



DuoPlavin

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
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/07/2024		PL	
IB/0070/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters	24/08/2023	n/a		

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).



and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method

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

B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS

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.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation

B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits

B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits

IA/0072	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	14/07/2023	n/a		
PSUSA/820/202211	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	06/07/2023	n/a		PRAC Recommendation - maintenance
IB/0069	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	04/07/2023	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/06/2023	09/02/2024	PL	
IB/0068	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2023	n/a		
IA/0067	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	11/04/2023	n/a		
II/0065	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/02/2023	09/02/2024	SmPC and PL	
T/0064	Transfer of Marketing Authorisation	23/11/2022	16/12/2022	SmPC, Labelling and	

				PL	
WS/2150	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Extension of indication to include clopidogrel in combination with acetylsalicylic acid in ST segment elevation acute myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI); as a consequence section 4.1, 4.2 and 5.1 of the SmPC is updated. Version 2.6 of the RMP has also been submitted. In addition, an editorial update has been made to the labelling.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>	10/11/2022	12/12/2022	SmPC and Labelling	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-WS-2150'
WS/2259	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.4 and 4.8 of the SmPC in order to update an existing warning on 'Bleeding and haematological disorders' by adding a statement on triple antiplatelet therapy (clopidogrel + aspirin + dipyridamole) for stroke secondary prevention. The Package Leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance</p>	20/10/2022	12/12/2022	SmPC and PL	Based on review of the MAH global Pharmacovigilance database, worldwide scientific literature, and main reference textbooks, the weighted cumulative evidence is sufficient to support a harmful effect of the triple antiplatelet therapy (clopidogrel plus acetylsalicylic acid plus dipyridamole) in stroke secondary prevention.

	data				
IB/0062/G	<p>This was an application for a group of variations.</p> <p>B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>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</p> <p>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</p>	21/06/2022	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021	02/12/2022	PL	
WS/2145	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/11/2021	02/12/2022	SmPC and PL	The available cumulative evidence is sufficient to support a causal association of clopidogrel with or without aspirin on rosuvastatin, leading to an increase in rosuvastatin AUC (1.4-fold after chronic 75 mg clopidogrel dose and 2-fold

	<p>Update of Section 4.5 of the SmPC to add the drug-drug interaction between clopidogrel and rosuvastatin based on a review of the available data including literature and the MAH safety database. The package leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>after a 300 mg clopidogrel loading dose), as such Section 4.5 of the SmPC and accordingly the package leaflet, is updated to add the drug-drug interaction between clopidogrel and rosuvastatin.</p>
N/0058	<p>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)</p>	25/02/2021	02/12/2022	PL	
WS/1848	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>To update section 4.4 and 4.5 of the SmPC to add drug-drug interaction information for rifampicin and clopidogrel based on a literature review and a review of the MAH pharmacovigilance database. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives and to update the SmPC for the excipient lactose in accordance with the Annex to the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal products for human use". The MAH also took the opportunity to update the product information regarding the standard term for the all aluminium unit-dose blisters.</p>	23/07/2020	16/11/2020	SmPC, Labelling and PL	<p>The MAH carried out a literature review and a review of the MAH pharmacovigilance database. It was found that in healthy subjects, co-administration of clopidogrel and rifampicin, a potent inducer of CYP2C19 which is mainly involved in the formation of the active metabolite of clopidogrel, increased significantly the formation and AUC of the active metabolite and therefore the PD effect, in particular the inhibition of platelet aggregation both after the loading dose and the maintenance dose. This shows an increased platelet inhibition from the drug-drug interaction of rifampicin and clopidogrel resulting in an increased risk of bleeding. The SmPC section 4.4 and 4.5 are updated accordingly.</p> <p>For more information, please refer to the Summary of Product Characteristics.</p>

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/820/201911	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	09/07/2020	n/a		PRAC Recommendation - maintenance
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2020	16/11/2020	PL	
T/0054	Transfer of Marketing Authorisation	10/10/2019	14/11/2019	SmPC, Labelling and PL	
WS/1690	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/11/2019	16/11/2020	SmPC and PL	
WS/1665	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	19/09/2019	14/11/2019	SmPC and PL	
WS/1433	This was an application for a variation following a worksharing procedure according to Article 20 of	13/09/2018	25/10/2018	SmPC and PL	Following the PRAC assessment and recommendation on the signal regarding insulin autoimmune syndrome, the

