



## Iscover

### Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification <sup>1</sup> issued on	Commission Decision Issued <sup>2</sup> / amended on	Product Information affected <sup>3</sup>	Summary
WS/1433	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>In response to PRAC recommendation for the signal of insulin autoimmune syndrome (EPITT ref 19155), update of section 4.8 of the SmPC with the new adverse reaction 'insulin autoimmune syndrome'. The Package Leaflet is updated accordingly.</p>	13/09/2018	25/10/2018	SmPC and PL	<p>Following the PRAC assessment and recommendation on the signal regarding insulin autoimmune syndrome, the new adverse reaction 'insulin autoimmune syndrome' is added in section 4.8 of the SmPC. The Package Leaflet is updated accordingly.</p> <p>In addition, at the request of the Agency, MA numbers of Plavix and Iscover were reviewed and updated as per the current format. The Plavix and Iscover Annex A and PI were</p>

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



	<p>In addition, at the request of the Agency, MA numbers of Plavix and Iscover were reviewed and updated as per the current format. The Plavix and Iscover Annex A and PI were updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				updated accordingly.
WS/1459	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 5.1 of the SmPC in order to reflect the clinical outcome data of 2 randomised investigator-sponsored studies regarding de-escalation of P2Y12 receptor inhibitor to clopidogrel in ACS.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	20/09/2018		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 (prasugrel, ticagrelor) to clopidogrel in Acute Coronary Syndrome.
WS/1258	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC in order to add the undesirable effect 'ageusia'. The PL is updated accordingly.</p> <p>In addition, the Worksharing applicant (WSA) took the opportunity to introduce a clarification in section 4.2 of</p>	18/01/2018	14/06/2018	SmPC and PL	

	<p>the Duoplavin and Clopidogrel/Acetylsalicylic acid Zentiva SmPC; update the German local representative in the Package Leaflet; and bring the PI in line with the latest QRD template version 10.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				
IB/0131/G	<p>This was an application for a group of variations.</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site</p> <p>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</p> <p>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold</p>	07/07/2017	14/06/2018	Annex II and PL	

PSUSA/820/2 01611	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	06/07/2017	n/a		PRAC Recommendation - maintenance
WS/1091	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.1 to clarify the indication and specify that clopidogrel is indicated for the secondary prevention of atherothrombotic events.</p> <p>In addition, the MAH took the opportunity to update the details of the German local representative in the Clopidogrel/Acetylsalicylic acid Zentiva Package Leaflet.</p> <p>C.1.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	23/02/2017	24/03/2017	SmPC and PL	
WS/1019	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC in order to add Kounis syndrome as a new ADR. The Package Leaflet is updated accordingly. In addition the Worksharing applicant (WSA) took the opportunity to make minor amendments to Annex II for Clopidogrel Zentiva, Iscover and Plavix, to update the contact details of the Bulgarian local representative in the Package Leaflet for all the products involved and the Italian, Hungarian and Lithuanian local representatives for Clopidogrel</p>	08/12/2016	24/03/2017	SmPC, Annex II, Labelling and PL	

	<p>Zentiva, Iscover and Plavix, to combine the two strengths SmPCs for all the products involved in this Worksharing application, to combine the two strengths Package Leaflet for DuoPlavin and Clopidogrel/Acetylsalicylic acid Zentiva. Furthermore, the PI is brought in line with the latest QRD template version 10.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				
WS/0994	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p>	22/09/2016	n/a		
IAIN/0126	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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC to add 2 new interactions (with medicinal products associated with bleeding risks and with CYP2C8 substrates) in order to align with the Company Core Data Sheet. The</p>	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

	<p>Package Leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>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.</p>
WS/0809	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 5.2 of the SmPC in order to address the PRAC recommendation adopted during the April 2015 meeting to submit a cumulative review of all literature and case reports following a signal of drug interaction with grapefruit juice for clopidogrel products (SDA 032). In addition, the Worksharing applicant (WSA) took the opportunity to update the contact details of the local representative in Romania and Italy in the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	24/09/2015	08/02/2016	SmPC and PL	<p>The active metabolite of clopidogrel is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4.</p>
WS/0795/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p>	17/09/2015	n/a		

	<p>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p>				
WS/0707	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to amend the information on CYP2C19 inhibitors. The package Leaflet has been updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	21/05/2015	08/02/2016	SmPC and PL	
WS/0682	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the "Undesirable effects" to add 2 new undesirable effects: "Acute generalised exanthematous pustulosis (AGEP) and "Gynaecomastia". Package Leaflet has been updated accordingly.</p>	26/02/2015	08/02/2016	SmPC and PL	

