Plavix

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/2808	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	27/03/2025	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).

	authorisation, including the RMP - Other variation				
IB/0158/G	This was an application for a group of variations. 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 B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	07/01/2025	n/a		
IA/0159	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	19/11/2024	n/a		
N/0156	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/08/2024		PL	
IA/0155/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	13/06/2024	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0152/G	This was an application for a group of variations. 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.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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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	16/08/2023	n/a		

	material/intermediate 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IA/0153	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	07/07/2023	n/a		
PSUSA/820/202211	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	06/07/2023	n/a		PRAC Recommendation - maintenance
N/0154	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/07/2023		PL	
IB/0151	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	28/06/2023	n/a		
IAIN/0150	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)	26/04/2023	n/a		

T/0148	Transfer of Marketing Authorisation	18/11/2022	16/12/2022	SmPC, Labelling and PL	
WS/2150	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	10/11/2022	16/12/2022	SmPC and Labelling	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-WS-2150'
WS/2259	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 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.	20/10/2022	16/12/2022	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.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0146/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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 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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites	21/06/2022	n/a		
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	16/12/2022	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

	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(1.4-fold after chronic 75 mg clopidogrel dose and 2-fold 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.
N/0144	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/11/2021	16/12/2022	PL	
WS/1820	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 4.2 and 4.4 of the SmPC with information concerning the addition of 600 mg as an alternative loading dose to the existing 300 mg to be used at initiation of treatment in the indication of secondary prevention of atherothrombotic events in adult patients <75 years of age suffering from acute coronary syndrome and when PCI is intended. This update is based on a bibliographic review of published studies. The Package Leaflet is updated accordingly. The RMP version 2.4 has also been submitted. Update of section 4.2 and 4.4 of the SmPC with information concerning the addition of 600 mg as an alternative loading dose to the existing 300 mg to be used at initiation of treatment in the	22/04/2021	21/05/2021	SmPC and PL	Section 4.2 and 4.4 have been updated to reflect that 600 mg can be used as an alternative loading dose to the existing 300 mg at initiation of treatment in the indication of secondary prevention of atherothrombotic events in adult patients <75 years of age suffering from acute coronary syndrome and when PCI is intended. The warning included in section 4.4 is that the use of clopidogrel 600 mg loading dose is not recommended in patients with non-ST segment elevation acute coronary syndrome and ≥75 years of age due to increased bleeding risk in this population. For more information, please refer to the Summary of Product Characteristics.

	indication of secondary prevention of atherothrombotic events in adult patients <75 years of age suffering from acute coronary syndrome and when PCI is intended. This update is based on a bibliographic review of published studies. The Package Leaflet is updated accordingly. The RMP version 2.4 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1769	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication in combination with aspirin to include adult patients with moderate to high risk Transient Ischemic Attack (TIA) (ABCD2 score ≥4) or minor Ischemic Stroke (IS) (NIHSS ≤3) within 24 hours of either the TIA or IS event for Iscover and Plavix. The new indication is based on the results of two double-blind, randomised, placebo-controlled phase III trials (studies POINT & CHANCE); as a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated, the PL is updated accordingly. Version 2.3 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	10/12/2020	29/01/2021	SmPC and PL	Please refer to Scientific Discussion WS1769-Iscover-Plavix

IB/0142	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	07/01/2021	21/05/2021	Annex II and PL	
WS/1848	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2020	18/11/2020	SmPC, Labelling and PL	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. For more information, please refer to the Summary of Product Characteristics.
PSUSA/820/201911	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	09/07/2020	n/a		PRAC Recommendation - maintenance
N/0137	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2020	18/11/2020	PL	

T/0136	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	18/11/2020	SmPC and PL	
IB/0135	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	18/10/2019	n/a		
IA/0134	A.7 - Administrative change - Deletion of manufacturing sites	26/09/2019	14/11/2019	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	14/11/2019	SmPC and PL	
WS/1433	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	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

	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				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	04/10/2019	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.
II/0127/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an	22/03/2018	28/05/2018	Annex II, Labelling and PL	

	initial or product specific inspection 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				
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	28/05/2018	SmPC and PL	
IB/0128/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	07/07/2017	28/05/2018	Annex II and PL	

	site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.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 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	23/02/2017	29/03/2017	SmPC and PL	

	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/0994	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	22/09/2016	n/a		

	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IAIN/0122	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/12/2015	08/02/2016	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	08/02/2016	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.	24/09/2015	08/02/2016	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.

