocytopenic purpura; UFH = Unfractionated heparin; ULN = upper limit of normal; US = United States.

SVII.4. Identified and Potential Interactions

SVII.4.1. Overview of Potential for Interactions

The absorption and metabolism of prasugrel are rapid, with peak plasma concentration of the active metabolite occurring in approximately 30 minutes. The active metabolite's exposure increases proportionally over the therapeutic dose range.

Prasugrel is rapidly metabolized. Its inactive metabolites are excreted primarily in the urine. The active metabolite has an elimination half-life of about 7.4 hours (range of 2 to 15 hours).

Prasugrel has been studied in combination with cytochrome P450 (CYP) 3A and CYP2B6 inhibitors, CYP3A inducers, statins, known substrates of CYP2C19 and the p-glycoprotein transporter, drugs that increase gastric pH, food, warfarin, heparin, and aspirin.

Of these drugs, food, and other substances, Table SVII.3 presents identified interactions and potential interactions.

SVII.4.2. Important Identified and Potential Interactions

Table SVII.3. Important Identified and Potential Interactions

Interacting Substance	Description
Warfarin	
Effect of Interaction	Bleeding times measured when prasugrel is given with warfarin exceed those measured when prasugrel or warfarin are given alone. Prasugrel treatment does not affect the pharmacokinetics of S- or R-warfarin. Prasugrel does not affect the International Normalised Ratio or prothrombin time produced by warfarin (Study TAAR). Concomitant use of coumarin and prasugrel was not allowed in Study TAAL; however, some subjects did receive concomitant coumarin. The concomitant use of prasugrel and coumarins did not increase the risk of spontaneous or instrumented haemorrhage (Study TAAL).
Evidence Source	Studies TAAR and TAAL.
Possible Mechanisms	Warfarin inhibits the synthesis of clotting factor II, VII, IX, and X, as well as protein C, protein S, and protein Z.
Potential Health Risk	Increased risk of haemorrhage.
Discussion	Prasugrel and warfarin interfere in the haemostatic process by distinct mechanisms. The concomitant use of warfarin and prasugrel was not extensively evaluated in the TAAL study although the incidence of non-CABG-related TIMI Major or Minor bleeding events was not influenced by the type of anti-thrombotic drug used concomitantly with prasugrel. Warfarin and prasugrel should be co-administered with caution because of the potential for increasing the risk of bleeding.

Important Identified and Potential Interactions

Interacting Substance	Description
Heparin	
Effect of Interaction	A single intravenous bolus dose of unfractionated heparin (100 U/kg) did not significantly alter the prasugrel-mediated inhibition of platelet aggregation. Likewise, prasugrel did not significantly alter the effect of heparin on measures of coagulation (Study TAAT).
Evidence Source	Study TAAT
Possible Mechanisms	Heparin inhibits thrombin and factor Xa by binding antithrombin III.
Potential Health Risk	Increased risk of haemorrhage.
Discussion	Prasugrel and heparin interfere in the haemostatic process by distinct mechanisms. The association of heparin with a potent antiplatelet drug may increase the risk of haemorrhage, although the incidence of Non-CABG-related TIMI Major or Minor bleeding events was not influenced by the type of anti-thrombotic drug used concomitantly with prasugrel (Study TAAL). Prasugrel can be concomitantly administered with heparin.
Fibrinolytics	
Effect of Interaction	Recombinant tissue plasminogen activator (rtPA) activates plasminogen and may increase the risk of bleeding. Concomitant use of fibrinolytic therapy and prasugrel was not allowed in Study TAAL.
Evidence Source	Very few subjects were concomitantly treated with fibrinolytics in Study TAAL.
Possible Mechanisms	Both drugs affect haemostasis and could increase the risk of bleeding.
Potential Health Risk	Increased risk of bleeding.
Discussion	Caution is advised if prasugrel is used in conjunction with fibrinolytics.
Interacting Substance	**Description**
NSAIDs[a]	
Effect of Interaction	The concomitant use of an antiplatelet drug and NSAIDs (non-ASA) is associated with an increased risk of haemorrhage.
Evidence Source	The evidence of an increased risk of bleeding by the association of prasugrel and chronic use of NSAIDs is limited in Study TAAL as the chronic use of NSAIDs was not allowed per protocol.
Possible Mechanisms	NSAIDs can increase the risk of GI bleeding by (a) impairment of prostaglandin (PG) E_2-mediated cytoprotection in the GI mucosa by inhibition of cyclooxygenase-1 and (b) direct contact of the drug with the gastric mucosa. Prasugrel is an antiplatelet drug that can increase the risk of bleeding by inhibiting platelet activation and aggregation mediated by the $P2Y_{12}$ receptor. The concomitant use of prasugrel and NSAID could affect haemostasis by independent mechanisms.
Potential Health Risk	Increased risk of bleeding.
Discussion	Caution is advised if prasugrel is used in conjunction with chronic NSAIDs.

Important Identified and Potential Interactions

Abbreviations: ASA = acetylsalicylic acid (aspirin); CABG = coronary artery bypass graft; GI = gastrointestinal; NSAIDs = non-steroidal anti-inflammatory drugs; PG = prostaglandin; rtPA = Recombinant tissue plasminogen activator; TIMI = Thrombolysis In Myocardial Infarction.

[a] All subjects were to receive aspirin as concomitant medication during Study TAAL.

Sources: Study TAAR; Study TAAT; Study TAAL; prasugrel core data sheet.

SVII.5. Pharmacological Class Effects

SVII.5.1. Pharmacological Class Risks already Included as Important Identified or Potential Risks

Table SVII.4. Pharmacological Class Risks included as Important Identified or Potential Risks

Risk	Frequency in Study TAAL for Prasugrel		Frequency with Other Products in Same Pharmacological Class (Source of Data/Journal Reference)	
	Prasugrel n/N (%)	Clopidogrel n/N (%)	Ticlopidine	Clopidogrel
Bleeding				
Gastrointestinal haemorrhage	275/6741 (4.08)[a] 63/6741 (0.93)[b] 51/6741 (0.76)[c]	214/6716 (3.19)[a] 43/6716 (0.64)[b] 42/6716 (0.63)[c]	0.5% (Hass et al. 1989)	1.0% (CDER 2002 [WWW])
Coronary artery bypass graph-related haemorrhage	30/213 (14.08)[d]	9/224 (4.02)[d]	Not available	9.6% (Fox et al. 2004)
Intracranial haemorrhage	19/6741 (0.28)[b]	17/6716 (0.25)[b]	0.4% (Gent et al. 1989); 0.5% (Hass et al. 1989)	0.11% (CDER 2002 [WWW])
Intraocular haemorrhage	1/6741 (0.01)[c]	0	Not available	≥0.001 to <0.01 (Plavix® SPC 2015)
Percutaneous coronary intervention-related haemorrhage	264/6741 (3.92)[a,e]	196/6716 (2.92)[a,e]	1.2% (Bertrand et al. 1998)	0.5%[b];1.4%[c] (Sabatine et al. 2005) 1.6% PCI to 30 days[b] 2.7% PCI to follow up[b] 1.0% PCI to 30 days[c] 3.5% PCI to follow up[c] (Mehta et al. 2001)

Pharmacological Class Risks included as Important Identified or Potential Risks

Risk	Frequency in Study TAAL for Prasugrel: Prasugrel n/N (%)	Frequency in Study TAAL for Prasugrel: Clopidogrel n/N (%)	Frequency with Other Products in Same Pharmacological Class (Source of Data/Journal Reference): Ticlopidine	Frequency with Other Products in Same Pharmacological Class (Source of Data/Journal Reference): Clopidogrel
Allergic Reactions				
Anaphylaxis and Anaphlyactoid Reactions[a]	2/6741 (0.03) 2/6741 (0.03)	4/6716 (0.06) 2/6716 (0.03)	<0.5% (Ticlid® package insert, 2005)[f]	<1/10,000 (Plavix SPC 2015)
Rash[a]	186/6741 (2.76)	160/6716 (2.38)	5.1% (Ticlid® package insert, 2005)	≥1/1,000 to <1/100 (Plavix® SPC 2015)
Pruritus[a]	53/6741 (0.79)	71/6716 (1.06)	1.3% (Ticlid® package insert, 2005)	≥1/1,000 to <1/100 (Plavix® SPC 2015)
Thrombocytopenia	43/6741 (0.64)[a]	40/6716 (0.60)[a]	0.6%[g] (Taniuchi et al. 2001)	<1% (Plavix® SPC, 2010)
Thrombotic thrombocytopenic purpura[a]	0	1/6716 (0.01)	0.02% (Steinhubl et al. 1999)	<1/10,000 (Plavix® SPC, 2010)

Abbreviations: CDER = Center for Drug Evaluation and Research; N = total number of patients; n = number of affected patients; PCI = percutaneous coronary intervention; SPC = Summary of Product Characteristics; WWW = World Wide Web.

a Reported as treatment-emergent adverse events.

b Adjudicated TIMI Major Haemorrhage.

c Adjudicated TIMI Minor Haemorrhage.

d Adjudicated TIMI Major or Minor Haemorrhage.

e MedDRA preferred terms included puncture site haemorrhage, vessel puncture site haematoma, and retroperitoneal haemorrhage.

f Allergic reactions (including angioedema, allergic pneumonitis, and anaphylaxis).

g Platelet count <100000 mm^3.

Sources: Q951; Q1686; Q1636, Q2106; Q1731; l0116_fqbldl11_bleed_gi; l0159_fqbldl11_bleed_cabghmami; l0158_fqbldl11_bleed_proc.

SVII.5.2. Important Pharmacological Class Effects not Discussed Above

Not applicable.

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Part II: Safety Specification

Module SVIII: Summary of the Safety Concerns

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

Table SVIII.1. Summary of Safety Concerns (Important Identified Risks, Important Potential Risks, and Important Missing Information)

Summary of Safety Concerns	

Important Identified Risks	• Bleeding:[a]
	  ○ 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

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin); CABG = coronary artery bypass graft; CHF = congestive heart failure; NSAID = non-steroidal anti-inflammatory drug; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack.

[a] The key important identified risk with prasugrel is bleeding, which includes important subcategories of bleeding as shown.

Part III: Pharmacovigilance Plan

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

III.1. Safety Concerns and Overview of Planned Pharmacovigilance Actions

Important Identified Risks

The important identified risks for prasugrel are shown in the following tables.

Table III.1. Bleeding Risks and Planned Pharmacovigilance Activities

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal (GI) Haemorrhage, Intraocular Haemorrhage, Epistaxis, Percutaneous Coronary Intervention (PCI)-Related Haemorrhage, CABG-Related Haemorrhage, Risk associated with prasugrel use prior to coronary angiography in NSTEMI patients, Other Procedure-Related Haemorrhage[a]		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance; targeted surveillance terms.	Implementation of the pharmacovigilance plan will allow for further elaboration of the risk profile as it relates to these important identified risks to better understand the identified risks in a real world setting and in a wider spectrum of ACS subjects.

Abbreviations: CABG = coronary artery bypass graft; NSTEMI = non-ST segment elevation myocardial infarction.

a GI haemorrhage, epistaxis, and risk associated with prasugrel use prior to coronary angiography in NSTEMI patients are not included as targeted surveillance terms.

Table III.2. Hypersensitivity (including Angioedema) and Planned Pharmacovigilance Activities

Hypersensitivity (including Angioedema)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance; targeted follow-up questionnaire	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.

Abbreviations: ACS = acute coronary syndrome.

Table III.3. Thrombocytopenia and Planned Pharmacovigilance Activities

Thrombocytopenia		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance; targeted follow-up questionnaire	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 real world setting and in a wider spectrum of ACS subjects.

Abbreviations: ACS = acute coronary syndrome.

Table III.4. Thrombotic Thrombocytopenic Purpura and Planned Pharmacovigilance Activities

Thrombotic Thrombocytopenic Purpura		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance; targeted follow-up questionnaire	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 real world setting and in a wider spectrum of ACS subjects.

Abbreviations: ACS = acute coronary syndrome.

Important Potential Risks

The important potential risks for prasugrel are shown in the following tables.