	C.1.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0454	C.1.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	17/07/2014	n/a		
PSUSA/820/201311	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	10/07/2014	n/a		PRAC Recommendation - maintenance
WS/0477	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of the section 4.8 of the SmPC to add information on Core Data Sheets linked to clopidogrel INN.</p> <p>C.1.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	23/01/2014	01/10/2014	SmPC	<p>Dermatitis exfoliative is one form of severe dermatitis, and as such deserves to be differentiated from other dermatitis, particularly since it may signal the presence of DRESS. MAH proposes a change in SmPC section 4.8 to address this difference.</p> <p>The report on dermatitis exfoliative has shown sufficient evidence that clopidogrel may induce exfoliative rashes either generalized or localized including hands and feet locations. This is supported particularly by sentinel and rechallenge cases.</p> <p>Update of section 4.8 of the SmPC in order to update the safety information in order to add information on Core Data Sheets linked to clopidogrel INN.</p>
WS/0476	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC in order to add information on Core Data Sheets linked to</p>	23/01/2014	01/10/2014	SmPC and PL	<p>The weighted cumulative evidence is sufficient to support a causal association between clopidogrel or clopidogrel + ASA fixed dose combination (FDC) and the risk of increased bleeding when administered with SSRIs.</p> <p>The WSA proposed the update of sections 4.4 "Special Warnings and Precautions for use" and 4.5 Interaction with</p>



	<p>clopidogrel INN.</p> <p>The Section 2 of the Package leaflet has been updated accordingly. The WSA also took this opportunity to update the phone number of the local representative for UK.</p> <p>C.1.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>other medicinal products" of the SmPC in order to add information on Core Data Sheets linked to clopidogrel INN.</p> <ul style="list-style-type: none"> <li>- Addition of an interaction with the selective serotonin reuptake inhibitors (SSRIs) in section 4.5.</li> <li>- Addition of information concerning this interaction in section 4.4.</li> </ul> <p>The Section 2 of the Package leaflet has been updated accordingly. The WSA also took this opportunity to update the phone number of the local representative for UK.</p> <p>The Package Leaflet was proposed to be updated accordingly. The WSA also took this opportunity to update the phone number of the local representative for UK.</p>
WS/0409	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.4 of the product SmPC and update of Local representatives in the package leaflet.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	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/0116/G	<p>This was an application for a group of variations.</p> <p>B.1.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>B.1.a.2.z - Changes in the manufacturing process of the AS - Other variation</p> <p>B.1.b.1.z - Change in the specification parameters</p>	14/08/2013	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation				
WS/0397	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>The WSA proposed the update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and Package Leaflet.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	27/06/2013	26/07/2013	SmPC and PL	<p>The WSA proposed the update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) in order to add information on "acquired haemophilia A (AHA)". The Package Leaflet was proposed to be updated accordingly.</p> <p>Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 9.</p>
WS/0378	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC and Package Leaflet.</p> <p>C.1.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH</p>	27/06/2013	17/07/2013	SmPC and PL	<p>The WSA proposed the update of section 4.8 of the SmPC in order to add "eosinophilic pneumonia" as a new undesirable effect under the System Organ Class Respiratory, thoracic and mediastinal disorders. In addition, the WSA took the opportunity to update the list of local representatives (Croatia) in the Package Leaflet.</p>
IG/0314	C.1.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		

WS/0366	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.8 of the SmPC.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	25/04/2013	30/05/2013	SmPC	<p>The WSA proposed the update of section 4.8 SOC "Skin and subcutaneous tissue disorders" of the SmPC in order to add information about "drug induced hypersensitivity syndrome (DIHS), drug rash with eosinophilia and systemic symptoms (DRESS)".</p> <p>The requested variation worksharing procedure proposed amendments to the SmPC.</p>
WS/0365	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of SmPC, Annex II, labelling and Package leaflet.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>	25/04/2013	30/05/2013	SmPC, Annex II, Labelling and PL	<p>The WSA proposed to update of the SmPC (sections 4.4 and 4.8 SOC "Immune system disorders") on "Allergic cross-reactivity to other thienopyridines". The labelling and Package Leaflet were proposed to be updated accordingly.</p> <p>In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.</p> <p>Furthermore, the PI is being brought in line with the latest QRD template version 8.3.</p> <p>The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, labelling and Package Leaflet.</p>
T/0109	Transfer of Marketing Authorisation	01/02/2013	13/03/2013	SmPC, Labelling and PL	
IA/0108	A.7 - Administrative change - Deletion of manufacturing sites	08/01/2013	n/a		
IA/0107	A.7 - Administrative change - Deletion of manufacturing sites	19/12/2012	n/a		

