Clopidogrel 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
II/0092	Extension of indication to include, in combination with acetylsalicylic acid (ASA), patients with ST segment elevation acute myocardial infarction (STEMI) who are undergoing percutaneous coronary intervention (PCI) for CLOPIDOGREL ZENTIVA. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the	24/07/2025	22/08/2025	SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.92'

[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).

	SmPC are updated. Version 0.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, introduce minor editorial changes to the PI and bring it in line with the latest QRD template version 10.4 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0091	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/06/2024	04/08/2025	SmPC and PL	
IA/0090/G	This was an application for a group of variations. B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	07/03/2024	n/a		
IA/0088	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	20/09/2023	n/a		

PSUSA/820/202211	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	06/07/2023	n/a		PRAC Recommendation - maintenance
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/06/2023	22/08/2025	Labelling and PL	
IA/0083	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/12/2022	n/a		
IAIN/0082	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	22/09/2022	n/a		
IB/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/06/2022	04/07/2023	SmPC and PL	
IB/0080	B.II.z - Quality change - Finished product - Other variation	12/01/2022	n/a		
IB/0079	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	27/10/2021	16/12/2021	SmPC and PL	
IAIN/0078	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	17/06/2021	n/a		

IB/0076	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	01/06/2021	09/07/2021	SmPC, Annex II, Labelling and PL	
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	11/05/2021	09/07/2021	Annex II and PL	
IAIN/0075	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/03/2021	n/a		
IB/0074	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	14/12/2020	09/07/2021	SmPC and PL	
IAIN/0073	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	23/11/2020	n/a		
IA/0072	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	07/08/2020	n/a		

IAIN/0071/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.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 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 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	10/07/2020	16/11/2020	Annex II and PL	
PSUSA/820/201911	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	09/07/2020	n/a		PRAC Recommendation - maintenance
IA/0070	A.7 - Administrative change - Deletion of manufacturing sites	13/05/2020	n/a		
WS/1690	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	14/11/2019	16/11/2020	SmPC and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0068	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	05/11/2019	n/a		
IA/0067	A.7 - Administrative change - Deletion of manufacturing sites	26/09/2019	16/11/2020	Annex II 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	16/11/2020	SmPC and PL	
IAIN/0064/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/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	18/07/2019	n/a		
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

	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				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.
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/10/2018	03/09/2019	PL	
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	03/09/2019	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.

T/0060	Transfer of Marketing Authorisation	13/04/2018	30/04/2018	SmPC, Labelling and PL	
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	30/04/2018	SmPC and PL	
IB/0058/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a	10/11/2017	30/04/2018	Annex II, Labelling and PL	

	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.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.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 B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
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	23/02/2017	03/04/2017	SmPC and PL	

	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. 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	08/12/2016	03/04/2017	SmPC, Annex II, Labelling and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
WS/0994	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	22/09/2016	n/a		
IAIN/0053	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/12/2015	26/02/2016	Annex II and PL	
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 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	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 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. 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	17/09/2015	n/a		

	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/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	
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	17/07/2014	n/a		

	PSMF location				
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	18/09/2014	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	23/01/2014	18/09/2014	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

	new quality, preclinical, clinical or pharmacovigilance data				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/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/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.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

	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				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	19/07/2013	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.
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		
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	25/04/2013	30/05/2013	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

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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	30/05/2013	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.
IA/0036	A.7 - Administrative change - Deletion of manufacturing sites	08/01/2013	n/a		
IA/0035	A.7 - Administrative change - Deletion of manufacturing sites	20/12/2012	n/a		
R/0034	Renewal of the marketing authorisation.	18/10/2012	17/12/2012	SmPC, Annex II and PL	
T/0033	Transfer of Marketing Authorisation	27/04/2012	25/05/2012	SmPC, Labelling and PL	
IA/0031/G	This was an application for a group of variations. 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	02/03/2012	25/05/2012	SmPC, Labelling and PL	

	the range of the currently approved pack sizes A.1 - Administrative change - Change in the name and/or address of the MAH				
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		
IAIN/0030/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the	13/02/2012	n/a		

	Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
IB/0029	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	06/01/2012	n/a		
IA/0026	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	23/08/2011	n/a	SmPC, Annex II, Labelling and PL	
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/0025	Update of sections 4.2 "Posology and method of administration" and 5.1 "Pharmacodynamic properties" of clopidogrel SPC to include new paediatric information available for clopidogrel. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/04/2011	07/06/2011	SmPC	A paediatric program was conducted to evaluate the efficacy of clopidogrel for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. The results of these studies and relevant recommendations are now included in the proposed labelling change.
II/0022	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	18/11/2010	13/01/2011	SmPC, Labelling 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