Table III.5. Drug-Induced Hepatic Injury and Planned Pharmacovigilance Activities

Drug-Induced Hepatic Injury		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance; Targeted follow-up questionnaire	To estimate and monitor the incidence of this potential risk in patients treated with prasugrel; to describe the treatment pattern of prasugrel use; and to better understand the potential risk.

Table III.6. Potential Off-Label Use in Patients with Prior TIA/Stroke and Planned Pharmacovigilance Activities

Potential off-label use in patients with prior TIA/stroke		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance	To monitor the potential risk in patients treated with prasugrel with a prior history of TIA/stroke.

Abbreviations: TIA = transient ischemic attack.

Table III.7. Colorectal Cancer and Planned Pharmacovigilance Activities

Colorectal Cancer		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance; Targeted follow-up questionnaire	To estimate and monitor the reporting rate of this potential risk, and to better understand the potential risk.

Important Missing Information

Important missing information for prasugrel is shown in the following tables.

Table III.8. Concomitant use with Fibrinolytics, other Thienopyridines, Warfarin, and Chronic use of NSAIDs (non-ASA) and Planned Pharmacovigilance Activities

Concomitant use with Fibrinolytics, other thienopyridines, warfarin, and Chronic use of NSAIDs (non-ASA)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Pharmacovigilance, targeted surveillance with specific follow-up form for bleeding with emphasis on concomitant medications temporally related with prasugrel use and haemorrhagic events.	Implementation of the pharmacovigilance plan will allow for further elaboration of this exposure condition, and will help to better understand the concomitant use of these products and prasugrel.

Abbreviations: ASA = acetylsalicylic acid (aspirin); NSAIDs = non-steroidal anti-inflammatory drugs.

Table III.9. Use in Populations not Studied and Planned Pharmacovigilance Activities

Paediatric population		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance	To collect information regarding the use of prasugrel in this subpopulation, and to better understand the risk profile in this subpopulation.
Pregnant or lactating women		
None	Routine surveillance with specific follow-up forms for women who are pregnant or lactating.	To collect information regarding the use of prasugrel in these subpopulations, and to better understand the risk profile in these subpopulations.

Table III.10. Use in Subjects with Coronary Artery Disease with no Symptoms of ACS and Planned Pharmacovigilance Activities

Subjects without clinical manifestation of ACS		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine surveillance	To collect information to allow for further elaboration of the risk profile within the context of usual clinical practice, and to better understand the risk profile in this subpopulation.

Abbreviations: ACS = acute coronary syndrome.

Table III.11. Use in Subjects with Severely Compromised Cardiac Status and Planned Pharmacovigilance Activities

Use in Subjects with Severely Compromised Cardiac Status (Cardiogenic Shock, Class IV CHF, Refractory Ventricular Arrhythmia)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine surveillance	To collect information to allow for further elaboration of the risk profile; and to better understand the risk profile in this subpopulation.

Abbreviations: CHF = congestive heart failure.

Table III.12. Use in Subjects with Severe Hepatic Impairment and Planned Pharmacovigilance Activities

Use in Subjects with Severe Hepatic Impairment		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine surveillance	To collect information to allow for further elaboration of the risk profile within the context of usual clinical practice, and to better understand the risk profile in this subpopulation.

III.2. Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

Table III.13. Assessment of Effectiveness of EU Risk Minimisation Measures

Physician education		
Component Measured	**Activities**	**Rationale**
Adherence to the SPC in real-world clinical practices	Review of treatment patterns via epidemiological Study B015 (Switzerland) revealed that physicians appear to be adhering to the SPC when prescribing prasugrel. This study demonstrated that physicians were less likely to prescribe prasugrel than clopidogrel to specific subgroups previously identified as being at higher risk for bleeding with prasugrel, including patients with a history of stroke or TIA (1.3% versus 4.8%, respectively), patients ≥75 years of age (7.5% versus 29.4%, respectively), and those with a body weight of <60 kg (3.0% versus 7.4%, respectively). Use of the 10-mg MD in patients 75 years of age and older will be monitored on a monthly basis as part of routine surveillance in post-marketing reports (see Section SVII.3 of this RMP).	Additional risk minimisation for patients ≥75 years of age and patients weighing <60 kg has been provided by health care professional education to ensure that the information and recommendations in the SPC are adequately communicated.

Assessment of Effectiveness of EU Risk Minimisation Measures

Physician education		
Component Measured	**Activities**	**Rationale**
Assessment of DHPC – (DHPC to inform prescribers of increased risk of serious bleeding in UA/NSTEMI patients undergoing PCI if prasugrel is administered prior to diagnostic coronary angiography).	The assessment included confirmation of the timely distribution of the DHPC to targeted physicians. A physician survey (Study B021) evaluated whether physicians have knowledge of the safety warning communicated and whether they are considering the safety warning when prescribing prasugrel to their UA/NSTEMI patients. This survey was distributed in France, Germany, Sweden and the Netherlands.	The optimal measure of effectiveness for the DHPC was a physician survey because the bleeding rates associated with pre-treatment as measured in studies are so low that it would not be possible to design a pharmacoepidemiology study large enough to demonstrate a decrease in the rate. Also, the exact time of the dose administration is not provided in the most registries, so the determination of pre-treatment as identified in the observational studies may in fact reflect loading dose administration just immediately prior to PCI rather than >2 hours prior to diagnostic coronary angiography (the timing associated with increased risk of bleeding in UA/NSTEMI patients). Most importantly, it was expected that some pre-treatment will persist based on a provider's individual benefit-risk assessment, and observational studies do not provide adequate information to assess the providers' consideration.

Abbreviations: DHPC = Dear Healthcare Professional Communication; EU = European Union; MD = maintenance dose; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; RMP = risk management plan; SPC = Summary of Product Characteristics; TIA = transient ischemic attack; UA = unstable angina.

III.3. Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

Table III.14. Studies and Other Activities Completed since Last Update of Pharmacovigilance Plan

Study B021: Assessment of the effectiveness of risk minimisation measures set up for new safety information of Efient® a multinational survey among physicians to evaluate their knowledge and consideration of the new safety warning of prasugrel in France, Germany, Sweden and the Netherlands.	
Safety concern(s) risk minimisation measure investigated	Study B021 evaluated whether the new safety information communicated in the risk minimisation measures (mainly the DHPC) was effective in educating physicians about the increased bleeding risk when pre-treating UA/NSTEMI patients undergoing PCI with a loading dose of Efient®. The objectives of the study were to evaluate the proportion of physicians knowledgeable of the new safety warning of Efient®, and whether physicians will consider it when prescribing a loading dose of Efient®.
Brief summary of results	The pre-defined criteria for judging success of the proposed risk minimisation measures was for the majority of responding physicians to demonstrate knowledge of the new safety information and acknowledge consideration of the new safety information when prescribing the loading dose to UA/NSTEMI patients. More than half of physicians (55.4%) were aware of the recommended timing of the loading dose of Efient® 60 mg to be given in UA/NSTEMI patients. A further 20% of physicians stated they would give the loading dose of Efient® 2 to 4 hours prior to PCI, 2% stated they would administer the loading dose >4 hours prior to PCI and the remaining approximately 23% stated they did not know/recall the loading dose timing. The physicians surveyed mainly learned of the latest safety information through the DHPC (42.4%), followed by the summary of product characteristics (SmPC, 29.5%), the presentation at the ESC congress (26.0%), and the publication in the New England Journal of Medicine (20.7%). Almost 90% of physicians declared that they consider or will consider this safety information when giving a loading dose of Efient (from 77.5% to 94.5% in the four countries).
Implications	The study results demonstrate that the goals of the risk minimization plan were met. The pobjectives evaluating that physicians were aware of the recommended loading dose and considering the new safety information were achieved. The DHPC was identified as the main source of safety information from which physicians were informed about the new loading dose timing. Together with the other risk minimisation measures implemented since 2013 (SmPC, presentation at ESC congress and publication in the New England Journal of Medicine) they contributed to inform physicians of the latest safety information.

Abbreviations: DHPC = Dear Healthcare Professional Communication; ESC = European Society of Cardiology; PCI = percutaneous coronary intervention; SmPC = Summary of Product Characteristics; STEMI = ST segment elevation myocardial infarction; UA = unstable angina.

III.4. Details of Outstanding Additional Pharmacovigilance Activities

III.4.1. Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit Risk)

Table III.15. Imposed Activities Considered Key to the Benefit-Risk of the Product

Description of activity	Milestone(s)	Due Date(s)
None	Not applicable	Not applicable

III.4.2. Mandatory Additional PhV Activity (being a Specific Obligation)

Table III.16. Specific Obligations

Description of Activity	Milestone(s)	Due Date(s)
None	Not applicable	Not applicable

III.4.3. Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

Table III.17. Additional Pharmacovigilance Activities

Description of activity	Milestone(s)	Due Date(s)
Study B021: A physician survey will serve as both a process and outcome indicator of effectiveness of the communication by asking questions that demonstrate whether physicians have knowledge of the safety warning communicated and whether they are considering the safety warning when prescribing prasugrel to their UA/NSTEMI patients. This survey will be fielded in countries where Efient® (prasugrel) is registered and marketed, observation or market research data show evidence of treatment with Efient® (prasugrel) before PCI, and there is sufficient Efient® (prasugrel) market share to achieve an adequate physician sample in the country.	Start of Data collection	June 2014
	Final Study report	Jan 2015; to be submitted along with PSUR 11.

Abbreviations: NSTEMI = non-ST segment elevated myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina.

III.4.4. Stated Additional Pharmacovigilance Activities

Table III.18. Stated Additional Pharmacovigilance Activities

Description of activity	Expected Date of Report
Study B007: TReatment with ADP receptor iNhibitorS: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (United States)	Final study report completed Dec 2014.
Study B012: Canadian Observational AntiPlatelet sTudy (COAPT): Description of the Length of Dual Antiplatelet Therapy, Patient Characteristics, Treatment Patterns, and Processes of Care in Canadian Patients with Myocardial Infarction Undergoing Percutaneous Coronary Intervention	Final study report completed Mar 2015.
Study B013: Post-Marketing Surveillance Study on Effient (Prasugrel) Use Among Patients in Korea	Oct 2016
Study B019: Comparison of Clinical Outcomes, Resource Utilization, and Costs in Patients Hospitalized for ACS Managed with PCI and Receiving Prasugrel or Ticagrelor (United States)	Final study report completed Nov 2014.

III.5. Summary of the Pharmacovigilance Plan

III.5.1. Table of Completed Studies/Activities from the Pharmacovigilance Plan

Table III.19 lists the completed pharmacovigilance studies/activities in the pharmacovigilance plan.

Table III.19. Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Report
Study B008: A prospective, non-interventional cohort study. "Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel and Prasugrel During the Index Hospitalisation in Germany" Category 3	To compare the incidence rates of any non-CABG related bleeding (requiring any blood transfusion of whole blood or red blood cell concentrates [RBCs]) and/or intracranial haemorrhage (ICH) between prasugrel and clopidogrel patients treated for ACS-PCI (the indicated population for prasugrel) during the index hospitalisation. To compare the incidence rates of any bleeding (requiring any blood transfusion of whole blood or RBCs) and/or ICH in all prasugrel initiators and all clopidogrel initiators, and in identified subgroups of patients at increased risk for bleeding. To describe incidence rates of any bleeding in all prasugrel and clopidogrel initiators quantified by receiving any transfusion or not and by number of units transfused, and by bleeding location. To describe the number, percentage, patient characteristics, and outcomes (for example, bleeding or death) in all prasugrel initiators who: are not indicated (elective PCI, non-ACS), are contraindicated (history of TIA/stroke), are treated with prasugrel and do not undergo angiography, receive loading dose prior to coronary visualisation, are treated with a 5-mg dose or any other maintenance dose, are very elderly (≥75 years), have a low body weight (<60 kg).	Bleeding risks (including bleeding risks associated with the timing of loading dose and the overall bleeding risks) during the index hospitalisation. Bleeding risk associated with prasugrel use prior to coronary angiography.	Study complete; final study report completed in August 2013.	The final study report was completed in August 2013, and was submitted alongside RMP ver 8.

Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Report
Study B010: A retrospective, non-interventional cohort study "Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel or Prasugrel During the Index Hospitalisation in Sweden" Category 3	To compare the incidence rates of SCAAR-defined major or minor bleeding between only-prasugrel-treated plus prasugrel/clopidogrel-treated patients and only-clopidogrel-treated patients with ACS undergoing PCI (the indicated population for prasugrel) during the index hospitalisation. To compare the incidence rates of SCAAR-defined major or minor bleeding in the following only-prasugrel-treated plus prasugrel/clopidogrel-treated ACS-PCI patients and only-clopidogrel treated ACS-PCI patients during the index hospitalisation: identified subgroups of patients at increased risk for bleeding (e.g., age ≥75 years, body weight <60 kg). To describe incidence rates of bleeding in only-prasugrel-treated plus prasugrel/clopidogrel-treated patients, only-prasugrel-treated plus prasugrel/clopidogrel-treated ACS patients, only prasugrel-treated plus prasugrel/clopidogrel-treated ACS-PCI patients, and only-clopidogrel treated ACS-PCI patients: by any bleeding, by SCAAR-defined major or minor, by need for blood transfusion. To describe treatment patterns and outcomes (for example, bleeding or death) in only-prasugrel-treated plus prasugrel/clopidogrel-treated patients based on: indications (i.e., non-ACS receiving an elective PCI), receiving loading dose prior to coronary visualisation, age (≥75 years versus <75 years), body weight (≥60 kg versus <60 kg).	Bleeding risks. Risks associated with off-label use, as defined in the European guidelines for clopidogrel.	Study complete; final study report completed October 2013.	Three annual study reports were provided for 3 consecutive years post-launch. The results of the first annual study report were reported along with the submission of PSUR 5, and the results of the second annual study report were reported along with the submission of PSUR 7. The final study report was submitted along with PSUR 9.

Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Report
Study B011: A retrospective, non-interventional cohort study "Prasugrel Treatment Patterns in Outpatient Setting in Germany, the United Kingdom, and France" Category 3	To describe the treatment patterns of prasugrel in outpatient practices in Germany and France using the IMS Disease Analyzer, and in the United Kingdom (UK) using the IMS Disease Analyzer and the General Practitioner Research Database (GPRD).	Treatment pattern of prasugrel in outpatient database	Study complete; final study report submitted with PSUR 8.	The final study report for Study B011 (which includes the third and final reports for the UK and France, as well as the final report for Germany that was included with the B011 interim report) was submitted with PSUR 8.

Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Report
Study B015: A retrospective, non-interventional cohort study: "Treatment Patterns and Bleeding Risks in ACS Patients Treated with Clopidogrel or Prasugrel During the Index Hospitalisation, 30 days, and 1-year Follow-Up in Switzerland" Category 3	To describe the incidence rates of bleeding in prasugrel- and clopidogrel treated ACS-PCI patients during the index hospitalisation, 30-day follow up and 12-month follow up by: TIMI major or minor; GUSTO severe or life-threatening, moderate, or mild bleeding; Bleeding Academic Research Consortium (BARC) types; bleeding location; identified subgroups of patients at increased risk for bleeding (for example, age ≥75 years, body weight <60 kg). To describe the incidence rates of bleeding in all ACS patients treated with prasugrel or clopidogrel during the index hospitalisation, 30-day follow up, and 12-month follow up by: TIMI major/minor; GUSTO severe or life-threatening, moderate, or mild bleeding; BARC types; bleeding location; identified subgroups of patients at increased risk for bleeding. To describe the incidence rates of bleeding in the core cohort of ACS-PCI patients (with age <75 years, body weight ≥60 kg, and no history of TIA/stroke) treated with prasugrel or clopidogrel during the index hospitalisation, 30-day follow up, and 12-month follow up by: TIMI major/minor; GUSTO severe or life-threatening, moderate, or mild bleeding; BARC types; bleeding location. To describe the treatment patterns in ACS patients and the major adverse cardiovascular events (MACE) such as cardiac death, myocardial infarction, stroke, urgent revascularisation due to ACS, and definite stent thrombosis according to the Academic Research Consortium (ARC) during the index hospitalisation, 30-day follow up, and 12-month follow up in all prasugrel initiators who: do not receive PCI; have a contraindication for prasugrel treatment (history of TIA/stroke); receive a loading dose prior to coronary visualisation; are very elderly (≥75 years); have a low body weight (<60 kg); by the 'core cohort' defined as ACS-PCI patients with age <75 years, body weight ≥60 kg, and no history of TIA/stroke.	Study B015 investigated bleeding events and major adverse cardiovascular events (MACE) in prasugrel- and clopidogrel-treated ACS patients. Effectiveness of risk minimisation was measured through the collection of treatment patterns during the index hospitalisation, 30-day follow-up, and 12-month follow-up in "high-risk" prasugrel patients (i.e., patients who did not receive PCI; had a history of TIA/stroke; received a loading dose prior to coronary visualisation; were very elderly [≥75 years]; or had a low body weight [<60 kg]), as well as "lower-risk" prasugrel patients (i.e., <75 years of age, body weight ≥60 kg, and no history of TIA/stroke).	Study complete; final study report completed April 2014.	The results of the first annual study report were reported along with the submission of PSUR 7. The 30-day follow-up report was submitted in October 2013 along with PSUR 9. The final 1-year follow-up report was completed in April 2014, and submitted along with PSUR 10.

Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Report
Study B016: A retrospective, non-interventional study (France; FAST-MI registry) "Treatment Patterns in Acute Myocardial Infarction Patients Initiated with Prasugrel or Clopidogrel During the Index Hospitalisation with 1 Year Follow-Up" Category 3	To describe prasugrel and clopidogrel routine use: characteristics of the treated population (characteristics of patients, type of ACS, revascularisation strategy), dosage, duration, interruption and modification of therapy, concomitant treatments. To describe clinical outcomes: during the index hospitalisation: ischaemic complications and bleeding complications (TIMI major and minor bleeding, minimal bleeding); during the follow-up period: any event requiring a new hospitalisation and any treatment modification (medication stopped, new medication, modification of dosage, date of any change); death and reason of death during the index hospitalisation and during the follow-up period.	Ischaemic complications and bleeding complications (TIMI major and minor bleeding, minimal bleeding)	Study complete; final study report completed in October 2013.	The results of the first annual study report were reported with PSUR 6. The results of the final study report were submitted along with PSUR 9.

Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date of Submission of Final Report
Study B021: A non-interventional cross-sectional survey "Assessment of the effectiveness of risk minimisation measures set up for new safety information of Efient® (Prasugrel): a multinational survey among physicians to evaluate their knowledge and consideration of the new safety warning of Prasugrel in four EU countries" Category 3	**Primary objective:** to evaluate the proportion of targeted physicians who are knowledgeable of the new safety warning for Prasugrel. **Secondary objective:** to evaluate whether the physicians will consider the safety warning when prescribing Prasugrel.	Assessment of DHPC – (DHPC to inform prescribers of increased risk of serious bleeding in UA/NSTEMI patients undergoing PCI if prasugrel is administered prior to diagnostic coronary angiography).	Study complete; Final study report completed Jan 2015	The results of the final study report are being reported along with PSUR 11

Abbreviations: ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; CABG = coronary artery bypass graft; DHPC = Dear Healthcare Professional Communication; FAST-MI = French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction; GUSTO = Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PSUR = Periodic Safety Update Report; RMP = Risk Management Plan; SCAAR = Swedish Coronary Angiography and Angioplasty Registry; TIA = transient ischaemic attack; TIMI = thrombolysis in myocardial infarction; UA = unstable angina.

Part IV: Plans for Post-authorisation Efficacy Studies

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

IV.1. Applicability to Efficacy to All Patients in the Target Population

Prasugrel has been studied in 2 large, randomised, prospective trials (TRITON and TRILOGY), in addition to other trials, which have exposed over 17,000 patients to prasugrel (***Note:*** the studies conducted in Japan by Daiichi-Sankyo, involving different demographics, dosing, and indication, are not applicable for assessment of efficacy). These trials included patients with comorbid conditions common to acute coronary syndrome-percutaneous coronary intervention (ACS-PCI) patients, such as diabetes, hypertension, hypercholesterolemia, and the elderly. These trials were global, and evaluated efficacy in many various ethnicities. Results from TRITON demonstrated that treatment with prasugrel in patients across the full spectrum of ACS with planned PCI, when compared with clopidogrel used at the standard approved dose, resulted in a statistically significant reduction in the rate of the primary composite efficacy endpoint (cardiovascular [CV] death, nonfatal myocardial infarction [MI], or nonfatal stroke) at a median follow-up of 14.5 months.

Prasugrel has not been studied in populations that were excluded from ACS clinical trials, such as paediatric patients, patients who are pregnant or breastfeeding, patients with severe hepatic impairment, and patients with comorbid CV conditions (such as cardiogenic shock, New York Heart Association [NYHA] Class IV congestive heart failure [CHF], refractory ventricular arrhythmia). However, reviews of case reports from postmarketing data involving these patients have not identified any significant safety issues or lack of efficacy in these populations.

There are no plans for further efficacy studies in the target population for the currently authorised indication.

IV.2. Tables of Postauthorisation Efficacy Studies

As stated above, there are no plans for further efficacy studies in the target population for the currently authorised indication.

IV.3. Summary of Postauthorisation Efficacy Development Plan

There are no plans for further efficacy studies in the target population for the currently authorised indication.

IV.4. Summary of Completed Postauthorisation for Authorized Indications

There are no completed post-authorisation efficacy studies in the target population for the currently authorised indication.

Part V: EU Risk Minimisation Measures

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

V.1. Risk Minimisation Measures by Safety Concern

Table V.1. Risk Minimisation Measures by Safety Concern

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Section 4.2: Posology and method of administration:** • The use of EFIENT in patients ≥75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician (see Section 4.4), treatment is deemed necessary in the patients age group ≥75 years, then following a 60-mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients ≥75 years of age have greater sensitivity to bleeding and higher exposure to the active metabolite of prasugrel (see Sections 4.4, 4.8, 5.1, and 5.2). • EFIENT should be given as a single 60-mg loading dose and then continued at a 5 mg once daily dose. The 10-mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight <60 kg when given a 10-mg once daily dose compared with patients ≥60 kg (see Sections 4.4, 4.8, and 5.2). **Section 4.3 Contraindication:** • History of stroke or TIA. • Active pathological bleeding. **Section 4.4: Special warnings and precautions for use** <u>Use EFIENT cautiously in patients:</u> • ≥75 years of age (see below). • With a propensity to bleed (e.g., due to recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, or active peptic ulcer disease) • With body weight <60 kg (see Sections 4.2 and 4.8). In these patients the 10-mg maintenance dose is not recommended. A 5-mg maintenance dose should be used. • With concomitant administration of medicinal product that may increase the risk of bleeding, including oral anticoagulants, clopidogrel, NSAIDs, and fibrinolytics. The use of EFIENT in patients ≥75 years of age is generally not recommended and should only be undertaken with caution after a careful individual benefit/risk evaluation by the prescribing physician indicates that benefits in terms of prevention of ischaemic events outweigh the risk of serious bleedings. In the Phase 3 clinical trial, these patients were at greater risk of bleeding, including fatal bleeding, compared to patients <75 years of age. If prescribed, a lower maintenance dose of 5 mg should be used; the 10-mg maintenance dose is not recommended (see Section 4.2 and 4.8).