IG/0147/G	<p>This was an application for a group of variations.</p> <p>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV</p> <p>C.I.9.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</p> <p>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</p> <p>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</p>	29/02/2012	n/a		
IAIN/0105/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p>	13/02/2012	n/a		

IB/0104	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		
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2011	n/a	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/0101	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	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 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/0098	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/0094	<p>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.</p> <p>Extension of Indication</p>	18/11/2010	13/01/2011	SmPC and PL	<p>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.</p>
IB/0100	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/0099	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/0097	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/0096	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, further to the CHMP request in	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

	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				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/0090	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/0095	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/0093	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/0091	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/0092	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	06/11/2009	n/a		
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2009	n/a	PL	
IA/0089	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/0084	<p>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.</p> <p>Paediatrics to validate Update of Summary of Product Characteristics, Labelling and Package Leaflet</p>	23/07/2009	27/08/2009	SmPC, Labelling and PL	In March 2009 a publication from JAMA reporting on a large epidemiological study that claimed patients treated simultaneously with clopidogrel 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 clopidogrel 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/0087	IB_10_Minor change in the manufacturing process of the active substance	11/08/2009	n/a		
IB/0086	IB_10_Minor change in the manufacturing process of the active substance	10/08/2009	n/a		
IB/0085	IB_10_Minor change in the manufacturing process of the active substance	10/08/2009	n/a		
II/0079	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	18/12/2008	27/01/2009	SmPC, Labelling and	

	storage conditions" to "Store below 30°C".  Change(s) to shelf-life or storage conditions			PL	
IB/0083	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	22/01/2009	n/a		
IB/0082	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/0081	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/0080	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/10/2008	n/a	SmPC	
IB/0078	IB_10_Minor change in the manufacturing process of the active substance	21/07/2008	n/a		
IB/0077	IB_10_Minor change in the manufacturing process of the active substance	21/07/2008	n/a		
II/0076	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/0075	Renewal of the marketing authorisation.	24/04/2008	19/06/2008	SmPC, Annex II, Labelling	

				and PL	
X/0072	<p>Application under Article 8(3) of Directive 2001/83/EC as an extension to the licence for the Iscover tablets (EU/1/98/070/001a - 007b) marketed by Bristol-Myers Squibb Pharma EEIG to add a new strength that contains 300 mg of clopidogrel.</p> <p>Annex I_2.(c) Change or addition of a new strength/potency</p>	21/02/2008	16/04/2008	SmPC, Labelling and PL	<p>This application was submitted under Article 8(3) of Directive 2001/83/EC as an extension to the licence for the Iscover tablets (EU/1/98/070/001a - 007b) marketed by Bristol-Myers Squibb Pharma EEIG to add a new strength that contains 300 mg of clopidogrel.</p> <p>In patients suffering from acute coronary syndrome Iscover 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 Iscover with a single tablet containing 300 mg of clopidogrel the Marketing Authorisation Holder applied for a new strength of the medicinal product.</p> <p>Iscover 300 mg film-coated tablets contain the same active ingredient and excipients as currently approved Iscover 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.</p>
IA/0074	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/11/2007	n/a		
IB/0073	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	10/10/2007	n/a		
II/0064	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	24/05/2007	21/06/2007	SmPC and PL	Please refer to the Scientific discussion: Iscover-H-175-II-64.

	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				
IB/0071	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/0070	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	19/03/2007	19/03/2007	SmPC, Labelling and PL	
IA/0069	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/0068	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_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/0062	IB_10_Minor change in the manufacturing process of the active substance	27/10/2006	n/a		
IB/0061	IB_10_Minor change in the manufacturing process of the active substance	27/10/2006	n/a		
IA/0057	IA_09_Deletion of manufacturing site	17/10/2006	n/a	Annex II and PL	
IA/0063	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/0060	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/10/2006	n/a		
IA/0059	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/10/2006	n/a		
IA/0058	IA_05_Change in the name and/or address of a manufacturer of the finished product	13/10/2006	n/a		
II/0054	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: Iscover-H-175-II-54.
II/0056	Update of Summary of Product Characteristics (4.4 and 4.5) and Package Leaflet further to the assessment of the 13th PSUR.	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.