	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				
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 specification parameter to the specification with its corresponding test method	17/09/2015	n/a		
WS/0707	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	21/05/2015	08/02/2016	SmPC and PL	

	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				
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	08/02/2016	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 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	23/01/2014	01/10/2014	SmPC	Dermatitis exfoliative is one form of severe dermatitis, and as such deserves to be differentiated from other dermatitis,

	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				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	01/10/2014	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.
IG/0325	A.1 - Administrative change - Change in the name and/or address of the MAH	07/10/2013	01/10/2014	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	01/10/2014	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/0111/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. The WSA proposed the update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and Package Leaflet.	27/06/2013	26/07/2013	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. Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 9.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
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	17/07/2013	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 of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	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 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/0104	A.7 - Administrative change - Deletion of manufacturing sites	08/01/2013	n/a		
IA/0103	A.7 - Administrative change - Deletion of manufacturing sites	20/12/2012	n/a		
IG/0171	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2012	29/10/2012	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	29/02/2012	n/a		

	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				
IAIN/0100/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 Ph. Eur. or with a national pharmacopoeia of a Member State - AS	13/02/2012	n/a		
IB/0099	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	16/01/2012	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/0098	Update of sections 4.2 "Posology and method of administration" and 5.1 "Pharmacodynamic properties" of clopidogrel SPC to include new	14/04/2011	27/05/2011	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

	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				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/0095	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	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 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/0091	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/0097	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/0096	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/0094	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	06/05/2010	n/a	Annex II	

	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				
II/0093	C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data 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.
IB/0087	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/0092	IA_41_a_01_Change in pack size - change in no. of	11/12/2009	11/12/2009	SmPC,	

	units within range of appr. pack size			Labelling and PL	
IB/0090	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/0088	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/0089	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	06/11/2009	n/a		
IA/0086	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/0082	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	23/07/2009	28/08/2009	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

	contents section in the Labelling has also been updated. Update of Summary of Product Characteristics, Labelling and Package Leaflet				Labelling has also been updated.
IB/0085	IB_10_Minor change in the manufacturing process of the active substance	11/08/2009	n/a		
IB/0084	IB_10_Minor change in the manufacturing process of the active substance	10/08/2009	n/a		
IB/0083	IB_10_Minor change in the manufacturing process of the active substance	10/08/2009	n/a		
II/0077	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	26/01/2009	SmPC, Labelling and PL	
IB/0081	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	22/01/2009	n/a		
IB/0080	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and PL	
IB/0079	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/10/2008	30/10/2008	SmPC, Labelling and	

				PL	
IB/0078	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/10/2008	n/a	SmPC	
IB/0076	IB_10_Minor change in the manufacturing process of the active substance	21/07/2008	n/a		
IB/0075	IB_10_Minor change in the manufacturing process of the active substance	21/07/2008	n/a		
II/0074	The Marketing Authorisation Holder applied to add an alternative route of synthesis of the active substance at one of the already approved manufacturing sites. Change(s) to the manufacturing process for the active substance	26/06/2008	30/06/2008		
R/0073	Renewal of the marketing authorisation.	24/04/2008	19/06/2008	SmPC, Labelling and PL	
X/0070	Application under Article 8(3) of Directive 2001/83/EC as an extension to the licence for the Plavix tablets (EU/1/98/069/001a - 007b) marketed by Sanofi Pharma Bristol-Myers Squibb SNC to add a new strength that contains 300 mg of clopidogrel. Annex I_2.(c) Change or addition of a new strength/potency	21/02/2008	14/04/2008	SmPC, Labelling and PL	This application was submitted under Article 8(3) of Directive 2001/83/EC as an extension to the licence for the Plavix tablets (EU/1/98/069/001a - 007b) marketed by Sanofi Pharma Bristol-Myers Squibb SNC to add a new strength that contains 300 mg of clopidogrel. In patients suffering from acute coronary syndrome Plavix treatment should be initiated with a single 300 mg loading dose, and therefore four tablets of 75 mg are currently administered to patients. In order to substitute the four 75 mg tablets of Plavix with a single tablet containing 300 mg of clopidogrel the Marketing Authorisation Holder applied