Risk Minimisation Measures by Safety Concern

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage (*continued*)	
Routine risk minimisation measures (*continued*)	Surgery: Patients should be advised to inform physicians and dentists that they are taking prasugrel before any surgery is scheduled and before any new medicinal product is taken. If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, EFIENT should be discontinued at least 7 days prior to surgery. Increased frequency (3-fold) and severity of bleeding may occur in patients undergoing CABG surgery within 7 days of discontinuation of EFIENT (see Section 4.8). The benefits and risks of EFIENT should be carefully considered in patients in whom the coronary anatomy has not been defined and urgent CABG is a possibility. **Section 4.8 Undesirable effects** **CABG-related bleeding** In the Phase 3 clinical trial, 437 patients underwent CABG during the course of the study. Of those patients, the rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the prasugrel group and 4.5% in the clopidogrel group. The higher risk for bleeding events in subjects treated with prasugrel persisted up to 7 days from the most recent dose of study drug. For patients who received their thienopyridine within 3 days prior to CABG, the frequencies of TIMI Major or Minor bleeding were 26.7% (12 of 45 patients) in the prasugrel group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.3% (3 of 90 patients) in the clopidogrel group. Beyond 7 days after drug discontinuation, the observed rates of CABG-related bleeding were similar between treatment groups [see SPC Section 4.4]. ***Listed in Table: Haemorrhagic and Non-haemorrhagic adverse reactions*** Common: Epistaxis, Gastrointestinal haemorrhage; Puncture site haemorrhage Uncommon: Eye haemorrhage, retroperitoneal haemorrhage, rectal haemorrhage, post-procedural haemorrhage
	Comment Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None

Risk Minimisation Measures by Safety Concern

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage (*continued*)	
Additional risk minimisation measure(s)	**Objective and justification:** To ensure that prescribers are appropriately informed about this risk not only through routine labelling changes but also through active communications. **Proposed actions/component and rationale:** Additional risk minimisation for patients ≥75 years of age and patients weighing <60 kg has been provided by health care professional education to ensure that the information and recommendations in the SPC are adequately communicated.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness of risk minimisation was measured through the collection of treatment patterns in the following completed epidemiological studies: B008 (Germany), B011 (Germany, United Kingdom, and France), B010 (Sweden), and B016 (France), and Study B015 (Switzerland). The CHMP endorsed that the phone survey to assess use of the 10-mg MD in the elderly was no longer feasible. Use of the 10-mg MD in patients 75 years of age and older will be monitored on a monthly basis as part of routine surveillance in post-marketing reports (see Section SVII.3 of this RMP).
Criteria for judging the success of the proposed risk minimisation measures	Limited use of the 10-mg dose in patients ≥75 years of age and patients weighing <60 kg.
Planned dates for assessments	B015 – 1-year follow-up report completed in April 2014, and submitted with PSUR 10.

Risk Minimisation Measures by Safety Concern

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage (*continued*)	
Results of effectiveness measurement	**Study B011:** Based on data from Study B011 describing patients who had at least 1 prasugrel prescription record in France from January 2010 to October 2012, in Germany from April 2009 to October 2011 using the IMS Disease Analyzer, and in the UK from July 2009 to October 2012 using the IMS Disease Analyzer and the GPRD, the majority of prasugrel prescriptions were for patients <75 years of age and ≥60 kg. This is consistent with data observed in the ALKK-PCI registry in Study B008, in which patients ≥75 years and patients <60 kg were less likely to receive prasugrel than clopidogrel. When prasugrel is used in the very elderly or lower body weight populations, it appears that the 10-mg dose is being prescribed. **Study B008:** The final study report for Study B008 includes cumulative data collected between 15 October 2009 and 28 February 2013. In Study B008: • A majority of patients were ACS-PCI patients (Population C: the indicated population for prasugrel). • A majority of patients were <75 years of age and had body weight ≥60 kg. Of those elderly and lower body weight patients who received a prasugrel MD during the index hospitalisation, the majority received 10 mg (≥75 years = 76.6%; <60 kg = 80.4%). • 1.5% (41 of 2689 prasugrel-treated patients receiving loading dose during the index hospitalisation) of the study population had a history of TIA or stroke. • The majority of patients received a 60-mg LD (approximately 85%). • There were no statistically significant differences between prasugrel- and clopidogrel-treated patients in the non-CABG-related bleeding rate (requiring any transfusion of whole blood or RBCs) and/or ICH (adjusted for quintiles of the propensity score) in the ACS-PCI population: (0.64% versus 0.76%; OR [95% CI]: 1.48 [0.74-2.97], p=0.267). It appears that physicians from these 32 hospitals in the German registry are selecting a patient population for prasugrel use in which these serious bleeding events are of no greater concern than for clopidogrel-treated patients.

Risk Minimisation Measures by Safety Concern

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage (*continued*)	
Results of effectiveness measurement (*continued*)	**Study B010:** The final study report for Study B010 includes data collected from 01 May 2010 through 02 April 2013, and is the third of three annual reports based on cumulative aggregate data. In Study B010: *Demographics and Treatment Patterns:* • The majority (80.4%) of patients treated with prasugrel were in the indicated population (ACS-PCI patients). • There were fewer elderly patients (≥75 years) in the prasugrel group versus clopidogrel (21.4% versus 29.6%). Both the prasugrel and clopidogrel groups had low rates of patients with body weight <60 kg (4.3% and 5.0%, respectively). • 38.1% received prasugrel before PCI. *Bleeding Rates:* • Bleeding event rates (any bleeding, SCAAR major bleeding, SCAAR minor bleeding, or need for blood transfusion) were low for both treatment groups in the ACS-PCI population. • The prasugrel group had a numerically lower rate of SCAAR major bleeding compared to clopidogrel group (0% versus 0.1%; p=0.079). • The prasugrel group had a significantly lower rate of SCAAR minor bleeding compared with clopidogrel (0.2% versus 1.3%; p<0.0001). • In patients ≥75 years and patients <60 kg, bleeding event rates were numerically lower for prasugrel- versus clopidogrel-treated ACS-PCI patients (SCAAR minor bleeding for patients ≥75 years was 0.3% versus 1.7%, respectively [p=0.020]; any bleeding for patients <60 kg was 1.6% versus 6.4%, respectively [p=0.053]).

Risk Minimisation Measures by Safety Concern

Bleeding Risks, including: Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage (*continued*)	
Results of effectiveness measurement (*continued*)	**Study B016:** The final study report for Study B016 contains a retrospective cohort analysis of data from the French FAST-MI 2010 registry database. The study assessed routine use of prasugrel and clopidogrel during the index hospitalisation in patients hospitalised with acute myocardial infarction (AMI). In this study: • The majority of the prasugrel patients (95.6%) underwent PCI, which demonstrates use consistent with the label. • Of the prasugrel patients who underwent PCI, 25.6% were STEMI patients and 8.4% were NSTEMI patients. Of the prasugrel patients who underwent PCI, 4% were ≥75 years of age, approximately 3% weighed <60 kg, and 0.3% had a history of TIA/stroke. • Overall in the study, there were more female patients in the clopidogrel group (29.9%) compared to the prasugrel group (12.7%). The mean age of the patients discharged on prasugrel was 56.3 years compared to 68.1 years on clopidogrel. Overall in the study, at the time of 12-months follow-up, the number of bleeding events was low in both treatment groups (1.56% in the clopidogrel group and 0.14% in the prasugrel group). The bleeding rates in real-world practice are consistently seen to be very low in this as well as the other registries. This data should be interpreted with caution, however, as the patients who received prasugrel and the patients who received clopidogrel in this study had notably different demographic and baseline characteristics (e.g., prasugrel was administered to a younger population, to more males vs. females, to more STEMI patients than NSTEMI patients, etc.).

Risk Minimisation Measures by Safety Concern

<table>
<tr><th colspan="2">Bleeding Risks, including:
Intracranial Haemorrhage, Gastrointestinal Haemorrhage, Intraocular Haemorrhage, Epistaxis, PCI-related Haemorrhage, CABG-related Haemorrhage, Other Procedure-Related Haemorrhage (continued)</th></tr>
<tr><td>Results of effectiveness measurement (continued)</td><td>Study B015:
Bleeding events (any) were lower in prasugrel-treated patients during hospitalisation compared to clopidogrel treated patients (2.9% vs 5.2%). Similar low rates of bleeding (any) events were observed in prasugrel-treated patients at 30-day and 1- year follow-up compared with clopidogrel (3.0% vs 6.0%, and 5.1% vs 9.3%, respectively).
Bleeding events in prasugrel-treated patients were also low in a subgroup of high-risk patients (≥75 years, body weight <60 kg, or history of stroke or TIA) compared with clopidogrel-treated patients, as shown in the table below. This was also observed in the low-risk group.
<table>
<tr><th></th><th colspan="2">Low-Risk Group</th><th colspan="2">High-Risk Group</th></tr>
<tr><th>Bleeding (any)</th><th>Prasugrel</th><th>Clopidogrel</th><th>Prasugrel</th><th>Clopidogrel</th></tr>
<tr><td>In-hospital</td><td>2.80%</td><td>3.60%</td><td>3.70%</td><td>8.10%</td></tr>
<tr><td>30 days</td><td>3.00%</td><td>4.20%</td><td>3.70%</td><td>9.50%</td></tr>
<tr><td>1 year</td><td>4.80%</td><td>6.60%</td><td>7.80%</td><td>14.50%</td></tr>
</table></td></tr>
<tr><td>Impact of risk minimisation</td><td>Overall, the final results from studies B008, B011, B010, B015, and B016 consistently show that the low percentages of prasugrel prescriptions recorded for patients ≥75 years of age or <60 kg compared to clopidogrel may indicate that guidance from the SPC is being considered by prescribing physicians. It appears that physicians are selecting a patient population for prasugrel use in which these serious bleeding events are of no greater concern than for clopidogrel-treated patients. These studies appear to demonstrate that the risk minimisation measures were effective.</td></tr>
<tr><td>Comment</td><td>N/A</td></tr>
</table>

Risk Minimisation Measures by Safety Concern

Bleeding Risk Associated with Prasugrel use Prior to Coronary Angiography in NSTEMI Patients	
Objective(s) of the risk minimisation measures	To optimize benefit-risk associated with prasugrel by informing practitioners of clinically relevant new safety data.
Routine risk minimisation measures	Wording regarding this risk has been added to the SmPC as follows: **SPC Section 4.2 (Posology and Method of Administration):** In UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should only be given at the time of PCI. **SmPC Section 4.4 (Special Warnings and Precautions for Use):** *Bleeding Risk Associated with Timing of Loading Dose in NSTEMI:* In a clinical trial of NSTEMI patients (the ACCOAST study), where patients were scheduled to undergo coronary angiography within 2 to 48 hours after randomisation, a prasugrel loading dose given on average 4 hours prior to coronary angiography increased the risk of major and minor peri-procedural bleeding compared with a prasugrel loading dose at the time of PCI. Therefore, in UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should be given at the time of PCI. **SmPC Section 4.8 (Undesirable Effects):** *Bleeding Risk Associated with Timing of Loading Dose in NSTEMI:* In a clinical study of NSTEMI patients (the ACCOAST study), where patients were scheduled to undergo coronary angiography within 2 to 48 hours after randomisation, patients given a 30 mg loading dose on average 4 hours prior to coronary angiography followed by a 30 mg loading dose at the time of PCI had an increased risk of non-CABG peri-procedural bleeding and no additional benefit compared to patients receiving a 60 mg loading dose at the time of PCI. **SmPC Section 5.1 (Pharmacodynamic Properties):** In a 30-day study (ACCOAST) in 4033 patients with NSTEMI with elevated troponin who were scheduled for coronary angiography followed by PCI within 2 to 48 hours after randomisation, subjects who received prasugrel 30 mg loading dose on average 4 hours prior to coronary angiography followed by a 30 mg loading dose at the time of PCI (n=2037) had an increased risk of non-CABG peri-procedural bleeding and no additional benefit compared to patients receiving a 60 mg loading dose at the time of PCI (n=1996). Specifically, prasugrel did not significantly reduce the frequency of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, urgent revascularisation (UR), or glycoprotein (GP) IIb/IIIa inhibitor bailout through 7 days from randomisation in subjects receiving prasugrel prior to coronary angiography compared to patients receiving the full loading dose of prasugrel at the time of PCI, and the rate of the key safety objective for all TIMI major bleeding (CABG and non-CABG events) through 7 days from randomisation in all treated subjects was significantly higher in subjects receiving prasugrel prior to coronary angiography versus patients receiving the full loading dose of prasugrel at the time of PCI. Therefore, in UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should be given at the time of PCI.
	Comment: Not applicable
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	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). Study results and new safety data were shared at international cardiology congress(es), and published in an internationally read journal, the New England Journal of Medicine, in 2013.

