Brilique

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/0063	Update of section 4.5 of the SmPC in order to add drug-drug interaction information between ticagrelor and rosuvastatin based on literature. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.	05/09/2024		SmPC	For more information, please refer to the Summary of Product Characteristics.

[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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2948/ 202312	Periodic Safety Update EU Single assessment - ticagrelor	05/09/2024	n/a		PRAC Recommendation - maintenance
II/0061	Update of sections 4.2 of the SmPC to add the option to discontinue the administration of acetylsalicylic acid after 3 months of dual anti-platelet therapy and continue ticagrelor single anti-platelet therapy in patients with acute coronary syndromes who have undergone a percutaneous coronary intervention procedure and have an increased risk of bleeding, and to provide additional information on this topic in section 4.4 of the SmPC. In addition, the marketing authorisation holder has taken the opportunity to update the list of local representatives in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2024	27/03/2024	SmPC and PL	
IAIN/0060/G	This was an application for a group of variations. 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer	12/06/2023	27/03/2024	Annex II and PL	

	responsible for batch release A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
IB/0058/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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	25/04/2023	n/a		
IB/0059/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation	15/02/2023	n/a		
IA/0057	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	09/09/2022	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IAIN/0056	B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	10/06/2022	n/a		
II/0054	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/03/2022	16/12/2022	SmPC and PL	
IAIN/0055/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites	21/12/2021	16/12/2022	Annex II and PL	
PSUSA/2948/ 202012	Periodic Safety Update EU Single assessment - ticagrelor	16/09/2021	15/11/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2948/202012.
II/0050	Update of the SmPC in order to add central sleep apnoea including Cheyne-Stokes respiration as a new warning in section 4.4., following collection of post-marketing data; the Package Leaflet is updated accordingly.	02/09/2021	15/11/2021	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0053	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	23/08/2021	29/09/2021	SmPC and Labelling	
IB/0052	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/05/2021	n/a		
II/0047/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/03/2021	29/09/2021	SmPC and PL	
IA/0048	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	20/12/2019	n/a		
II/0045	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/09/2019	24/10/2019	SmPC	
IB/0046/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	14/06/2019	n/a		

	variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
II/0044	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/05/2019	24/10/2019	SmPC, Labelling and PL	
IB/0043/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	26/11/2018	n/a		
II/0042	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/11/2018	24/10/2019	SmPC	
II/0041	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/11/2018	24/10/2019	SmPC and PL	

PSUSA/2948/201712	Periodic Safety Update EU Single assessment - ticagrelor	26/07/2018	21/09/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2948/201712.
IA/0040	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/06/2018	n/a		
II/0038	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/05/2018	21/09/2018	SmPC and PL	Section 4.5 of the SmPC has been updated to indicate that a delayed and decreased exposure to ticagrelor has been observed in healthy volunteers and patients with acute coronary syndromes (ACS) treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and applies to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered. The package leaflet has been updated accordingly.
IA/0037/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	28/07/2017	n/a		

PSUSA/2948/ 201612	Periodic Safety Update EU Single assessment - ticagrelor	06/07/2017	n/a		PRAC Recommendation - maintenance
X/0034	Annex I_2.(d) Change or addition of a new pharmaceutical form	23/03/2017	18/05/2017	SmPC, Labelling and PL	Please refer to the published Assessment Report Brilique H-1241-X-34-AR.
IA/0036/G	This was an application for a group of variations. 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 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 A.7 - Administrative change - Deletion of manufacturing sites	11/05/2017	n/a		
II/0033	Update of sections 4.4 and 4.9 of the SmPC in order to reflect the results of a platelet transfusion study. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct the spelling of ischaemic stroke. Changes are also made to the PI to bring it in line with the current QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	15/09/2016	18/05/2017	SmPC	Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding.