	Update of Summary of Product Characteristics and Package Leaflet				
IA/0055	IA_13_a_Change in test proc. for active substance - minor change	23/03/2006	n/a		
II/0053	Update of Summary of Product Characteristics (4.8), Labelling and Package Leaflet following the assessment of the 13th PSUR  Update of Summary of Product Characteristics, Labelling and Package Leaflet	14/12/2005	20/01/2006	SmPC, Annex II, Labelling and PL	Addition of very rare cases of Toxic epidermal necrolysis (following an update of the Company Core Safety Information (CCSI)).
IA/0051	IA_01_Change in the name and/or address of the marketing authorisation holder	03/11/2005	n/a	SmPC, Labelling and PL	
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/10/2005	n/a	PL	
IB/0049	IB_33_Minor change in the manufacture of the finished product	08/09/2005	n/a		
IA/0050	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/0048	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/08/2005	n/a		
IB/0047	IB_33_Minor change in the manufacture of the finished product IA_32_a_Change in batch size of the finished product	15/04/2005	n/a		

	- up to 10-fold				
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 Leaflet following the assessment of the 11th PSUR.  Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	22/12/2004	SmPC and PL	Addition of very rare cases of stomatitis, hepatic failure, serum sickness and interstitial 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		
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/04/2003	12/05/2003	PL	
I/0031	Minor change in the manufacture of the medicinal product.  15_Minor changes in manufacture of the medicinal product	27/03/2003	01/04/2003		
I/0030	Change of batch size of finished product.  16_Change in the batch size of finished product	27/03/2003	01/04/2003		
I/0032	30_Change in pack size for a medicinal product	14/02/2003	20/03/2003	SmPC, Labelling and PL	
I/0028	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/0027	20_Extension of shelf-life as foreseen at time of authorisation	20/12/2002	03/02/2003	SmPC	



I/0029	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/0022	Extension of Indication	30/05/2002	09/09/2002	SmPC and PL	
I/0025	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/0026	01_Change in the name of a manufacturer of the medicinal product	27/05/2002	27/05/2002		
I/0023	01_Change in the name of a manufacturer of the medicinal product	13/12/2001	19/02/2002	Annex II and PL	
I/0021	03_Change in the name and/or address of the marketing authorisation holder	03/10/2001	19/02/2002	SmPC, Labelling and PL	
II/0020	Update of Summary of Product Characteristics and Package Leaflet	23/08/2001	29/01/2002	SmPC and PL	
I/0019	11_Change in or addition of manufacturer(s) of active substance	19/07/2001	n/a		
II/0016	Update of Summary of Product Characteristics and Package Leaflet	29/03/2001	16/07/2001	SmPC and PL	
I/0018	12_Minor change of manufacturing process of the	04/03/2001	15/03/2001		

	active substance				
I/0017	13_Batch size of active substance	04/03/2001	15/03/2001		
II/0015	Update of Summary of Product Characteristics and Package Leaflet	16/11/2000	06/03/2001	SmPC and PL	
II/0013	Quality changes	21/09/2000	15/01/2001	SmPC, Labelling and PL	
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/08/2000	25/09/2000	Labelling	
II/0011	Update of Summary of Product Characteristics	12/04/2000	13/07/2000	SmPC and Annex II	
I/0012	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	04/05/2000	16/05/2000		
I/0010	11_Change in or addition of manufacturer(s) of active substance	12/01/2000	22/02/2000		
I/0009	12_Minor change of manufacturing process of the active substance	19/10/1999	04/11/1999		
I/0008	13_Batch size of active substance	19/10/1999	04/11/1999		
I/0007	11_Change in or addition of manufacturer(s) of active substance	31/08/1999	14/09/1999		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	21/05/1999	07/09/1999	SmPC and PL	

I/0005	14_Change in specifications of active substance	06/07/1999	16/07/1999		
I/0002	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/0004	32_Change of imprints/bossing/markings on tablets/printing on capsules, incl. addition/change of inks	13/05/1999	08/07/1999	SmPC and PL	
I/0003	15_Minor changes in manufacture of the medicinal product	22/03/1999	16/06/1999		
I/0001	08_Change in the qualitative composition of immediate packaging material	01/04/1999	11/06/1999	SmPC	