Risk Minimisation Measures by Safety Concern

Bleeding Risk Associated with Prasugrel use Prior to Coronary Angiography in NSTEMI Patients (*continued*)	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The assessment included confirmation of the timely distribution of the DHPC to targeted physicians. A physician survey (Study B021) evaluated whether physicians have knowledge of the safety warning communicated and whether they are considering the safety warning when prescribing prasugrel to their UA/NSTEMI patients. This survey was sent to Cardiologists and Emergency Room physicians in France, Germany, Sweden and the Netherlands.
Criteria for judging the success of the proposed risk minimisation measures	The risk minimisation communication was to be considered successful if the majority of responding physicians demonstrated knowledge of the new safety information and acknowledged consideration of the new safety information when prescribing the loading dose to UA/NSTEMI patients.
Planned dates for assessments	The assessment was executed in Q2 and Q3, 2014.
Results of effectiveness measurement	More than half of physicians (55.4%) were aware of the recommended timing of the loading dose of Efient® 60 mg to be given in UA/NSTEMI patients. A further 20% of physicians stated they would give the loading dose of Efient® 2-4 hours prior to PCI, 2% stated they would administer the loading dose >4 hours prior to PCI and the remaining approximately 23% stated they did not know/recall the loading dose timing. The physicians surveyed mainly learned of the latest safety information through the DHPC (42.4%), followed by the summary of product characteristics (SmPC, 29.5%), the presentation at the ESC congress (26.0%), and the publication in the New England Journal of Medicine (20.7%). Almost 90% of physicians declared that they consider or will consider this safety information when giving a loading dose of Efient (from 77.5% to 94.5% in the four countries).
Impact of risk minimisation	The study results demonstrate that the goals of the risk minimization plan were met. The objectives of evaluating physician awareness and consideration of the new safety information were achieved.
Comment	None

Risk Minimisation Measures by Safety Concern

Hypersensitivity (including angioedema)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.3 Contraindication** • Hypersensitivity to the active substance or to any of the excipients. **4.4 Special warnings and precautions for use** *Hypersensitivity including angioedema* Hypersensitivity reactions including angioedema have been reported in patients receiving prasugrel, including in patients with a history of hypersensitivity reaction to clopidogrel. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised **Section 4.8 Undesirable Effects** *Listed in Table : Haemorrhagic and Non-haemorrhagic adverse reactions* Hypersensitivity including angioedema, Uncommon
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted, and wording on *Hypersensitivity including angioedema was added in March 2011.*
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Thrombotic Thrombocytopenic Purpura (TTP)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.4 Special warnings and precautions for use** *Thrombotic Thrombocytopaenic Purpura (TTP)* TTP has been reported with the use of prasugrel. TTP is a serious condition and requires prompt treatment. **Section 4.8 Undesirable Effects** *Listed in Table : Haemorrhagic and Non-haemorrhagic adverse reactions* Thrombotic thrombocytopaenic purpura (TTP), frequency not known.
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since April 2011.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.
Thrombocytopenia	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Section 4.8 Undesirable Effects** *Listed in Table : Haemorrhagic and Non-haemorrhagic adverse reactions* Thrombocytopaenia, Rare
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since April 2011.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	None

Risk Minimisation Measures by Safety Concern

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Concomitant use with fibrinolytics, other thienopyridines, warfarin, and chronic use of NSAIDs (non-ASA)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	Prescribing information states: use EFIENT cautiously in patients with concomitant administration of medicinal product that may increase the risk of bleeding, including oral anticoagulants, clopidogrel, NSAIDs, and fibrinolytics. **4.5 Interaction with other medicinal products and other forms of interaction** *Non-steroidal anti-inflammatory drugs (NSAIDs):* Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs (including COX-2 inhibitors) and Efient should be co-administered with caution.
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	**Objective and justification:** None
	Proposed actions/component and rationale: None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Paediatrics	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.2 Posology and method of administration** *Children and adolescents* Efient is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Pregnancy/Lactation	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.6 Fertility, pregnancy, and lactation** No clinical study has been conducted in pregnant or lactating women. 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 of prasugrel during breastfeeding is not recommended. Prasugrel had no effect on fertility of male and female rats at oral doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m^2).
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Use in subjects without clinical manifestation of ACS	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.1 Therapeutic indications** 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).
	Comment This risk has been included in the wording of the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	**Objective and justification:** None
	Proposed actions/component and rationale: None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Use in Subjects with Severely Compromised Cardiac Status (Cardiogenic Shock, Class IV CHF, Refractory Ventricular Arrhythmia)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.1 Therapeutic indications** • 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).
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	**Objective and justification:** None
	Proposed actions/component and rationale: None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.

Risk Minimisation Measures by Safety Concern

Use in Subjects with Severe Hepatic Impairment	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**4.3 Contraindications** Severe hepatic impairment (Child Pugh class C).
	Comment: Wording regarding this risk has been included in the prasugrel SmPC since marketing authorisation was granted.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	**Objective and rationale:** None
	Proposed actions/component and rationale: None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Current risk minimisation activities are deemed adequate.

Abbreviations: ACS = acute coronary syndrome; ALKK-PCI = Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte-Percutaneous Coronary Intervention; CABG = coronary artery bypass graft; CHF = congestive heart failure; CHMP = Committee for Medicinal Products for Human Use; CI = confidence interval; ESC = European Society of Cardiology; EU = European Union; FAST-MI = French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction; GPRD = General Practitioner Research Database; ICH = intracranial haemorrhage; LD = loading dose; MD = maintenance dose; NCA = National Competent Authority; PSUR = Periodic Safety Update Report; RBCs = red blood cells; RMP = Risk Management Plan; SCAAR = Swedish Coronary Angiography and Angioplasty Registry; SmPC = Summary of Product Characteristics; STEMI = ST segment elevation myocardial infarction; TIA = transient ischaemic attack; TIMI = thrombolysis in myocardial infarction; UK = United Kingdom.

V.2. Risk Minimisation Measure Failure

Not applicable.

V.2.1 Analysis of Risk Minimisation Measure(s) Failure

Not applicable.

V.2.2 Revised Proposal for Risk Minimisation

Not applicable

V.3. Summary Table of EU Risk Minimisation Measures

Table V.2. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Bleeding risk(s): • including: intracranial, GI, intraocular, epistaxis, PCI-related, CABG-related, and other procedure-related	Routine risk minimisation through appropriate wording in the SmPC.	• Additional risk minimisation for patients ≥75 years of age and patients weighing <60 kg has been provided by health care professional education to ensure that the information and recommendations in the SPC are adequately communicated.
• associated with prasugrel use prior to coronary angiography in UA/NSTEMI patients	Routine risk minimisation through appropriate wording in the SmPC.	• A Direct Healthcare Professional Communication (DHPC) was distributed in all countries where prasugrel is marketed in the EU (the DHPC has been completed in all EU Member States). Study results and new safety data were shared at international cardiology congress(es), and published in an internationally read journal, the New England Journal of Medicine, in 2013. The risk minimisation assessment survey indicated that the risk minimisation measures were effective in increased awareness and consideration of the new safety risk.
Hypersensitivity (including angioedema)	Routine risk minimisation through appropriate wording in the SmPC.	None Proposed
Thrombocytopenia	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Thrombotic thrombocytopenic purpura (TTP)	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Important Potential Risks		
Drug-induced liver injury	None proposed	None proposed
Potential off-label use in patients with prior TIA/stroke	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Colorectal cancer	None proposed	None proposed

Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Missing Information		
Concomitant use with fibrinolytics, other thienopyridines, warfarin, and chronic use of NSAIDs (non-ASA)	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Paediatric population	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Pregnant/lactating women	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Subjects without clinical manifestations of ACS	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Subjects with severe hepatic impairments	Routine risk minimisation through appropriate wording in the SmPC.	None proposed

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin); CABG = coronary artery bypass graft; CHF = congestive heart failure; EU = European Union; GI = gastrointestinal; NSAIDs = non-steroidal anti-inflammatory drugs; NSTEMI = non-ST elevated myocardial infarction; PCI = percutaneous coronary intervention; SmPC = Summary of Product Characteristics; TIA = transient ischaemic attack; UA = unstable angina.

Part VI: Summary of Activities in the Risk Management Plan by Product

Active Substance	prasugrel hydrochloride INN prasugrel
Product(s) concerned	EFIENT
MAH/MAA name	Eli Lilly Nederland BV

Data lock point for this module	25 February 2015
Version number of RMP when this module was last updated	10

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VI.1. Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.1.1. Summary Table of Safety Concerns

Table SVI.1. Summary of Safety Concerns

Summary of Safety Concerns	

Important Identified Risks	• Bleeding:[a]
	  ○ 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

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin); CABG = coronary artery bypass graft; CHF = congestive heart failure; NSAIDs = non-steroidal anti-inflammatory drugs; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

VI.1.2. Table of EU Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Not applicable

VI.1.3. Summary of Post-authorisation Efficacy Development Plan

There are no plans for further efficacy studies in the target population for the currently authorised indication.

VI.1.4. Summary Table of Risk Minimisation Measures

Table SVI.2. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Bleeding risk(s): • including: intracranial, GI, intraocular, epistaxis, PCI-related, CABG-related, and other procedure-related	Routine risk minimisation through appropriate wording in the SmPC.	• Additional risk minimisation for patients ≥75 years of age and patients weighing <60 kg has been provided by health care professional education to ensure that the information and recommendations in the SPC are adequately communicated.
• associated with prasugrel use prior to coronary angiography in UA/NSTEMI patients	Routine risk minimisation through appropriate wording in the SmPC.	• A Direct Healthcare Professional Communication (DHPC) was distributed in all countries where prasugrel is marketed in the EU (the DHPC has been completed in all EU Member States). Study results and new safety data were shared at international cardiology congress(es), and published in an internationally read journal, the New England Journal of Medicine, in 2013. The risk minimisation assessment survey indicated that the risk minimisation measures were effective in increased awareness and consideration of the new safety risk.
Hypersensitivity (including angioedema)	Routine risk minimisation through appropriate wording in the SmPC.	None Proposed
Thrombocytopenia	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Thrombotic thrombocytopenic purpura (TTP)	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Important Potential Risks		
Drug-induced liver injury	None proposed	None proposed
Potential off-label use in patients with prior TIA/stroke	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Colorectal cancer	None proposed	None proposed

Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Missing Information		
Concomitant use with fibrinolytics, other thienopyridines, warfarin, and chronic use of NSAIDs (non-ASA)	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Paediatric population	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Pregnant/lactating women	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Subjects without clinical manifestations of ACS	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory	Routine risk minimisation through appropriate wording in the SmPC.	None proposed
Subjects with severe hepatic impairments	Routine risk minimisation through appropriate wording in the SmPC.	None proposed

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin); CABG = coronary artery bypass graft; CHF = congestive heart failure; EU = European Union; GI = gastrointestinal; NSAIDs = non-steroidal anti-inflammatory drugs; NSTEMI = non-ST elevated myocardial infarction; PCI = percutaneous coronary intervention; SmPC = Summary of Product Characteristics;TIA = transient ischemic attack; UA = unstable angina.

VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Acute coronary syndrome (ACS) is a condition in which patients have symptoms from a blockage of the blood vessels that supply oxygen to the heart. The most common symptom is chest pain, often spreading down the left arm or the jaw, and may seem more like pressure in the chest. Patients may also feel sick to their stomach and have sweating.

Men tend to be diagnosed more often than women. Patients have an average age of approximately 65 in men and approximately 71 in women at the time of diagnosis.

Percentage of Patients with ACS

In European countries, approximately 26 to 60.6 adults per 10,000 have ACS.

In non-European countries approximately 50 to 202 adults per 100,000 have ACS.