	<p>Commission Regulation (EC) No 1234/2008.</p> <p>In response to PRAC recommendation for the signal of insulin autoimmune syndrome (EPITT ref 19155), update of section 4.8 of the SmPC with the new adverse reaction 'insulin autoimmune syndrome'. The Package Leaflet is updated accordingly.</p> <p>In addition, at the request of the Agency, MA numbers of Plavix and Iscover were reviewed and updated as per the current format. The Plavix and Iscover Annex A and PI were updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>new adverse reaction 'insulin autoimmune syndrome' is added in section 4.8 of the SmPC. The Package Leaflet is updated accordingly.</p> <p>In addition, at the request of the Agency, MA numbers of Plavix and Iscover were reviewed and updated as per the current format. The Plavix and Iscover Annex A and PI were updated accordingly.</p>
WS/1459	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 5.1 of the SmPC in order to reflect the clinical outcome data of 2 randomised investigator-sponsored studies regarding de-escalation of P2Y12 receptor inhibitor to clopidogrel in ACS.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	20/09/2018	03/09/2019	SmPC	<p>The SmPC section 5.1 has been updated to describe the results of the 2 studies TOPIC and TROPICAL-ACS investigating the effect of switching from more potent P2Y12 receptor inhibitors (prasugrel, ticagrelor) to clopidogrel in Acute Coronary Syndrome.</p>
WS/1258	<p>This was an application for a variation following a worksharing procedure according to Article 20 of</p>	18/01/2018	25/10/2018	SmPC and PL	

	<p>Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC in order to add the undesirable effect 'ageusia'. The PL is updated accordingly.</p> <p>In addition, the Worksharing applicant (WSA) took the opportunity to introduce a clarification in section 4.2 of the Duoplavin and Clopidogrel/Acetylsalicylic acid Zentiva SmPC; update the German local representative in the Package Leaflet; and bring the PI in line with the latest QRD template version 10.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				
PSUSA/820/201611	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	06/07/2017	n/a		PRAC Recommendation - maintenance
WS/1091	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.1 to clarify the indication and specify that clopidogrel is indicated for the secondary prevention of atherothrombotic events.</p> <p>In addition, the MAH took the opportunity to update the details of the German local representative in the Clopidogrel/Acetylsalicylic acid Zentiva Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to</p>	23/02/2017	03/04/2017	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
WS/1019	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC in order to add Kounis syndrome as a new ADR. The Package Leaflet is updated accordingly. In addition the Worksharing applicant (WSA) took the opportunity to make minor amendments to Annex II for Clopidogrel Zentiva, Iscover and Plavix, to update the contact details of the Bulgarian local representative in the Package Leaflet for all the products involved and the Italian, Hungarian and Lithuanian local representatives for Clopidogrel Zentiva, Iscover and Plavix, to combine the two strengths SmPCs for all the products involved in this Worksharing application, to combine the two strengths Package Leaflet for DuoPlavin and Clopidogrel/Acetylsalicylic acid Zentiva. Furthermore, the PI is brought in line with the latest QRD template version 10.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	08/12/2016	03/04/2017	SmPC, Annex II, Labelling and PL	
WS/1020	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	08/12/2016	03/04/2017	SmPC, Annex II, Labelling and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/0930	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC in order to add oedema as a new adverse drug reaction with a very rare/not known frequency. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives for Italy, Lithuania and Hungary in the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	26/05/2016	08/12/2016	SmPC and PL	
WS/0856	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to include information regarding a potential interaction with tenofovir. The Package Leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	14/01/2016	08/12/2016	SmPC and PL	Tenofovir, a medicine to treat HIV (human immunodeficiency virus) infections, when taken with NSAIDs (nonsteroidal anti-inflammatory drug) used to treat inflammation and pain, may increase the risk of renal failure. Acetylsalicylic acid is a NSAID, and therefore its use along with tenofovir may increase the risk of renal impairment.

WS/0813	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC in order to update the safety information regarding the interactions with "Medicinal products associated with bleeding risks", "Levothyroxine", "Valproic acid", "Varicella vaccine" and "Alcohol". In addition, local representatives for Lithuania have also been amended. The Package Leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	19/11/2015	02/03/2016	SmPC and PL	<p>This type II variation is related to modifications of the Product Information further to the update of the CCDS version 11 of clopidogrel/acetylsalicylic acid, linked to acetylsalicylic acid INN.</p> <p>Update of sections 4.4 and 4.5 of the SmPC in order to update the safety information regarding the interactions with "Medicinal products associated with bleeding risks", "Levothyroxine", "Valproic acid", "Varicella vaccine" and "Alcohol". The Package Leaflet is updated accordingly. The worksharing procedure leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.</p>
WS/0815	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC to add 2 new interactions (with medicinal products associated with bleeding risks and with CYP2C8 substrates) in order to align with the Company Core Data Sheet. The Package Leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	24/09/2015	02/03/2016	SmPC and PL	<p>As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions. It should also be used with caution in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or other medicinal products associated with bleeding risk such as pentoxifylline, as there is an increased risk of bleeding due to the potential additive effect.</p> <p>Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of</p>

					CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.
WS/0809	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 5.2 of the SmPC in order to address the PRAC recommendation adopted during the April 2015 meeting to submit a cumulative review of all literature and case reports following a signal of drug interaction with grapefruit juice for clopidogrel products (SDA 032). In addition, the Worksharing applicant (WSA) took the opportunity to update the contact details of the local representative in Romania and Italy in the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	24/09/2015	02/03/2016	SmPC and PL	The active metabolite of clopidogrel is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4.
WS/0795/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF</p>	17/09/2015	n/a		

	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/0707	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to amend the information on CYP2C19 inhibitors. The package Leaflet has been updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	21/05/2015	02/03/2016	SmPC and PL	
WS/0686	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC to include the new ADRs 'Kounis syndrome', Henoch Schonlein purpura' and 'acute pancreatitis'. The Package Leaflet has been updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	26/02/2015	02/03/2016	SmPC and PL	<p>All three ADRs are reported in published information for ASA with frequency "not known".</p> <p>Kounis syndrome and acute pancreatitis were reported in the context of a hypersensitivity reaction due to acetylsalicylic acid.</p>

WS/0685	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to include information about an interaction with acetazolamide. The Package Leaflet has been updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	26/02/2015	02/03/2016	SmPC and PL	Caution is recommended when co administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.
WS/0682	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the "Undesirable effects" to add 2 new undesirable effects: "Acute generalised exanthematous pustulosis (AGEP) and "Gynaecomastia". Package Leaflet has been updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	26/02/2015	02/03/2016	SmPC and PL	
R/0033	Renewal of the marketing authorisation.	25/09/2014	19/11/2014	SmPC, Labelling and PL	<p>DuoPlavin is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoPlavin is a fixed dose combination medicinal product for continuation of therapy in:</p> <ul style="list-style-type: none"> • Non-ST segment elevation acute coronary syndrome

					<p>(unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention</p> <ul style="list-style-type: none"> • ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy <p>Based on the review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP consider that the risk-benefit balance of DuoPlavin in the treatment and prophylaxis of the mentioned approved indications remains favourable and therefore recommends the renewal of the marketing authorisation. The CHMP recommend that the renewal be granted with unlimited validity.</p>
WS/0572	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to add information about an interaction with metamizole.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	24/07/2014	18/09/2014	SmPC	<p>Further to an analysis of the Sanofi Pharmacovigilance Database, literature review and Pharmacovigilance Textbooks concerning possible metamizole – ASA interactions, it has been found that Metamizole may reduce the effect of ASA on platelet aggregation when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose ASA for cardioprotection.</p>
WS/0554	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.9 of the Summary of Product Characteristics related to overdose information on clopidogrel/acetysalicylic acid (ASA) fixed dose</p>	24/07/2014	18/09/2014	SmPC	<p>Following review of the submitted data, the CHMP concluded that an update of the Product Information related to the overdose information on clopidogrel/ASA fixed combination was necessary to include the following information:</p> <ul style="list-style-type: none"> - Overdose with ASA/ clopidogrel fixed dose combination may be associated with increased bleeding and subsequent

	<p>combination.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				bleeding complications due to the pharmacological activity of clopidogrel and ASA.
WS/0538	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the Summary of Product Characteristics to add known ADRs of acetylsalicylic acid (ASA). Section 4.4 is also updated to include a warning related to patients with G6PD deficiency and risk of haemolysis. Section 4.6 is updated to include information related to uncertainties with regard to alteration of fertility with ASA dose contained in ASA/clopidogrel fixed combination products. Sections 2 and 4 of the PL are updated accordingly. An editorial change is also made to section 4.3.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	24/07/2014	18/09/2014	SmPC and PL	<p>Following review of the submitted data, the CHMP concluded that an update of the Product Information was adequate, to add new ADRs (bone marrow failure, bicytopenia, haemolytic anaemia in patients with G6PD deficiency, chronic hepatitis, fixed eruption, renal failure) and include the following information:</p> <ul style="list-style-type: none"> - This medicinal product must be administered under close medical supervision in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency due to risk of haemolysis - It is unknown whether ASA dose in DuoPlavin/Duocover alters fertility.
IG/0454	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	17/07/2014	n/a		
PSUSA/820/201311	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	10/07/2014	n/a		PRAC Recommendation - maintenance