	data				
PSUSA/2948/201512	Periodic Safety Update EU Single assessment - ticagrelor	07/07/2016	n/a		PRAC Recommendation - maintenance
II/0031	Submission of final study report for a Drug Utilisation Study (DUS), as per MEA008; this DUS is a Post-Authorisation Safety Study (PASS) in line with Article 1(15) of Directive 2001/83/EC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	n/a		
X/0029/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	18/02/2016	SmPC, Labelling and PL	
IG/0633	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	09/12/2015	n/a		
R/0027	Renewal of the marketing authorisation.	21/05/2015	17/07/2015	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the benefit-risk balance of Brilique in the approved indication remains favourable and therefore recommended the

					renewal of the marketing authorisation with unlimited validity.
PSUSA/2948/ 201412	Periodic Safety Update EU Single assessment - ticagrelor	09/07/2015	n/a		PRAC Recommendation - maintenance
IB/0026/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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 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 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	15/12/2014	n/a		
IB/0025	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/10/2014	n/a		
II/0022	Update of section 5.1 of the SmPC to add information	24/07/2014	17/07/2015	SmPC and PL	The MAH provided additional information on the proposed

	about an additional mechanism of action (adenosine pathway) supported by pharmacodynamic data from nonclinical and clinical publications. In addition, the MAH took the opportunity to update the contact details for the Bulgarian local representative in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				mechanism of action; the non-clinical data provided support that ticagrelor increases the level of adenosine. In addition, several clinical studies on the adenosine effects have been provided. Three main clinical studies are noteworthy; one in healthy volunteers and 2 in ACS. The studies of Wittfeldt et al 2013 and Bonello et al 2013 provided clearest evidence of these effects. In the third study of Alexopoulos et al 2013, as previously noted, a link between the observed increases in adenosine and clinical outcomes has not been clearly elucidated, limiting the usefulness of the data. However, overall available data show that ticagrelor increases the levels of adenosine. Based on these data the CHMP consider it acceptable to include additional information in section 5.1 of the SmPC.
II/0021	Update of sections 4.2 and 5.2 of the SmPC, based on data from the clinical study D5130C00070, in order to add information about the bioequivalence of crushed tablets mixed with water and administered orally or via nasogastric tube compared to whole tablets. In addition, sections 4.4 and 4.5 of the SmPC have been updated in order to delete dexamethasone from the list of strong CYP3A inducers with the potential to decrease the exposure and efficacy of ticagrelor. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details for the Bulgarian local representative in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	17/07/2015	SmPC and PL	To support the changes of SmPC sections 4.2 and 5.2 the MAH conducted a comparative bioavailability study (D5130C00076) to evaluate alternative methods of administration in which the administration of crushed Ticagrelor tablets, 90 mg, was compared to whole Ticagrelor tablets, 90 mg. Based on the results of the study it can be concluded that there is no difference in the bioavailability of 90 mg ticagrelor crushed tablet administered orally and 90 mg ticagrelor when administered as a whole tablet and also no difference between the dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube and 90 mg ticagrelor when administered as a whole tablet. The t max of ticagrelor shifted and was found at 1 hour for the crushed tablet administered orally and through a nasogastric tube versus 2 hours for the whole tablet, however this shift is not considered clinically relevant.

					Dexamethasone is currently described as a strong CYP3A inducer with a potential decrease in exposure and efficacy. Recent guidance and literature indicate that dexamethasone can be removed from the list of examples of strong CYP3A4 inducers that may result in reduced efficacy of ticagrelor. The MAH provided appropriate justifications to support the changes in section 4.4 and 4.5 of the SmPC. Based on the provided references on the potential for interaction with dexamethasone it is agreed that dexamethasone should not be classified as a strong inducer of CYP3A4 as the inducing effect of dexamethasone seems to be less pronounced than the effect of rifampicin. This conclusion is mainly based on the study by Hellmann et all. Although it is still not clear whether dexamethasone should be classified as a weak or a moderate 3A4 inducer, the deletion of dexamethasone from the list of strong inhibitors is sufficiently justified.
PSUV/0023	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
IG/0402	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	27/02/2014	n/a		
PSUV/0019	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0018	Update to sections 4.5 and 4.7 of the SmPC in order to add warnings regarding concomitant use of ticagrelor with the grapefruit juice (section 4.5) and dizziness in acute coronary syndrome patients taking ticagrelor (section 4.7). In addition, update to	21/11/2013	23/06/2014	SmPC and PL	Following the assessment of PSUR No 4, the PRAC recommended to modify sections 4.5, 4.7 and 4.8 of the SmPC to include respectively: - Information about results of the Holmberg food interaction study with grapefruit juice with the proposed