VI.2.2. Summary of Treatment Benefits

Since the first approval of prasugrel in 2009, it has been used by more than 2.1 million patients world-wide. Prasugrel is taken together with aspirin to prevent atherothrombotic events (problems caused by blood clots and hardening of the arteries) in patients with ACS who are undergoing percutaneous coronary intervention (PCI). Acute coronary syndrome is a group of conditions that includes unstable angina (a severe type of chest pain) and heart attack. Percutaneous coronary intervention is an operation used to unblock narrowed coronary arteries (blood vessels in the heart).

In one main study, prasugrel, given as a 60-mg starting dose followed by 10-mg "maintenance" dose, was compared with clopidogrel (another inhibitor of platelet aggregation); both medicines were taken in combination with aspirin. The study involved almost 14,000 adults with ACS who were about to undergo PCI. The main measure of effectiveness was the reduction in the total number of cardiovascular (CV) deaths (deaths due to problems in the heart or blood vessels), heart attacks, or strokes. The patients were followed up for an average of 14.5 months.

Prasugrel was more effective than clopidogrel at reducing the total number of CV deaths, heart attacks, or strokes. At the end of the study, 9% of the patients taking prasugrel had died from CV causes or had a heart attack or stroke (643 out of 6813) compared with 11% of the patients taking clopidogrel (781 out of 6795).

VI.2.3. Unknowns Relating to Treatment Benefits

There is not much information about prasugrel use in children, women who are pregnant or breastfeeding, patients with other kinds of severe heart disease, or patients with advanced liver disease. Doctors should think carefully about whether prasugrel is needed in these patient populations because the benefit of taking prasugrel is unknown.

VI.2.4. Summary of Safety Concerns

Table VI.3. Important Identified Risks

Risk	What is Known	Preventability
Bleeding (haemorrhage), including: • Bleeding in the skull (intracranial haemorrhage) or stroke (blood flow to a part of the brain stops) • Bleeding in the stomach or intestine (gastrointestinal haemorrhage) • Bleeding in the eye (intraocular haemorrhage) • Nosebleeds (epistaxis) • Bleeding related to medical procedures (percutaneous coronary intervention-related haemorrhage, coronary artery bypass graft haemorrhage, and other procedure-related haemorrhage)	Medications like prasugrel can increase the risk of bleeding. The bleeding risk is greater for people who are 75 years of age or older, people who weigh less than 60 kg, and people who are taking other medications that may increase their risk of bleeding. The risk of bleeding is also greater for people with major injuries, recent surgery, a history of bleeding in the stomach or intestine, and/or severe liver or kidney disease.	You should not take prasugrel if you have severe bleeding, a history of stroke, or history of mini stroke. If you are 75 years of age or older, you need to ask your doctor if the benefits of prasugrel outweigh the risk of prasugrel because of your age. If your doctor does prescribe prasugrel and you are 75 years of age or older, then you should only be taking a 5-mg daily dose of prasugrel. If you weigh less than 60 kg, then you should only be taking a 5-mg daily dose. Because of this increased bleeding risk on prasugrel, it should be stopped at least 7 days before any planned surgery or dental procedure. It is very important to tell your doctor if you are being treated with Plavix® (a medicine that keeps your blood from clotting) warfarin (a blood thinner), or non-steroidal anti-inflammatory drugs for pain and fever (such as ibuprofen, naproxen, etoricoxib). If these medicines are taken with prasugrel, it can increase your risk for bleeding. If you have any other possible medical conditions that could cause increased bleeding, you should be sure to tell your doctor before you start taking prasugrel.

Important Identified Risks

Risk	What is Known	Preventability
Prasugrel should be used as directed on the drug label. It is recommended that prasugrel is used only after a doctor knows by X-ray that you can be treated without surgery for clogged blood vessels that provide oxygen to your heart. If prasugrel is given before this time, there could be greater risk of bleeding.	Some doctors give patients prasugrel before learning if they can be treated without surgery for clogged blood vessels that provide oxygen to the heart. If this happens, then the risk of bleeding may be increased.	Prasugrel should be used as directed on the drug label. It is recommended that prasugrel is used only after a doctor knows by X-ray that you can be treated without surgery for clogged blood vessels that provide oxygen to your heart. If prasugrel is given before this time, the risk of bleeding could be higher.
Allergic reactions (hypersensitivity), presenting as hives or itchy welts on the skin or swelling of the face including the lips, tongue, and throat that can affect your breathing (angioedema)	Allergic reactions have been seen in patients who have had allergic reactions to other medications like prasugrel.	You should not take prasugrel if you are allergic to prasugrel or any ingredients of prasugrel, or if you are allergic to any medications that are like prasugrel.
Low platelet count – platelets are a part of blood that help in blood-clotting (thrombocytopaenia)	Low platelet count has been seen in patients who take prasugrel or other medications like prasugrel. This can cause people to bleed more easily.	The risk of low platelet count with prasugrel can be lessened by minimising bleeding risks as described above in the section regarding bleeding.
Blood clots form in small blood vessels throughout the body (thrombotic thrombocytopaenic purpura)	Thrombotic thrombocytopenic purpura (TTP) has been seen with medications that are like prasugrel (clopidogrel and ticlopidine), and has been seen very rarely with prasugrel use. These small blood clots can cause numerous small red spots on the skin called "petechiae." These small blood clots can damage many organs including the kidneys, heart, and brain.	There is no known way to avoid TTP while taking prasugrel or medications like prasugrel. If you think that you may have this condition, you should tell your doctor immediately.

Table VI.4. Important Potential Risks

Risk	What is known (including Reason Why it is Considered a Potential Risk)
Damage to the liver caused by taking prasugrel (Drug-Induced Hepatic Injury)	None of the studies with prasugrel have shown that use of prasugrel causes liver damage. However, because liver damage is a risk with many medications, and because similar medications have caused changes in liver lab results, it is considered a potential risk for prasugrel.
Healthcare professional decision to use prasugrel in patients with a history of stroke or mini stroke (Potential off-label use in patients with prior TIA/stroke).	Patients who have had a prior stroke or mini stroke are at an increased risk for bleeding in the skull (intracranial haemorrhage) or stroke (blood flow to a part of the brain stops) when using prasugrel.
Cancer of the colon or rectum (parts of the large intestine) (Colorectal Cancer)	There have been patients treated with prasugrel who have been diagnosed with cancer of the colon or rectum. Many of these cancers are found because the patient has some bleeding from their colon or rectum while on prasugrel. Bleeding like this can happen more frequently while on prasugrel due to the expected effect of the drug. While it seems like the bleeding risk on prasugrel is the reason for finding these cancers, it is not known if prasugrel increases the risk for cancer growth.

Abbreviations: TIA = transient ischemic attack.

Table VI.5. Important Missing Information

Risk	What is Known
Use of prasugrel along with blood thinners (Concomitant use with fibrinolytics other thienopyridines, warfarin) and/or frequent use of anti-inflammatory medications (NSAIDs [non-ASA])	Because prasugrel use can cause bleeding, it should not be used at the same time as blood thinners or other medications that can cause bleeding such as anti-inflammatory medications.
Children (Paediatric Population)	Prasugrel should not be used in children below age 18 because it has not been studied.
Pregnant/Breastfeeding (Lactating) Women	No clinical study has been done in pregnant or breastfeeding women. Therefore, prasugrel should not be used in these patients.
Patients who do not have symptoms or evidence of a heart attack treated by a procedure to open clogged vessels (Subjects without clinical manifestation of ACS)	Prasugrel has not been studied in these patients.
Patients who have severe heart disease who cannot be treated with a procedure or surgery (Subjects with severely compromised cardiac status [cardiogenic shock, Class IV CHF, refractory ventricular arrhythmia])	Prasugrel has not been studied in these patients.
Patients with severe liver disease (Subjects with severe hepatic impairment)	Prasugrel should not be used in patients with severe liver disease because they have a higher risk of bleeding.

Abbreviations: ACS = acute coronary syndrome; ASA = acetylsalicylic acid (aspirin); CHF = congestive heart failure; NSAIDs = non-steroidal anti-inflammatory drugs.

VI.2.5. Summary of Additional Risk Minimisation Measures by Safety Concern

These additional risk minimisation measures are for the following risks:

Table VI.6. Bleeding (Haemorrhage) in patients ≥75 years of age and patients weighing <60 kg

Risk Minimisation Measure(s): Additional actions taken to reduce bleeding events for patients 75 years of age or older and patients who weigh less than 60 kg are provided by teaching health care professionals (doctors and nurses) the right way to use prasugrel in these patients.
Objective and Rationale
To teach health care providers so that patients are treated with the best dose of medication for each patient.

Table VI.7. Risk Minimisation Measures for Bleeding (Haemorrhage) in Patients ≥75 Years of Age and Patients Weighing <60 kg

Risk Minimisation Measure(s): Healthcare Professional Education
Objective and Rationale: Provide medical education to health care providers
Main Additional Risk Minimisation Measures • Training materials have been given to health care professionals, beginning from the time when the prasugrel was available. • Different scientific groups helped create more training materials on how to use prasugrel in very elderly patients (patients 75 years of age or older) and patients who weigh less than 60 kg.

Table VI.8. Bleeding Risk if Prasugrel is Given Before a Doctor Confirms by X-Ray that Treatment without Surgery for Clogged Blood Vessels that Provide Oxygen to the Heart will Be Safe (Bleeding Risk Associated with Prasugrel use Prior to Coronary Angiography in NSTEMI Patients)

Risk Minimisation Measure(s): Additional actions taken to reduce the risk of bleeding with the use of prasugrel before coronary angiography will be to send a detailed letter to health care professionals (doctors and nurses) to inform them of this increased risk, and to inform them not to give prasugrel before confirming by X-ray that treatment without surgery for clogged blood vessels that provide oxygen to the heart will be safe, as giving prasugrel before this time could increase the risk of bleeding.
Objective and Rationale
To inform doctors not to give prasugrel before confirming by X-ray that treatment without surgery for clogged blood vessels that provide oxygen to the heart will be safe, as giving prasugrel before this time could cause a higher risk of bleeding.

Table VI.9. Risk Minimisation Measures for Bleeding Risk Associated with Prasugrel use Prior to Coronary Angiography in NSTEMI Patients

Risk Minimisation Measure(s): Healthcare Professionals
Objective and Rationale: To help health care professionals understand the risk of giving prasugrel prior to coronary angiography and how to minimise its occurrence and its severity.
Main Additional Risk Minimisation Measures • Direct healthcare professional communication (DHPC - Dear Healthcare Professional Letter). • Information about this increased bleeding risk was also shared at an educational meeting for physicians, and was published in a journal written for physicians taking care of patients with heart disease.

VI.2.6. Planned Post-authorisation Development Plan

As noted in Table VI.10 below, there are currently no planned studies in the post-authorisation development plan. (***Note:*** Study B015 was completed in April 2014, and was provided with Periodic Safety Update Report [PSUR] 10).

Table VI.10. List of Studies in the Postauthorisation Development Plan

Study/Activity (including Study Number)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
None -- there are currently no planned studies in the postauthorisation development plan.	Not applicable	Not applicable	Not applicable	Not applicable

Studies which are a Condition of the Marketing Authorisation

Not applicable – as noted above, there are currently no planned studies in the postauthorisation development plan.

VI.2.7. Summary of Changes to the Risk Management Plan over Time

Table VI.11. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
3.0	19 Oct 2010	• Allergic reactions (hypersensitivity), presenting as hives or itchy welts on the skin or swelling of the face including the lips, tongue and throat which can affect your breathing (including angioedema), was classified as an important identified risk, and labelling (SPC Section 4.8) was updated. • Low platelet (platelets are a part of the blood that help in blood clotting) count (thrombocytopenia) was classified as an important identified risk, and labelling (SPC Section 4.8) was updated. • Blood clots forming in small blood vessels throughout the body (thrombotic thrombocytopenic purpura [TTP]) was classified as an important **identified** risk, and labelling (SPC Sections 4.4 and 4.8) was updated.	

Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
4.0	18 Apr 2011	Labelling was updated to reflect allergic reactions presenting as hives or itchy welts on the skin or swelling of the face including the lips, tongue, and throat which can affect your breathing (hypersensitivity including angioedema) in prasugrel patients, including those with a history of allergic reaction to clopidogrel.	"Hypersensitivity including angioedema" had been identified as a new important risk in RMP revision (3), and labelling was in the process of being updated. As of RMP rev 4, the SPC was updated to include the risk of hypersensitivity including angioedema in prasugrel patients, including those with a history of allergic reaction to clopidogrel.
8.0	August 2013	A higher rate of bleeding was seen in patients who were given prasugrel before confirming by X-ray that treatment without surgery for clogged blood vessels that provide oxygen to the heart will be safe, as giving prasugrel before this time could cause a higher risk of bleeding.	The former potential risk of 'off-label use' has now been better characterised as "bleeding associated with prasugrel use prior to coronary angiography in NSTEMI patients." Further characterisation and information surrounding this risk are reflected in the changes in this RMP. (It should be noted that this is not a newly identified risk).
8.1	November 2013	None	Per instruction from the EMA Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur, the post-authorisation safety study (PASS) categories were changed, and the risk of potential off-label use in patients with prior TIA/stroke was included.

Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
9.0	October 2013	A review of all information about neutropenia (low numbers of cells that fight infections) in patients given prasugrel was completed. A review of patients taking prasugrel who developed neutropenia did not identify any serious health outcomes or public risks that suggest that this is an important potential risk.	Neutropenia has been removed as an important potential risk in all sections of the RMP. No activities will change. This potential risk will continue to be closely monitored by identifying and evaluating any reports suggestive of low numbers of cells that fight infections.
9.1	January 2014	None	Per instruction from the EMA Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur, the post-authorisation safety study (PASS) categories were changed, and the risk of potential off-label use in patients with prior TIA/stroke was included.
10	April 2014	A review of all information about anaemia (low red blood cell count) and phototoxicity (sensitivity of the skin to light or sunlight) in patients given prasugrel was completed. A review of patients taking prasugrel who developed anaemia or phototoxicity did not identify serious health outcomes or public risks consistent with an "important" risk.	Anaemia and phototoxicity have been removed as important risks in all sections of the RMP. No activities will change. These risks will continue to be routinely monitored through the safety review process of the company.

Abbreviations: EMA = European Medicines Agency; NSTEMI = non-ST elevated myocardial infarction; RMP = Risk Management Plan; SPC = Summary of Product Characteristics; TIA = transient ischaemic attack; TTP = thrombotic thrombocytopenic purpura.

Annex 7. Routine Pharmacovigilance Activities Specific to Medicinal Product not Covered in the PSMF and Specific Adverse Event Follow-up Forms

A7.1. Routine Pharmacovigilance Activities Specific to Medicinal Product not Covered in the PSMF Licensing Status in the EEA

There are no routine pharmacovigilance activities specific to prasugrel that are not covered in the PSMF licensing status in the EEA.

A7.2. Specific Adverse Event Follow-up Forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the form
Form #1: Spontaneous Follow-up Form – Cerebral Haemorrhage	Cerebral Haemorrhage
Form #2: Spontaneous Follow-up Form – General Bleeding	General Bleeding
Form #3: Spontaneous Follow-up Form – Procedural Bleeding	Procedural Bleeding
Form #4: Spontaneous Follow-up Form – Photosensitivity	Photosensitivity
Form #5: Spontaneous Follow-up Form – Angioedema	Possible Angioedema
Form #6: Spontaneous Follow-up Form – Allergy	Allergic Reaction (*the form specifies to include relevant exposure and whether an allergist or dermatologist was consulted*)
Form #7: Spontaneous Follow-up Form – Hepatic Disorders	Hepatic Disorders
Form #8: Spontaneous Follow-up Form – Thrombotic Disorders	Blood Clotting and Thrombotic Disorders
Form #9: Spontaneous Follow-up Form – Cancer	Cancer/Neoplasm
Form #10: Spontaneous Follow-up Form – Blood and Bone Marrow Disorders	Blood and Bone Marrow Disorders

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cerebral Hemorrhage

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

If a CABG was performed, was Effient therapy prior to visualization of coronary arteries? ○ Yes ○ No

Was Effient discontinued prior to the procedure? ○ Yes, Date: _____ ○ No

Did the bleeding occur at an arterial puncture site? ○ Yes, Site: _____ ○ No

Was an arterial closure device used at the puncture site? ○ Yes ○ No

Was arterial compression performed when the arterial sheath was withdrawn? ○ Yes ○ No

Presenting Signs/Symptoms

- ☐ Headache
- ☐ Hypertension
- ☐ Altered mental status
- ☐ Impaired consciousness
- ☐ Nausea
- ☐ Vomiting
- ☐ Visual impairment
- ☐ Dizziness/vertigo
- ☐ Seizure
- ☐ Focal neurologic signs: _____
- ☐ Other symptoms/signs: _____

Concurrent/Recent Events (CNS)

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Head trauma
☐ Renal failure
☐ Hepatic failure
☐ Neurosurgery (type):
_____

☐ Ischemic stroke
☐ TIA
☐ Sepsis
☐ Other:
_____

☐ Hypertensive crisis
☐ Gastritis
☐ Corticosteroid use
☐ Eclampsia
☐ Meningitis

Relevant Past Medical History (CNS)

☐ Ischemic stroke
☐ Hemorrhagic stroke
☐ TIA
☐ Head trauma
☐ Other:
_____

☐ Intracranial neoplasm
☐ CNS AV malformation
☐ Hypertension
☐ Cirrhosis
☐ Bleeding disorder:
_____

☐ Chronic liver disease
☐ Renal impairment
☐ Alcoholism
☐ Sepsis
☐ Smoking

Concomitant Meds/Substances (include prescription, OTC and herbal)

☐ NSAIDS:_____
☐ Warfarin
☐ Other:
_____

☐ Antiplatelet agents:_____
☐ Heparin

Relevant Laboratory Tests

	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
Hematocrit				
WBC				
Platelets				
INR/Prothrombin time				
aPTT				
d-Dimer				
Creatinine				
Other:_____				
Other:_____				

Imaging Results (Ultrasound, MRI, CT)

Treatment

Was special treatment required? ☐ Yes ☐ No

☐ Blood Transfusion: #units: Date:
☐ Platelet transfusion(s): #units: Date:
☐ FFP/Plasma concentrate transfusion(s): # Date:
☐ Inotropic support:
☐ Surgery/surgical procedure: (please specify)

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Other:

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

General Bleeding

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

If a CABG was performed, was Effient therapy prior to visualization of coronary arteries? ○ Yes ○ No

Was Effient discontinued prior to the procedure? ○ Yes, Date: _____ ○ No

Did the bleeding occur at an arterial puncture site? ○ Yes, Site: _____ ○ No

Was an arterial closure device used at the puncture site? ○ Yes ○ No

Was arterial compression performed when the arterial sheath was withdrawn? ○ Yes ○ No

Medical History/Risk Factors:

☐ Hematological Disorder ☐ Liver Disease ☐ Esophageal Varices
☐ Prior Bleeding Episodes ☐ Alcohol use/abuse ☐ Gastric Ulcer
☐ Other _____

Medications at the time of event: ***please include prescription, OTC and herbal preparations***

☐ Heparin ☐ Aspirin
☐ Clopidogrel ☐ NSAID

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Glycoprotein IIb/IIIa Inhibitor ☐ Oral anticoagulant
☐ Anti-thrombin therapy ☐ Fibrinolytic/Thrombolytic therapy
☐ Acetaminophen or Paracetamol ☐ Other, please specify:_____

Laboratory Tests/Investigations ***(please fill in the appropriate lab values with units, dates and lab values for your institution where applicable)***

Lab Data	Normal Range	Baseline Value	Most Abnormal Value	Improvement Value
		Date:	Date:	Date:
INR/Prothrombin Time (PT)				
Platelet Count				
APTT				
Serum Creatinine				
Hemoglobin				
Hematocrit				
Other:_____				

Relevant Diagnostic Testing

☐ Ultrasound
Other testing performed:

Special Treatment Provided

☐ Prolonged Arterial Compression ☐ Surgical intervention
☐ Fluid administration #of units:_____ ☐ Inotropic support
☐ Blood transfusion #of units:_____ ☐ Other, please specify:
☐ Platelet transfusion #of units:_____

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering
○ Not Recovered ○ Unknown
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Procedural Bleeding

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

If a CABG was performed, was Effient therapy prior to visualization of coronary arteries? ○ Yes ○ No

Was Effient discontinued prior to the procedure? ○ Yes, Date: _____ ○ No

Did the bleeding occur at an arterial puncture site? ○ Yes, Site: _____ ○ No

Was an arterial closure device used at the puncture site? ○ Yes ○ No

Was arterial compression performed when the arterial sheath was withdrawn? ○ Yes ○ No

Information on Procedure/Surgery

☐ Elective Surgery/Procedure
☐ Urgent Surgery/Procedure
☐ Describe reason for surgery/procedure: _____

☐ Describe surgery/procedure: _____
☐ Estimated blood loss (mL): _____

Medical History

☐ Prior surgical/procedural bleed
☐ Bleeding disorder: _____
☐ Prior hemorrhage
☐ Chronic liver disease

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Family history of bleeding
☐ Chemotherapy
☐ Chronic renal disease
☐ Other:_____

Concomitant Meds/Substances (include prescription, OTC and herbal)

☐ NSAIDS:_____
☐ Warfarin
☐ Aspirin (dose):_____
☐ Antithrombin agents:
☐ Antiplatelet agents:_____
☐ Thrombolytic agents:_____
☐ Heparin (dose)_____
☐ Other:

Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelets				
INR/Prothrombin time				
aPTT				
Other:_____				
Other:_____				

Other Relevant Study	Results
Ultrasound	
Renal CT/MRI	
Other:_____	

Treatment

☐ Intravenous fluids
☐ Platelet transfusion (units):_____
☐ Other (specify):_____
☐ RBC transfusion (units):_____
☐ Fresh frozen plasma (units):_____

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered
○ Not Recovered
○ Worsened
○ Unknown
○ Recovering
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Photosensitivity

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Pre-existing History of Photosensitivity

☐ Polymorphous light eruption ☐ Solar Urticaria
☐ Smith-Lemli-Opitz Syndrome (SLOS) ☐ Photosensitivity to cosmetics or topical product
☐ Other (please describe): _____

Other Medical History

☐ Psoriasis ☐ Lupus ☐ Dysplastic Nevi ☐ Atopic dermatitis
☐ Significant System Disease ☐ Blemishes ☐ Sunburn ☐ Infection
☐ Diabetes ☐ Skin cancer ☐ Uneven skin tone ☐ Glaucoma
☐ Excessive tan ☐ Cataracts ☐ Other skin pathology: _____
☐ Other (please describe): _____

Presenting Signs and Symptoms/Cutaneous Phototoxic Occurrences

☐ Erythema ☐ Erythema with edema
☐ Large vesiculo-bullous reaction ☐ Erythema with infiltration

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Other:_____

Did the event begin on sun exposed skin? ○ Yes ○ No Did the event spread to other areas? ○ Yes ○ No

Presenting Signs and Symptoms/Visual Occurrences

☐ Blurred vision ☐ Scotoma ☐ Cataract

☐ Pain ☐ Other:_____

Most Recent Visual Acuity (after event)	Baseline Visual Acuity (prior to event)
Right eye: Uncorrected 20/___	Right eye: Uncorrected 20/___
Corrected 20/___	Corrected 20/___
Left eye: Uncorrected 20/___	Left eye: Uncorrected 20/___
Corrected 20/___	Corrected 20/___

Diagnostic Tests and Studies

**Please provide copy of report(s) for biopsy/autoimmune screening results, lab tests or other diagnostic testing.

Treatment provided (please describe)

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Possible Angioedema (AE)

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Pre-Existing History: *Please specify type and date of diagnosis:*

☐ Angioedema (Angioneurotic edema)

Reaction to: _____

☐ Idiopathic recurrent AE

☐ Allergic AE (IgE mediated)

☐ Medication-Induced AE (e.g. ACE inhibitors)

☐ Physically Induced AE (cold, heat, vibration, trauma, emotional stress, ultraviolet light)

☐ Cytokine Mediated AE syndrome (Gleich's syndrome)

☐ Thyroid autoimmune disease-associated AE

If Hereditary AE:

☐ Type 1: deficiency of C1 INH protein

☐ Type 2: dysfunction of C1 INH protein

☐ Type 3: coagulation factor XII mutation

If Acquired AE:

☐ Type 1: associated lymphoproliferative disease

☐ Type 2: autoimmune (anti-C1 INH antibody)

☐ Other allergic disease

☐ Anaphylactic Reactions

☐ Allergies to medications:

If yes, reaction to what (if known)?

