Clopidogrel/Acetylsalicylic acid Zentiva

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
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		SmPC and PL	

[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).

WS/1433	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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. 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/09/2018	25/10/2018	SmPC and PL	Following the PRAC assessment and recommendation on the signal regarding insulin autoimmune syndrome, the new adverse reaction 'insulin autoimmune syndrome' is added in section 4.8 of the SmPC. The Package Leaflet is updated accordingly. 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.
WS/1459	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 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/09/2018		SmPC	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 (prasugel, ticagrelor) to clopidogrel in Acute Coronary Syndrome.

WS/1258	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 4.8 of the SmPC in order to add the undesirable effect 'ageusia'. The PL is updated accordingly. 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/01/2018	25/10/2018	SmPC and PL	
PSUSA/820/201611	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	06/07/2017	n/a		PRAC Recommendation - maintenance
WS/1091	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 4.1 to clarify the indication and specify that clopidogrel is indicated for the secondary prevention of atherothrombotic events. In addition, the MAH took the opportunity to update the details of the German local representative in the Clopidogrel/Acetylsalicylic acid Zentiva Package Leaflet.	23/02/2017	29/03/2017	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1019	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 4.8 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/12/2016	29/03/2017	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/12/2016	29/03/2017	SmPC, Annex II, Labelling and PL	
WS/0930	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 4.8 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/05/2016	29/03/2017	SmPC and PL	
IB/0044	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	15/01/2016	26/02/2016	SmPC, Labelling and PL	
WS/0856	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	14/01/2016	26/02/2016	SmPC and PL	Tenofovir, a medicine to treat HIV (human immunodeficiency virus) infections, when taken with NSAIDs (nonsteriodal anti-inflammatory drug) used to treat inflammation and pain, may increase the risk of renal failure. Acetylsalicylic

	Update of section 4.5 of the SmPC to include information regarding a potential interaction with tenofovir. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				acid is a NSAID, and therefore its use along with tenofovir may increase the risk of renal impairment.
WS/0813	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 4.4 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	26/02/2016	SmPC and PL	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. 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.
WS/0815	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 4.4 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	24/09/2015	26/02/2016	SmPC and PL	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

	Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with bleeding risk such as pentoxifylline, as there is an increased risk of bleeding due to the potential additive effect. 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 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	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 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	26/02/2016	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	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	17/09/2015	n/a		

	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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	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 4.5 of the SmPC to amend the information on CYP2C19 inhibitors. The package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	26/02/2016	SmPC and PL	
WS/0686	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 4.8 of the SmPC to include the new ADRs 'Kounis syndrome', Henoch Schonlein purpura' and 'acute pancreatits'. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	26/02/2016	SmPC and PL	All three ADRs are reported in published information for ASA with frequency "not known". Kounis syndrome and acute pancreatitis were reported in the context of a hypersensitivity reaction due to acetylsalicylic acid.

WS/0685	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 4.5 of the SmPC to include information about an interaction with acetazolamide. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	26/02/2016	SmPC and PL	Caution is recommended when co administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.
WS/0682	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 4.8 of the "Undesirable effects" to add 2 new undesirable effects: "Acute generalised exanthematous pustulosis (AGEP) and "Gynaecomastia". Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	26/02/2016	SmPC and PL	
R/0033	Renewal of the marketing authorisation.	25/09/2014	19/11/2014	SmPC, Annex II, Labelling and PL	DuoCover is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoCover is a fixed dose combination medicinal product for continuation of therapy in: • Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction)

					including patients undergoing a stent placement following percutaneous coronary intervention • ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy 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 DuoCover 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.
WS/0572	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 4.5 of the SmPC to add information about an interaction with metamizole. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	01/09/2014	SmPC	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.
WS/0554	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 4.9 of the Summary of Product Characteristics related to overdose information on clopidrogrel/acetylsalicylic acid (ASA) fixed dose combination.	24/07/2014	01/09/2014	SmPC	Following review of the submitted data, the CHMP concluded that an update of the Product Information related to the overdose information on clopidrogrel/ASA fixed combination was necessary to include the following information: - Overdose with ASA/ clopidogrel fixed dose combination may be associated with increased bleeding and subsequent bleeding complications due to the pharmacological activity of clopidogrel and ASA.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/0538	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 4.8 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/clopidrogel fixed combination products. Sections 2 and 4 of the PL are updated accordingly. An editorial change is also made to section 4.3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	01/09/2014	SmPC and PL	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: - 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	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the section 4.8 of the SmPC to add information on Core Data Sheets linked to clopidogrel INN. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/01/2014	01/09/2014	SmPC	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. 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. 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.
WS/0476	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 4.4 and 4.5 of the SmPC in order to add information on Core Data Sheets linked to clopidogrel INN. 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/01/2014	01/09/2014	SmPC and PL	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. 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. - 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. 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. The Package Leaflet was proposed to be updated accordingly. The WSA also took this opportunity to update the phone number of the local representative for UK.

WS/0397	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The WSA proposed the update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and 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	27/06/2013	13/11/2013	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. Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 9.
WS/0378	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 4.8 of the SmPC and Package Leaflet. 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	27/06/2013	13/11/2013	SmPC and PL	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.
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.	19/09/2013	01/09/2014	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.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
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 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		
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		
IB/0023	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	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the section 4.4 and 4.8 of the SmPC and 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	25/04/2013	27/05/2013	SmPC and PL	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 colitis. The package leaflet has been amended accordingly.

WS/0368	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 4.8 and 4.9 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	27/05/2013	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	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 4.3 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	27/05/2013	SmPC	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". The requested variation worksharing procedure proposed amendments to the SmPC.
WS/0366	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 4.8 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	27/05/2013	SmPC	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)". The requested variation worksharing procedure proposed amendments to the SmPC.

WS/0365	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC, Annex II, labelling and 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	25/04/2013	27/05/2013	SmPC, Annex II, Labelling and PL	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.
T/0015	Transfer of Marketing Authorisation	01/02/2013	28/02/2013	SmPC, Labelling and PL	
IA/0014/G	This was an application for a group of variations. 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) 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 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	21/01/2013	n/a		

IA/0013	A.7 - Administrative change - Deletion of manufacturing sites	20/12/2012	n/a		
II/0011	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 DuoCover European annexes in order to implement the QRD template version 8.
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		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2011	n/a	PL	

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/0006	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/0005	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/0004	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		

II/0002	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, futher to the CHMP request in December 2009 CHMP meeting. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	28/07/2010	SmPC	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). 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. 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.
IB/0003/G	This was an application for a group of variations. - 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 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	31/05/2010	n/a		

	specification limits 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.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.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.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				
IG/0004/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the	06/05/2010	n/a	Annex II	

	back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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				
IA/0001	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	22/04/2010	22/04/2010	SmPC, Labelling and PL	