WS/0477	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of the section 4.8 of the SmPC to add information on Core Data Sheets linked to clopidogrel INN.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	23/01/2014	18/09/2014	SmPC	<p>Dermatitis exfoliative is one form of severe dermatitis, and as such deserves to be differentiated from other dermatitis, particularly since it may signal the presence of DRESS. MAH proposes a change in SmPC section 4.8 to address this difference.</p> <p>The report on dermatitis exfoliative has shown sufficient evidence that clopidogrel may induce exfoliative rashes either generalized or localized including hands and feet locations. This is supported particularly by sentinel and rechallenge cases.</p> <p>Update of section 4.8 of the SmPC in order to update the safety information in order to add information on Core Data Sheets linked to clopidogrel INN.</p>
WS/0476	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC in order to add information on Core Data Sheets linked to clopidogrel INN.</p> <p>The Section 2 of the Package leaflet has been updated accordingly. The WSA also took this opportunity to update the phone number of the local representative for UK.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	23/01/2014	18/09/2014	SmPC and PL	<p>The weighted cumulative evidence is sufficient to support a causal association between clopidogrel or clopidogrel + ASA fixed dose combination (FDC) and the risk of increased bleeding when administered with SSRIs.</p> <p>The WSA proposed the update of sections 4.4 "Special Warnings and Precautions for use" and 4.5 Interaction with other medicinal products" of the SmPC in order to add information on Core Data Sheets linked to clopidogrel INN.</p> <ul style="list-style-type: none"> - Addition of an interaction with the selective serotonin reuptake inhibitors (SSRIs) in section 4.5. - Addition of information concerning this interaction in section 4.4. <p>The Section 2 of the Package leaflet has been updated accordingly. The WSA also took this opportunity to update the phone number of the local representative for UK.</p> <p>The Package Leaflet was proposed to be updated accordingly. The WSA also took this opportunity to update</p>

					the phone number of the local representative for UK.
IG/0325	A.1 - Administrative change - Change in the name and/or address of the MAH	07/10/2013	18/09/2014	SmPC, Labelling and PL	
WS/0409	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the product SmPC and update of Local representatives 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	19/09/2013	18/09/2014	SmPC and PL	Section 4.4 of the SmPC was updated in order to add a warning concerning haematological cross reactions to thienopyridines. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet.
IB/0025/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.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	14/08/2013	n/a		
WS/0397	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	27/06/2013	19/07/2013	SmPC and PL	The WSA proposed the update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) in order to add information on "acquired haemophilia A (AHA)". The Package Leaflet was proposed to be updated accordingly.

	<p>The WSA proposed the update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and Package Leaflet.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>				<p>Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 9.</p>
WS/0378	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC and Package Leaflet.</p> <p>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH</p>	27/06/2013	19/07/2013	SmPC and PL	<p>The WSA proposed the update of section 4.8 of the SmPC in order to add "eosinophilic pneumonia" as a new undesirable effect under the System Organ Class Respiratory, thoracic and mediastinal disorders. In addition, the WSA took the opportunity to update the list of local representatives (Croatia) in the Package Leaflet.</p>
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		
IB/0022	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	25/06/2013	n/a		
WS/0369	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of the section 4.4 and 4.8 of the SmPC and</p>	25/04/2013	30/05/2013	SmPC and PL	<p>The WSA proposed the update of sections 4.8 SOC "Gastrointestinal disorders" and 4.4 of the Summary of Product Characteristics (SmPC) in order to add information about the upper and lower gastrointestinal disorders and</p>

	<p>package leaflet.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>				colitis. The package leaflet has been amended accordingly.
WS/0368	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.8 and 4.9 of the SmPC.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	25/04/2013	30/05/2013	SmPC	Update of SmPC sections 4.8 the in order to add "non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to ASA" to the respective SOC and 4.9 regarding the addition of consequential information concerning "non-cardiogenic pulmonary edema" that may occur with ASA overdose".
WS/0367	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.3 of the SmPC.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	25/04/2013	30/05/2013	SmPC	<p>The WSA proposed the update of section 4.3 of the SmPC in order to add a new "Contraindications" about "Patients with pre-existing mastocytosis".</p> <p>The requested variation worksharing procedure proposed amendments to the SmPC.</p>
WS/0366	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC.</p>	25/04/2013	30/05/2013	SmPC	<p>The WSA proposed the update of section 4.8 SOC "Skin and subcutaneous tissue disorders" of the SmPC in order to add information about "drug induced hypersensitivity syndrome (DiHS), drug rash with eosinophilia and systemic symptoms (DRESS)".</p> <p>The requested variation worksharing procedure proposed</p>

