Cyanokit

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/0033/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.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	27/11/2018		Annex II 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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

	including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IB/0032	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/02/2018	n/a		
II/0031	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on renal disorders and to update the safety information on skin and subcutaneous tissue disorders, renal and urinary disorders following a safety signal on renal disorders and based on a safety review including review of clinical data, preclinical data, literature and cumulative review of renal disorders cases occurring after hydroxocobalamin administration. 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	20/07/2017	30/07/2018	SmPC and PL	Oxalate crystals have been observed in the urine of healthy volunteers given hydroxocobalamin. Cases of acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals present have been reported in patients treated with hydroxocobalamin following known or suspected cyanide poisoning. In some situations, hemodialysis was required to achieve recovery. Therefore, as a precaution, after Cyanokit administration, regular monitoring of renal function (including blood urea nitrogen and serum creatinine) should be performed until 7 days after drug onset. Most patients will experience a reversible red colouration of the skin and mucous membranes that can last up to 15 days after administration of Cyanokit. Chromaturia is also an undesirable effect observed following treatment with Cyanokit. All patients will show a dark red colouration of the urine quite marked during the first three days following administration. Urine colouration may last up to 35 days after administration of Cyanokit.
PSUSA/10228	Periodic Safety Update EU Single assessment -	06/07/2017	n/a		PRAC Recommendation - maintenance

/201611	hydroxocobalamin (only for products for chemical poisoning)				
IA/0029	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	09/03/2017	n/a		
IA/0028	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/01/2017	n/a		
IA/0027	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	16/12/2016	n/a		
IA/0026	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/11/2016	n/a		
IB/0025/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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	02/09/2015	n/a		

T/0024	Transfer of marketing authorisation from Merck Santé s.a.s to SERB. S.A. Transfer of Marketing Authorisation	03/06/2015	12/08/2015	SmPC, Labelling and PL	
II/0016/G	This was an application for a group of variations. This was an application for a group of variations. B.I.a.1.b - Addition of a manufacturing site responsible for manufacture and testing of the active substance, supported by an ASMF. B.III.1.a.3 - Submission of a new Ph. Eur. certificate of suitability for starting material from a new manufacturer. 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.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)	18/12/2014	n/a		
IG/0500	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	17/11/2014	n/a		

IB/0022	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/11/2014	22/06/2015	SmPC, Annex II, Labelling and PL	
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2014	22/06/2015	PL	
IG/0461	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	22/07/2014	n/a		
PSUSA/1690/ 201311	Periodic Safety Update EU Single assessment - hydroxocobalamin (centrally authorised product)	13/06/2014	n/a		PRAC Recommendation - maintenance
IA/0018/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	07/05/2014	n/a		
II/0014	Widen the specification of the pH of the reconstituted	24/10/2013	n/a		

	solution at release and end of shelf life. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
IG/0224	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2012	n/a		
R/0012	Renewal of the marketing authorisation.	24/05/2012	20/07/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the risk-benefit balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Cyanokit continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
IB/0010/G	This was an application for a group of variations. 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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process 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.z - Change in the specification parameters and/or limits of an AS, starting	05/09/2011	n/a		

	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.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.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.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.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.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.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) 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) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IG/0076/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	01/07/2011	n/a		

	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				
IB/0009	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	18/04/2011	n/a	SmPC, Annex II and PL	Following the line extension for Cyanokit 5 g (procedure number: EMEA/H/000806/X/0007), Merck Santé undertakes to harmonise the Product Information for Cyanokit 2.5 g and Cyanokit 5 g. Update of PI for Cyanokit 5 g with the MA number in section 8 of the SmPC and sections 12 of the Labelling. Also, a correction has been made in section 10 of the SmPC ('medicinal' missing). Annex II has been updated according to the October 2010 CHMP Monthly report: Deletion of version number of the Detailed Description of the Pharmacovigilance System from Annex II.B.
IA/0008	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	06/01/2011	n/a		
X/0007	Additional presentation of 5 g hydroxocobalamin per vial Annex I_2.(c) Change or addition of a new strength/potency	22/07/2010	07/10/2010	SmPC, Annex II, Labelling and PL	
II/0006	Update of the Detailed Description of the Pharmacovigilance system (DDPS).	22/04/2010	26/05/2010	SmPC and Annex II	With this variation the MAH submitted a new version of the DDPS (core version 9.0) in accordance with the current Pharmacovigilance guideline. After assessing the

	Update of DDPS (Pharmacovigilance)				documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
IA/0005	IA_09_Deletion of manufacturing site	16/11/2009	n/a		
IA/0004	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/11/2009	n/a		
IA/0003	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	16/11/2009	n/a		
II/0001	Update to sections 4.6 and 5.3 of Summary of Product Characteristics to include results of reproduction toxicity studies performed in rats and rabbits. The package leaflet section 2 is amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	16/01/2009	SmPC, Annex II and PL	At the time of the marketing authorization application of Cyanokit, only limited data were available to evaluate the embryo-fetotoxic potential of hydroxocobalamin. The applicant agreed to perform new studies in line with current guidelines and these studies showed that hydroxocobalamin administered daily throughout organogenesis was teratogenic in rats and rabbits. The product information and the Risk Management Plan have been amended to reflect this information. Overall, the benefit-risk ratio of Cyanokit is still positive, and considering the potentially life-threatening situations in which hydroxocobalamin can be administered the updating of the SCP and package leaflet is sufficient as risk minimization measure. Nevertheless, the CHMP considered that a follow-up of any exposed pregnancies is needed. The routine pharmacovigilance activities now include the sending to the reporting physicians of 2 follow-up pregnancy forms, one sent after initial report and one after the expected date

					of delivery.
IB/0002	The Marketing Authorisation Holder applied to tighten the finished product specification. IB_37_a_Change in the specification of the finished product - tightening of specification limits	16/01/2009	n/a		