Efient

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0037	Submission of an updated RMP version 13.0 in order to remove of a region-specific additional risk-minimisation activity following previous PSUSA procedure (EMEA/H/C/PSUSA/00002499/202102), as well as to align content and format with new requirements according to GVP Module V Rev. 2.	16/05/2024		Annex II and PL	Not applicable

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	In addition, the MAH took the opportunity to update Annex II of the PI and to update the list of local representatives in the Package Leaflet. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
IAIN/0038	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/05/2024	n/a		
IA/0036	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	14/04/2023	n/a		
T/0035	Transfer of Marketing Authorisation	04/08/2022	29/09/2022	SmPC, Labelling and PL	
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/11/2021	29/09/2022	PL	
PSUSA/2499/202102	Periodic Safety Update EU Single assessment - prasugrel	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0032	A.7 - Administrative change - Deletion of manufacturing sites	22/10/2020	14/12/2020	Annex II and PL	

IB/0031	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/10/2020	14/12/2020	SmPC, Annex II and PL	
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/05/2020	14/12/2020	PL	
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/03/2020	14/12/2020	PL	
IB/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2019	14/12/2020	SmPC, Annex II, Labelling and PL	
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2019	19/11/2019	PL	
IB/0025/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	10/12/2018	19/11/2019	Annex II and PL	

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
PSUSA/2499/ 201802	Periodic Safety Update EU Single assessment - prasugrel	20/09/2018	22/11/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2499/201802.
IB/0024/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/10/2018	n/a		

	B.II.a.3.a.2 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Increase or reduction				
PSUSA/2499/ 201702	Periodic Safety Update EU Single assessment - prasugrel	28/09/2017	n/a		PRAC Recommendation - maintenance
IB/0021	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	16/03/2017	20/12/2017	SmPC	
IB/0020	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	16/01/2017	20/12/2017	SmPC, Labelling and PL	
PSUSA/2499/ 201602	Periodic Safety Update EU Single assessment - prasugrel	02/09/2016	n/a		PRAC Recommendation - maintenance
T/0018	Transfer of Marketing Authorisation Transfer of Marketing Authorisation	25/11/2015	10/12/2015	SmPC, Labelling and PL	Transfer of the Marketing Authorisation from Eli Lilly Nederland B.V. to Daiichi Sankyo Europe GmbH.
PSUSA/2499/ 201502	Periodic Safety Update EU Single assessment - prasugrel	10/09/2015	n/a		PRAC Recommendation - maintenance
PSUV/0016	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
PSUV/0015	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance

II/0014	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to optimize the instructions with regard to the timing of the loading dose of prasugrel in patients with non-ST segment elevation myocardial infarction undergoing percutaneous coronary intervention based on data from TADF (ACCOAST) Study and ALKK PCI registry (Study B008). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	18/12/2013	SmPC	The TADF (ACCOAST) study showed that there was no benefit in non-ST segment elevation myocardial infarction (NSTEMI) patients with elevated troponin who received a 30 mg loading dose prior to coronary angiography followed by a 30 mg loading dose at the time of percutaneous coronary intervention (PCI) compared to patients who received the conventional 60 mg loading dose at the time of the PCI. On the contrary, the experimental pre-treatment regimen was associated with a significantly increased risk of TIMI major bleedings compared to the conventional regimen. The higher rate in the pre-treatment group was driven by the non-CABG-related bleedings in the PCI-only group during the first 7 days following the first loading dose. The German registry study showed that at least in some regions of Europe it is common practice to administer the loading dose of prasugrel prior to coronary angiography in an unstable angina (UA)/NSTEMI population. Even if this did not appear to increase the bleeding rate compared to patients receiving the loading dose after coronary visualisation in this particular study, it is a somewhat worrying finding given the similarities of the used front-loading regimen with the experimental arm in the TADF study. Consequently, the changes to the SmPC were introduced to reflect the results of the TADF study to inform the healthcare providers on increased risk of serious bleeding in UA/NSTEMI patients undergoing PCI when prasugrel is administered prior to diagnostic coronary angiography.
R/0013	Renewal of the marketing authorisation.	19/09/2013	13/11/2013	SmPC, Labelling and PL	Although bleeding was increased with prasugrel, an analysis of the composite endpoint of death from any cause, nonfatal MI, nonfatal stroke, and non-CABG-related