☐ Food allergies

☐ Family history of angioedema

☐ Familial allergies

☐ Other relevant history:

Medications at Time of Event: *Please include prescription, OTC and Herbal Preparations*

☐ Aspirin

☐ ACE Inhibitors/ARBs

☐ NSAIDS

☐ Beta-blockers

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Contrast Agents ☐ Other: _____

Presenting Signs and Symptoms:

Edema? Location/description: _____ Rash? ☐ No ☐ Yes - Location: _____

Was edema pitting? ☐ Yes ☐ No ☐ Other: _____

Laboratory Tests/Diagnostic Testing*(Please include results if available)*

☐ IgE: _____ ☐ C4: _____

☐ IgG: _____ ☐ C1q: _____

☐ IgM: _____ ☐ Platelet Count: _____

☐ C1-INH: _____ ☐ Other: _____

CBC With Differential:

☐ Red Blood Cell Count: _____ ☐ Hematocrit: _____

☐ Hemoglobin: _____

White Blood Cell Differential:

☐ neutrophils: _____ ☐ eosinophils: _____

☐ lymphocytes: _____ ☐ basophils: _____

☐ monocytes: _____

Treatment:

What treatment was provided?

Was an immunologist consulted?

☐ Yes

☐ No

Was another specialist consulted?

☐ Yes - specify: _____

☐ No

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Allergy

Reaction Description *(include any relevant exposure and whether an allergist or dermatologist was consulted)*

Medical History/Risk Factors

- ☐ Angioneurotic edema
- ☐ Drug allergy
- ☐ Family history of allergies
- ☐ Latex allergy
- ☐ Other allergic disease
- ☐ Other Allergy
- ☐ Phototoxicity
- ☐ Skin disease
- ☐ Vasculitis
- ☐ Atopy

Medications at Time of Event: *Please include prescription, OTC and Herbal Preparations*

- ☐ Aspirin
- ☐ ACE Inhibitors/ARBs
- ☐ Contrast Agents
- ☐ NSAIDS
- ☐ Beta-blockers
- ☐ Other: _____

Diagnostic Test	Results (include units of measurement)
Blood Pressure (mmHg)	
Pulse (beats per minute)	
Anti APC antibody Test	Base line: _____, Nadir: _____, Current: _____
Autoimmune screening (specify)	
WBC Total:	Neutrophilis: _____ Eosinophils: _____ Lymphocytes: _____
ECG	
Biopsy (provide pathology report)	
Sensitivity testing (describe)	
Other (specify)	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Hepatic Disorders

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

- ☐ Fever
- ☐ Rash
- ☐ Joint Effusions
- ☐ Urticaria
- ☐ Arthralgias
- ☐ Jaundice
- ☐ Edema
- ☐ Nausea
- ☐ Confusion
- ☐ Other: _____
- ☐ Abdominal Pain
- ☐ Ascites
- ☐ Palmar Erythema
- ☐ Asterixis

Concurrent Events and Disease(s)

- ☐ Sepsis
- ☐ Hypotension
- ☐ Kidney Failure
- ☐ Other: _____
- ☐ Bleeding

Concurrent Disease(s)

- ☐ HIV
- ☐ Tuberculosis
- ☐ Congestive heart failure
- ☐ Cor pulmonale
- ☐ Autoimmune disease
- ☐ Diabetes
- ☐ Malignancy
- ☐ Inflammatory bowel disease
- ☐ Other: _____

Relevant Past Medical History

- ☐ None
- ☐ Hepatitis A
- ☐ Liver toxin exposure
- ☐ Cirrhosis Child Pugh B or C
- ☐ Budd-Chiari syndrome
- ☐ Hepatic encephalopathy

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Hepatitis B ☐ Alcoholic liver disease ☐ Ascites
☐ Hepatitis C ☐ Autoimmune hepatitis ☐ Hepatorenal syndrome
☐ Gall bladder disease ☐ Hyperbilirubinemia/Jaundice ☐ Portal Hypertension
☐ Fatty liver ☐ Abnormal liver laboratory results ☐ Other:_____

Concomitant Meds/Substances (include prescription, OTC and herbal):

☐ Current Alcohol ☐ Current Tobacco ☐ Current Cocaine/Methamphetamine
☐ Past Alcohol ☐ Past Tobacco ☐ Past Cocaine/Methamphetamine
☐ Other:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
PT-INR				
PT				
Ammonia				
Albumin				
CPK				
Creatinine				
WBC				
Hemoglobin				
Platelet Count				

Serologic Studies (check positive)

☐ Anti-nuclear Antibody (ANA)
☐ Anti-liver Kidney Microsomal (antiLKM)
☐ Anti-actin
☐ Anti-smooth Muscle Antibody (ASMA)
☐ Cytomegalovirus (CMV) Antibody IgM
☐ Ebstein Barr (EBV) Serology
☐ Other:_____
☐ Hepatitis A Virus Antibody IgM (anti-HAV IgM)
☐ Hepatitis A Virus Antibody IgG (anti-HAV IgG)
☐ Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)
☐ Hepatitis B Virus Surface Antibody (anti-HBs)
☐ Hepatitis B Virus Surface Antigen (HBs Ag)
☐ Hepatitis C Virus Antibody (anti-HCV)
☐ Hepatitis C Virus RNA (HCV RNA)

Other Study	Results
Liver Biopsy	
Hepatic Ultrasound	
MRI	
CT Scan	
Other:_____	

Treatment provided (please describe)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Clotting and/or Coagulation Disorders

Primary Diagnosis for the Reported Event(s)

- ☐ Disseminated Intravascular Coagulopathy
- ☐ Hemolytic Uremic Syndrome
- ☐ Thrombocytopenia
- ☐ Thrombotic Microangiopathy
- ☐ Thrombotic Thrombocytopenia
- ☐ Other: _____

Hospitalization for this event? ○ Yes ○ No

Presenting Signs and Symptoms

- ☐ Petechiae
- ☐ Bleeding (site): _____
- ☐ Recent viral infection (e.g., CMV, HIV, EBV)
- ☐ Recent sepsis
- ☐ Neurologic findings: _____
- ☐ Pseudothrombocytopenia ruled out
- ☐ Anemia
- ☐ Recent chemotherapy
- ☐ Recent massive trauma
- ☐ Recent pregnancy
- ☐ Clinical DIC
- ☐ Renal failure
- ☐ Thrombosis (site): _____
- ☐ Diarrhea
- ☐ Cardiac Symptoms
- ☐ Other (please specify): _____

Medical History/Risk Factors

- ☐ Thrombocyopenia
- ☐ Idiopathic thrombocytopenic purpura
- ☐ Malignancy (type): _____
- ☐ Hematologic disorder
- ☐ Bleeding disorder
- ☐ Cancer chemotherapy
- ☐ Autoimmune disorder
- ☐ Hypersplenism
- ☐ Liver disease
- ☐ Hemolytic uremic syndrome
- ☐ Renal failure
- ☐ Alcohol abuse
- ☐ Myelodysplasia

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Other (please specify):_____

Concomitant Meds/Substances (include OTC, herbal, recently discontinued drugs)

☐ Heparin/LMWH
☐ Glycoprotein IIb/IIIa Inhibitor:_____
☐ Other antiplatelet agents:_____
☐ Oral anticoagulant:_____
☐ Quinine
☐ Immunosuppressants
☐ Aspirin
☐ Chemotherapy
☐ Radiation therapy
☐ NSAIDs
☐ Hydrochlorthiazide
☐ Other (please specify):_____

Laboratory Tests/Investigation

	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelets				
INR/Prothrombin Time				
aPTT				
d-Dimer				
Serum creatinine				
Lactate dehydrogenase				
Platelet associated IgG				
Antinuclear antibodies				
Anti-PF4 antibodies				
ATAMTS13 assay				
Other:_____				

Test	Result (include units of measurement)
Peripheral smear	Schistocytes ○ Present ○ Absent ○ Unknown Other:
Bone marrow examination	Megakaryocytes ○ Normal ○ Increased ○ Decreased ○ Unknown Other:
Other:_____	

☐ Platelet transfusion (units):_____
☐ Plasmapheresis
☐ Other:_____
☐ RBC transfusion (units):_____
☐ Fresh frozen plasma (units):_____

Treatment provided (please describe)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cancer \ Neoplasm

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

☐ Please specify primary site: _____

☐ Neoplasm (benign mass/lesions) ☐ Possible malignant tumor - not yet confirmed

☐ Malignant tumor (please attach copy of pathology report or provide the information of Stage/Grade, Staging classification and tissue source):

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Relevant Tests/Studies (please attach copy of pathology report if available)

Study	Result
Histopathology (please indicate stage/grade, staging classification and tissue source)	
Ultrasound	
CAT Scan	
MRI	
Other: _____	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Medical History/Risk Factors

- ☐ Cancer:_____
- ☐ Chemotherapy
- ☐ Estrogen use _____years
- ☐ Diabetes mellitus
- ☐ Alcohol
- ☐ Immunosuppression:_____
- ☐ Other (please describe):
- ☐ Family history of cancer:_____
- ☐ Radiation therapy
- ☐ Tobacco use
- ☐ Obesity
- ☐ No known predisposing factors
- ☐ Environmental risk:_____

Treatment provided (please describe)

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

- ○ Recovered
- ○ Worsened
- ○ Recovering
- ○ Not Recovered
- ○ Unknown
- ○ Recovered with Sequellae (Please provide details): _____
- ○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Effient® (prasugrel)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Blood and Bone Marrow Disorders

Primary Diagnosis for the Reported Events:

☐ Aplastic Anemia ☐ Bone Marrow Aplasia ☐ Bone Marrow Depression
☐ Bone Marrow Failure ☐ Bone Marrow Hypoplasia ☐ Polycythemia
☐ Pancytopenia ☐ Neutropenia ☐ Other _____

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Clinical Findings:

☐ Fever ≥ 101◦ ☐ Pallor ☐ Hypotension (systolic < 90 mmHg) ☐ Sepsis
☐ Fever < 101◦ ☐ Chemotherapy within last 30 days ☐ Sore throat ☐ Radiotherapy with last 30 days
☐ Petechiae ☐ Recent viral illness ☐ Hemorrhage ☐ Other

Past Medical History:

☐ Autoimmune disease ☐ Liver disease ☐ Solid tumor
☐ Bone marrow transplantation ☐ Myelodysplastic syndrome ☐ Thrombocytopenia
☐ Hematologic disorder ☐ Neutropenia ☐ Toxic agent exposure
☐ Hematologic malignancy ☐ Paroxysmal Nocturnal Hemoglobinuria ☐ Viral illness (e.g. HIV, CMV, EBV)
☐ Renal insufficiency ☐ Chronic obstructive lung disease ☐ Other

Laboratory Tests/Investigations

	Normal Range for your institution	Baseline Value for patient	Abnormal Value	Improvement Value

Eli Lilly and Company - Global Patient Safety **Case Number:**

		Date:	Date:	Date:
WBC				
Neutrophil Count				
Hemoglobin				
MCV				
Platelets				
ALT				
Viral Studies (CMV, EBV, HIV)				
Hematocrit				
Other_____				

Other Studies

Study	Results
Bone marrow examination	
Imaging studies (CXR, CT)	
Microbiologic studies	
Serologic studies (HIV, EBV, CMV, other)	
Other: _____	

Treatment Provided

☐ Antibiotics	☐ G-CSF
☐ RBC transfusion (units): _____	☐ Platelet transfusion (units): _____
☐ Other (please specify): _____	

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Annex 10. Details of Proposed Additional Risk Minimisation Measures

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