	section 4.8 of the SmPC to add information regarding fatal intracranial bleedings in the postmarketing experience. These modifications were proposed following the recommendations from the Assessment Report for PSUR 4. The Package Leaflet was updated accordingly. 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				wording: 'A 2-fold increase of ticagrelor exposure was observed after consumption of large quantities of grapefruit juice (3x 200ml)', - A warning that patients who are affected by dizziness should be advised not to drive or use machinery given that cumulatively 68 cases of dizziness have been reported post-marketing, - A statement that cases of intracranial bleedings, including fatal cases, have been reported during post-marketing. It was not possible to reliably estimate frequency of events during post-marketing use, thus the estimated frequency refers to the PLATO study. Fatal intracranial haemorrhage (ICH) in PLATO was 0.12% which meets the criteria for a frequency of uncommon. The Product Information was updated accordingly.
II/0017	Update of sections 4.4 and 4.5 of the SmPC regarding drug-drug interaction (DDI) between ticagrelor and cyclosporine following the assessment of the study D5130C00074 within post-authorisation measure MEA 005. Update of Section 5.2 of the SmPC to correct the statement regarding patients with severe renal impairment. Furthermore, the PI is being brought in line with the latest QRD template version 9.3. The list of local representatives was updated in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	23/06/2014	SmPC, Annex II and PL	In the drug-drug interaction study between cyclosporine and ticagrelor, a significant increase of the Cmax (2.3 fold) and AUC (2.8 fold) of ticagrelor was observed and the AUC of its active metabolite AR-C124910XX was increased by approximately 33% while the Cmax was approximately 17% lower. The pharmacokinetics of cyclosporine was not affected by the presence of ticagrelor. Ticagrelor, administered alone and concomitantly with cyclosporine was generally well tolerated.
IB/0016/G	This was an application for a group of variations.	28/05/2013	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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				
IA/0015	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/03/2013	n/a		
IG/0273	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/02/2013	n/a		
IB/0013	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	05/02/2013	n/a		
WS/0343	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. -To extend the re-test period of the active substance. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	17/01/2013	17/01/2013		

WS/0342	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. -To introduce a change in the manufacturing process of the active substance. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/01/2013	17/01/2013		
WS/0317/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a	13/12/2012	13/12/2012		

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
WS/0292	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.8 of the SmPC in order to add safety information regarding hypersensitivity including angioedema. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to propose minor corrections in sections 4.8, 5.1 and 5.2 of the SmPC and to bring the PI in line with the latest QRD template version 8.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC, Annex II and PL	Several events which could possibly be associated with hypersensitivity reactions coming from postmarketing and clinical trials experience were reported by the MAH. From the 75 cases reported 12 were considered serious and 3 were identified as possibly related to treatment with ticagrelor. These events included angioedema as adverse hypersensitivity event and were all retrieved from post-marketing experience. Based on these results the CHMP supported the inclusion of "hypersensitivity including angioedema" under frequency "uncommon" in section 4.8 of the SmPC.
IB/0007	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	13/07/2012	n/a		
WS/0260/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. -To introduce a change in the manufacturing process of the active substance.	21/06/2012	21/06/2012		

	-To introduce a change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
WS/0246	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. -To introduce a change in the manufacturing process of the finished product. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	24/05/2012	24/05/2012		
IG/0151/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	29/02/2012	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0003	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	06/02/2012	n/a		
IG/0124/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	18/11/2011	n/a		
IB/0001	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)	17/10/2011	n/a	SmPC, Annex II and PL	