					TIMI major haemorrhage favored prasugrel compared to clopidogrel (HR = 0.87; 95% CI, 0.79 to 0.95; p = 0.004). In TRITON, for every 1000 patients treated with prasugrel, there were 22 fewer patients with MI, and 5 more with non–CABG-related TIMI major haemorrhages, compared with patients treated with clopidogrel. The TRILOGY study showed the relative safety of the 5 mg MD in those patients at increased risk of bleeding (although TRILOGY did not show superior efficacy of prasugrel versus clopidogrel in the ACS-MM population). Thus, the overall benefit/risk profile for prasugrel is favorable, particularly given that prasugrel achieved significant superiority over clopidogrel, an active comparator already demonstrated to be safe and effective in the setting of ACS managed by PCI (CURE 2001; PCI-CURE Mehta et al. 2001). The CHMP concluded that the safety profile for prasugrel remains unchanged. Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of prasugrel remains positive. The CHMP recommends that the renewal be granted with unlimited validity.
II/0012	Update of section 5.1 of the SmPC in order to include the data from the completed pharmacodynamic study (TAEH) regarding the use of prasugrel in patients previously receiving clopidogrel. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	13/11/2013	SmPC	In order to provide more data on switching between clopidogrel and prasugrel, the pharmacodynamic data from 276 patients with acute coronary syndrome (ACS) managed with percutaneous coronary intervention (PCI) were analysed. Switching from an initial loading dose of 600 mg clopidogrel or placebo administered upon presentation to the hospital prior to coronary angiography to a 60 mg loading dose of prasugrel administered at the time of percutaneous coronary intervention, resulted in a similar increased inhibition of platelet aggregation for the 72 hour

					duration of the study.
II/0011	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC regarding the reduced 5-mg maintenance dose recommendation in patients ≥75 years of age and in patients <60 kg following the ARs for 3 post authorisation measures: FUM 008 (TABY study), FUM 005 (TACY study) and FUM 006 (TADI study). Furthermore, section 4.3 of the SmPC and Annex II and the package leaflet were brought in line with the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	13/11/2013	SmPC, Annex II and PL	The results of 3 studies were previously assessed by the CHMP within post-authorisation measures (FUM005, 006 and 008). The subject of these studies was the use of 5 mg prasugrel in patients > 75 years old and patients < 60 kg. The first two studies evaluated the pharmacokinetic/pharmacodynamic (PK/PD) data and the third one evaluated the efficacy and safety of 5 and 10 mg of prasugrel during 30 months. The conclusion is that the use of 5 mg prasugrel in patients aged > 75 years or with a weight of < 60 kg is effective and safe.
N/0009	Update the contact details for the local representatives for Germany and Ireland in the package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/09/2012	13/11/2013	PL	
II/0008	To update Sections: 4.4 and 5.1 of the SmPC with results from the pharmacodynamic/pharmacogenomic study as requested in the CHMP AR for FU2 007.1. Section 2 of the PL was updated accordingly. In addition some minor linguistic changes were introduced in French annexes. C.I.3.b - Implementation of change(s) requested	22/09/2011	24/10/2011	SmPC and PL	Results of a pharmacodynamic/pharmacogenomic study in 720 Asian ACS PCI patients demonstrated that higher levels of platelet inhibition are achieved with prasugrel compared to clopidogrel, and that prasugrel 60-mg loading dose/10-mg maintenance dose is an appropriate dose regimen in Asian subjects who weigh at least 60 kg and are less than 75 years of age. The conducted study does not suggest the subjects of Asian origin be at an increased risk of adverse reactions to

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				prasugrel. The study did not identify any pharmacogenetic biomarkers associated with efficacy or adverse events. Therefore a warning that therapeutic experience is limited in Asian patients and the product should be used with caution in this population of patients was deleted.
II/0006	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	20/04/2011	SmPC and PL	Sections 4.4 and 4.8 of the SmPC were updated in line with the recommendations in the assessment reports for PSUR 2 and PSUR 3. The three adverse drug reactions (ADRs), namely: hypersensitivity including angioedema, thrombotic thrombocytopaenic purpura and thrombocytopaenia were included in section 4.8 and hypersensitivity including angioedema and modification of wording of thrombotic thrombocytopaenic purpura were included in section 4.4 of the SmPC. In parallel, a new signal associated with prasugrel was detected in EudraVigilance database. This signal concerned reports of serious hypersensitivity reactions including angioedema in patients receiving prasugrel, including in patients with a history of hypersensitivity reaction to clopidogrel. Therefore, based on these reports it was agreed to strengthen the wording so that angioedema is listed in sections 4.4 and 4.8 with a specific mention of the possibility of this reaction in patients who experienced an angioedema with clopidogrel and that the initiation of treatment with prasugrel in patients who previously experienced angioedema or other hypersensitivity reactions with clopidogrel should be performed with extreme caution and under medical supervision. PL was updated to reflect the changes to the SmPC. In addition a DHCP letter to draw the attention of physicians on the possible occurrence of this serious reaction should be disseminated in line with the

					agreed communication plan.
IA/0007/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	28/03/2011	n/a		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2009	n/a	PL	
IA/0004	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/09/2009	21/09/2009	SmPC and Labelling	
IA/0003	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/09/2009	21/09/2009	SmPC and Labelling	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/06/2009	n/a	PL	
IA/0001	IA_06_a_Change in ATC code: Medicinal products for human use	18/05/2009	n/a	SmPC, Labelling and PL	