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				amendments to the SmPC.
WS/0365	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of SmPC, Annex II, labelling and Package leaflet.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	25/04/2013	30/05/2013	SmPC, Annex II, Labelling and PL	<p>The WSA proposed to update of the SmPC (sections 4.4 and 4.8 SOC "Immune system disorders") on "Allergic cross-reactivity to other thienopyridines". The labelling and Package Leaflet were proposed to be updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, labelling and Package Leaflet.</p>
IA/0014/G	<p>This was an application for a group of variations.</p> <p>A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)</p> <p>B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer</p> <p>B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer</p>	17/01/2013	n/a		
IA/0013	A.7 - Administrative change - Deletion of	21/12/2012	n/a		

	manufacturing sites				
II/0010	Update of SmPC section 4.8 Undesirable Effects. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SmPC, Labelling and PL	Update of SmPC section 4.8 Undesirable Effects of the DuoPlavin European SmPC by the addition of new adverse reactions in System Organ Class "Hepatobiliary disorders" occurring with ASA alone. Additionally, some other changes were included in the DuoPlavin European annexes in order to implement the QRD template version 8 and the local representatives for UK and PT.
IG/0171	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2012	25/05/2012	SmPC, Labelling and PL	
IG/0147/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.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.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities 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	29/02/2012	n/a		

IB/0007	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	08/08/2011	n/a		
IG/0091	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	05/07/2011	n/a		
II/0004	Update SPC to include new information on the variability of response to clopidogrel due to either genetic variations of the CYP2C19 enzyme or concomitant use of drugs that inhibit the CYP2C19 enzyme such as proton pump inhibitor (PPI). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC and PL	The marketing authorisation holder (MAH) proposes to update sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use", 4.5 "Interaction with other medicinal products and other forms of interaction" and 5.2 "Pharmacokinetic properties" of clopidogrel/acetylsalicylic acid (ASA) SPC to include new information on the variability of response to clopidogrel due to either genetic variations of the CYP2C19 enzyme or concomitant use of drugs that inhibit the CYP2C19 enzyme such as proton pump inhibitor (PPI). Section 4.8 has been amended with minor details on the CURE study. In addition to the above-mentioned changes, minor editorial changes are also proposed to the Product Information to bring it in line with the recently Product Information submitted for clopidogrel.
IB/0006	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/09/2010	n/a		
IB/0005	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other	10/09/2010	n/a		

	variation				
II/0001	<p>Update sections 4.4 and 4.5 of clopidogrel SPC to include new information on the interaction between clopidogrel and CYP2C19 inhibitors including some proton pump inhibitors, further to the CHMP request in December 2009 CHMP meeting.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	24/06/2010	06/08/2010	SmPC and PL	<p>The current variation is submitted in response to the CHMP's request following their December 2009 meeting to further update the Product Information of clopidogrel, following a further review of the available data on the interaction between clopidogrel and PPIs (including data from MAHs for PPIs).</p> <p>It provides an overview and discussion of the data generated from the comprehensive research program undertaken to further elucidate the variability of PK and PD response of clopidogrel.</p> <p>The study results require an update of the sections 4.4 "Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" of the SPC. The Patient Information Leaflets have been updated to reflect these SPC modifications. In addition, SPC section 4.2 was corrected by deleting information on the loading dose.</p>
IB/0003/G	<p>This was an application for a group of variations.</p> <ul style="list-style-type: none"> - To add a test method for the active substance - To tighten acceptance criteria in the active substance - To replace test methods for the active substance <p>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</p>	31/05/2010	n/a		

	<p>material/intermediate</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>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</p> <p>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</p> <p>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</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p>				
IG/0004/G	<p>This was an application for a group of variations.</p> <p>C.I.9.a - Changes to an existing pharmacovigilance</p>	06/05/2010	n/a	Annex II	

	<p>system as described in the DDPS - Change in the QPPV</p> <p>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV</p> <p>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV</p> <p>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</p> <p>C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database</p>				
IA/0002	<p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p>	23/04/2010	23/04/2010	SmPC, Labelling and PL	