					for a new strength of the medicinal product. Plavix 300 mg film-coated tablets contain the same active ingredient and excipients as currently approved Plavix 75 mg film-coated tablets, including the coating material. Bioequivalence data submitted proved that 300 mg tablet is equivalent to the sum of four 75 mg film-coated tablets and that 300 mg film-coated tablets is therapeutically interchangeable with 4 x 75 mg film-coated tablets which are already marketed.
IA/0072	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/11/2007	n/a		
IB/0071	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	10/10/2007	n/a		
II/0061	Update of Summary of Product Characteristics and Package Leaflet to reword the indication as follows: "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, in combination with acetylsalicylic acid (ASA)." Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	22/06/2007	SmPC and PL	Please refer to the Scientific discussion: Plavix-H-174-II-61.
IB/0069	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	10/05/2007	10/05/2007	SmPC, Labelling and PL	

IB/0068	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	10/05/2007	10/05/2007	SmPC, Labelling and PL	
IA/0067	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/03/2007	13/03/2007	SmPC, Labelling and PL	
IA/0066	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/03/2007	13/03/2007	SmPC, Labelling and PL	
IA/0065	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/03/2007	13/03/2007	SmPC, Labelling and PL	
IA/0064	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/03/2007	13/03/2007	SmPC, Labelling and PL	
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/02/2007	n/a	PL	
IA/0062	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/01/2007	n/a		
IB/0059	IB_10_Minor change in the manufacturing process of the active substance	27/10/2006	n/a		
IB/0058	IB_10_Minor change in the manufacturing process of the active substance	27/10/2006	n/a		
IA/0054	IA_09_Deletion of manufacturing site	17/10/2006	n/a	Annex II and PL	

IA/0060	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/10/2006	n/a		
IA/0057	11a_Change in the name of a manufacturer of the active substance	13/10/2006	n/a		
IA/0056	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/10/2006	n/a		
IA/0055	IA_05_Change in the name and/or address of a manufacturer of the finished product	13/10/2006	n/a		
II/0051	Extension of the acute coronary syndrome (ACS) indication as follows: "ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy". Extension of Indication	27/07/2006	01/09/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific discussion: Plavix-H-174-II-51.
II/0053	Update of Summary of Product Characteristics (4.4 and 4.5) and Package Leaflet further to the assessment of the 13th PSUR. Update of Summary of Product Characteristics and Package Leaflet	01/06/2006	26/06/2006	SmPC and PL	Update of the SPC to reflect a potential interaction with Cox-2 inhibitors resulting in a possible increased risk of bleeding, as currently stated for NSAIDs.
IA/0052	IA_13_a_Change in test proc. for active substance - minor change	23/03/2006	n/a		
II/0050	Update of Summary of Product Characteristics (4.8), Labelling and Package Leaflet following the	14/12/2005	20/01/2006	SmPC, Annex II, Labelling	Addition of very rare cases of Toxic epidermal necrolysis (following an update of the Company Core Safety

	assessment of the 13th PSUR. Update of Summary of Product Characteristics, Labelling and Package Leaflet			and PL	Information (CCSI)).
IB/0048	IB_33_Minor change in the manufacture of the finished product	08/09/2005	n/a		
IA/0049	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/08/2005	n/a	Annex II and PL	
IA/0047	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/08/2005	n/a		
IB/0046	IB_33_Minor change in the manufacture of the finished product IA_32_a_Change in batch size of the finished product - up to 10-fold	15/04/2005	n/a		
IA/0045	IA_05_Change in the name and/or address of a manufacturer of the finished product	23/02/2005	n/a	Annex II and PL	
II/0040	Update of Summary of Product Characteristics (4.8) and Package Leafletfollowing the assessment of the 11th PSUR. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	05/01/2005	SmPC and PL	Addition of very rare cases of stomatitis, hepatic failure, serum sickness and intestitial pneumonitis.
IB/0042	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	23/11/2004	n/a		