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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.
II/0017	The MAH is applying for an extension of indication of clopidogrel film-coated tablets for the prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation who have at least one risk factor for vascular events and who cannot take vitamin K antagonist (VKA) therapy. Extension of Indication	18/11/2010	13/01/2011	SmPC and PL	A randomized double-blind, placebo-controlled, superiority study of clopidogrel (75 mg once daily) in combination with acetylsalicylic acid (75-100 mg once daily recommended) versus acetylsalicylic acid alone has been conducted in patients with atrial fibrillation patients and at least one risk factor for vascular events who cannot take VKA (EFC4912/ACTIVE-A study). In the (ACTIVE) trial program, patients with atrial fibrillation and one or more additional risk factors for stroke were enrolled in one of two trials. If they were considered suitable candidates for warfarin therapy, they were enrolled in ACTIVE-W, a comparison of warfarin with the combination of clopidogrel and aspirin. The results of ACTIVE-W showed that use of a vitamin-K antagonist reduced the risk for stroke by 42% over clopidogrel and aspirin. Those considered unsuitable for warfarin therapy were enrolled in ACTIVE-A and randomized to receive clopidogrel (75 mg/day) or placebo on a background of aspirin therapy. The safety profile of clopidogrel is well established and no new safety concerns were discovered during the analysis of ACTIVE A and W trials what must be analysed is the rates on known risks namely bleeding in the context of the benefits.

IB/0024	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/0023	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		
IA/0021	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/05/2010	n/a		
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 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	06/05/2010	n/a	Annex II	

II/0020	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	18/03/2010	29/04/2010	SmPC and PL	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). The current variation 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 MAH submitted a type II Variation application to request 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.
T/0018	Transfer of Marketing Authorisation	17/12/2009	29/01/2010	SmPC, Labelling and PL	The Marketing Authorisation Holder was transferred from Sanofi Pharma Bristol-Myers Squibb SNC to Sanofi-Aventis.
IB/0013	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	17/12/2009	n/a		
IA/0019	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	11/12/2009	11/12/2009	SmPC, Labelling and PL	
IB/0016	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec. IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	10/11/2009	n/a		
IB/0014	IA_12_a_Change in spec. of active subst./agent used	10/11/2009	n/a		

	in manuf. of active subst. - tightening of spec. IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)				
IB/0015	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	06/11/2009	n/a		
IA/0012	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/10/2009	n/a		
II/0008	Update of SPC 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", 5.1 "Pharmacodynamic properties" and 5.2 "Pharmacokinetic properties" to include information on the clopidogrel metabolism pathway, the role of CYP2C19 genetic polymorphism on clopidogrel variability of response, and the potential interaction between clopidogrel and CYP2C19 inhibitors including some proton pump inhibitors, further to the CHMP recommendations taken during the April and May 2009 CHMP meetings. The pharmaceutical form and contents section in the Labelling has also been updated. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/07/2009	13/08/2009	SmPC, Labelling and PL	In March 2009 a publication from JAMA reporting on a large epidemiological study that claimed patients treated simultaneously with clopidrogel and Proton Pump Inhibitors PPI had worse cardiovascular outcomes than those not exposed to PPI was discussed by the PhVWP and CHMP. The CHMP reviewed the evidence pertaining to the drug-drug interaction between clopidrogel and PPIs and analysed this evidence, critical in terms of its methodological and clinical value. Following CHMP recommendations, , the MAH submit a variation to update the sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SPC (and the corresponding sections of the Package Leaflet) to include available information on this topic. The pharmaceutical form and contents section in the Labelling has also been updated.
IB/0011	IB_10_Minor change in the manufacturing process of the active substance	11/08/2009	n/a		

IB/0010	IB_10_Minor change in the manufacturing process of the active substance	10/08/2009	n/a		
IB/0009	IB_10_Minor change in the manufacturing process of the active substance	10/08/2009	n/a		
II/0003	The Marketing Authorisation Holder applied to change the storage conditions of the 75 mg film-coated tablets packed in the PVC/PVDC/Alu blisters from "No special storage conditions" to "Store below 30°C". Change(s) to shelf-life or storage conditions	18/12/2008	13/02/2009	SmPC, Labelling and PL	
IB/0007	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	22/01/2009	n/a		
IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	03/11/2008	03/11/2008	SmPC, Labelling and PL	
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	03/11/2008	03/11/2008	SmPC, Labelling and PL	
IB/0004	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/10/2008	n/a	SmPC	
IB/0002	IB_10_Minor change in the manufacturing process of the active substance	11/08/2008	n/a		
IB/0001	IB_10_Minor change in the manufacturing process of the active substance	11/08/2008	n/a		
