EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clopidogrel ratiopharm GmbH

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
IAIN/0036	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2019		SmPC and PL	
IB/0035/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO	28/05/2019		SmPC and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	new additional data is required to be submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH				
IB/0034	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	13/04/2018	25/03/2019	SmPC and PL	
IB/0033/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	23/05/2017	16/06/2017	SmPC, Labelling and PL	

IB/0032/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	15/01/2016	02/06/2016	SmPC and PL	
IB/0031	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	27/05/2015	02/06/2016	SmPC and PL	
PSUSA/820/201311	Periodic Safety Update EU Single assessment - acetylsalicylic acid / clopidogrel, clopidogrel	10/07/2014	n/a		PRAC Recommendation - maintenance

R/0027	Renewal of the marketing authorisation.	20/03/2014	22/05/2014	PL	The CHMP recommended renewal for an unlimited period of time.
IB/0030/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	29/04/2014	13/04/2015	SmPC and PL	
II/0023/G	This was an application for a group of variations. - to introduce a new manufacturer of the active substance via the Active Substance Master File (ASMF) procedure and as a result - to change the storage conditions of the finished product B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the	23/01/2014	22/05/2014	SmPC, Labelling and PL	

	diluted/reconstituted product				
IB/0028	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	09/01/2014	22/05/2014	SmPC and PL	
IB/0024/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.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	09/12/2013	n/a		
IB/0026/G	This was an application for a group of variations. 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)	02/12/2013	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.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)				

IB/0022/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	14/11/2013	22/05/2014	SmPC and PL	
IA/0025	A.7 - Administrative change - Deletion of manufacturing sites	05/11/2013	n/a		
IB/0021/G	This was an application for a group of variations. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH	30/07/2013	22/05/2014	SmPC, Annex II, Labelling and PL	

IAIN/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/04/2013	n/a		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2012	22/05/2014	PL	
T/0018	Transfer of Marketing Authorisation	17/08/2012	17/09/2012	SmPC, Labelling and PL	
IAIN/0017	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	04/04/2012	n/a		
IB/0014	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH	22/07/2011	n/a	SmPC	To include information on the clopidogrel metabolism pathway, the role of CYP2C19 genetic polumorphism on clopidogrel variability of response and the potential interaction between clopidogrel and CYP2C19 inhibitors including some proton pump inhibitors. The MAH also took the oportunity to make align to align to the originator products. Furthermore the Marketing Authorisation numbers were seperated.
IA/0013	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/06/2011	n/a		

IB/0012	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH	29/04/2011	n/a	SmPC, Annex II and PL	To update the Summary of Product Characteristics (SmPC) and Package Leaflet 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). In addition, section 4.8 has been amended with minor details on the CURE study. Additional changes have been added to the SmPC and Package Leaflet in order to bring it in line with the revised QRD template (version 7.3) In addition, the deletion of DDPS number version and date was introduced in Annex IIB as requested by the EMA with the procedural announcement in October and November 2010. Minor linguistic changes have been introduced in the product information, to bring the product in line with the reference product.
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/01/2011	n/a	PL	
WS/0052	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To add a new active substance manufacturer. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	18/11/2010	18/11/2010		

	Introduction of a new manufacturer of the AS that is supported by an ASMF				
WS/0053/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. - To change the genotoxic impurities specifications of the active substance; - To replace the current analytical method for the determination of genotoxic impurities acid in the active substance and finished product with a new one; - To change the genotoxic impurities specifications of the finished product. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS 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.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside	21/10/2010	21/10/2010		

	the approved specifications limits range				
IB/0010	To include information on the clopidogrel metabolism pathway, the role of CYP2C19 genetic polumorphism on clopidogrel variability of response and the potential interaction between clopidogrel and CYP2C19 inhibitors including some proton pump inhibitors. The MAH also took the oportunity to make align to align to the originator products. Furthermore the Marketing Authorisation numbers were seperated. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data are submitted by the MAH	06/08/2010	n/a	SmPC, Labelling and PL	
A20/0009	Pursuant to Article 20 of Regulation (EC) No 726/2004 of 31 March 2004, the European Commission requested on 18 March 2010, the opinion of the CHMP on measures necessary to ensure the quality of the above mentioned medicinal product further to GMP deficiencies of the API manufacturing site Glochem Industries Ltd. (Unit II).	18/03/2010	29/03/2010		Please refer to the Assessment Report: Clopidogrel ratiopharm GmbH-H-1165-A20-09-Assessment Report-Article 20
II/0008	To register a revised version of the ASMF for clopidogrel besilate from the existing active substance manufacturer, introducing changes in the manufacturing process of the active substance.	21/01/2010	04/02/2010		

	Quality changes				
II/0007	To introduce a new active substance manufacturer. Quality changes	21/01/2010	04/02/2010		
IA/0006	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	14/10/2009	n/a		
IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	17/09/2009	n/a		
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	11/09/2009	n/a		
IB/0003	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	28/08/2009	28/08/2009	SmPC, Labelling and PL	
IA/0002	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	24/08/2009	n/a	Annex II and PL	