IB/0041	IB_33_Minor change in the manufacture of the finished product	22/11/2004	n/a		
IA/0043	IA_32_a_Change in batch size of the finished product - up to 10-fold	04/11/2004	n/a		
II/0038	Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	02/08/2004	SmPC and PL	
IA/0039	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	11/06/2004	n/a	SmPC, Annex II, Labelling and PL	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2003	22/12/2003	PL	
R/0035	Renewal of the marketing authorisation.	22/05/2003	08/10/2003	SmPC, Annex II, Labelling and PL	
II/0036	Change(s) to the manufacturing process for the active substance	25/09/2003	02/10/2003		
I/0032	Minor changes in manufacture of the medicinal product. 15_Minor changes in manufacture of the medicinal product	27/03/2003	01/04/2003		
I/0031	Change in the batch size of finished product.	27/03/2003	01/04/2003		

	16_Change in the batch size of finished product				
I/0034	30_Change in pack size for a medicinal product	14/02/2003	24/03/2003	SmPC, Labelling and PL	
I/0033	30_Change in pack size for a medicinal product	14/02/2003	24/03/2003	SmPC, Labelling and PL	
I/0029	Minor change in the test procedure of a starting material. 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	19/02/2003	03/03/2003		
I/0028	20_Extension of shelf-life as foreseen at time of authorisation	20/12/2002	03/02/2003	SmPC	
I/0030	Increase in the batch size of Iscover active substance (Clopidogrel) without any affect on the specifications of the active substance. 13_Batch size of active substance	10/01/2003	16/01/2003		
II/0024	Extension of Indication	30/05/2002	09/09/2002	SmPC and PL	
I/0026	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	16/05/2002	19/06/2002	Annex II and PL	
I/0027	01_Change in the name of a manufacturer of the medicinal product	27/05/2002	27/05/2002		

I/0025	01_Change following modification(s) of the manufacturing authorisation(s)	13/12/2001	19/02/2002	Annex II and PL	
II/0022	Update of Summary of Product Characteristics and Package Leaflet	23/08/2001	28/01/2002	SmPC and PL	
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/10/2001	17/12/2001	PL	
I/0021	11_Change in or addition of manufacturer(s) of active substance	19/07/2001	n/a		
II/0018	Update of Summary of Product Characteristics and Package Leaflet	29/03/2001	16/07/2001	SmPC and PL	
I/0020	12_Minor change of manufacturing process of the active substance	04/03/2001	n/a		
I/0019	13_Batch size of active substance	04/03/2001	n/a		
II/0012	Update of Summary of Product Characteristics	12/04/2000	13/07/2000	SmPC and Annex II	
I/0014	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	04/05/2000	16/05/2000		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/03/2000	03/05/2000	PL	
I/0011	11_Change in or addition of manufacturer(s) of active substance	12/01/2000	22/02/2000		

I/0010	12_Minor change of manufacturing process of the active substance	19/10/1999	04/11/1999		
I/0009	13_Batch size of active substance	19/10/1999	04/11/1999		
I/0008	11_Change in or addition of manufacturer(s) of active substance	31/08/1999	14/09/1999		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	21/05/1999	07/09/1999	SmPC and PL	
I/0006	14_Change in specifications of active substance	06/07/1999	16/07/1999		
I/0005	32_Change of imprints/bossing/marking on tablets/printing on capsules, incl. addition/change of inks	13/05/1999	16/07/1999	SmPC and PL	
I/0003	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/03/1999	16/07/1999	Annex II and PL	
I/0002	08_Change in the qualitative composition of immediate packaging material	05/02/1999	11/06/1999	SmPC and PL	
I/0004	16_Change in the batch size of finished product	22/03/1999	n/a		
I/0001	03_Change in the name and/or address of the marketing authorisation holder	03/12/1998	01/02/1999	SmPC, Labelling and PL	