Cystadane

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
IB/0038	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/07/2021	n/a		
IAIN/0037	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is	30/04/2021	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).

	not an integrated part of the primary packaging - Device with CE marking				
IA/0036	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	29/01/2021	n/a		
PSUSA/390/202002	Periodic Safety Update EU Single assessment - betaine anhydrous (centrally authorised product only)	01/10/2020	n/a		PRAC Recommendation - maintenance
IG/1085/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/05/2019	23/04/2020	SmPC, Annex II, Labelling and PL	
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2019	23/04/2020	PL	
IAIN/0032	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	11/10/2018	n/a		

	site				
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2018	23/04/2020	Labelling and PL	
IB/0030/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.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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	25/10/2017	n/a		
PSUSA/390/201702	Periodic Safety Update EU Single assessment - betaine anhydrous (centrally authorised product only)	28/09/2017	n/a		PRAC Recommendation - maintenance
II/0029	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	14/09/2017	n/a		
IG/0773/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a	14/02/2017		Annex II and PL	

	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 including batch control/testing				
IA/0026	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/01/2017	n/a		
PSUSA/390/201602	Periodic Safety Update EU Single assessment - betaine anhydrous (centrally authorised product only)	13/10/2016	08/12/2016	SmPC, Annex II, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/390/201602.
R/0024	Renewal of the marketing authorisation.	15/09/2016	21/11/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Cystadane in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0025	Submission of the final report of Cystadane Surveillance Protocol (in collaboration with E-HOD) registry: to obtain long-term clinical and safety information in patients with cystathionine betasynthase (CBS), 5, 10-Methylenetetrahydrofolate reductase (MTHFR) or cobalamin cofactor metabolism (Cbl) and treated with Cystadane. C.I.13 - Other variations not specifically covered	15/09/2016	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/0686	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/05/2016	n/a		
PSUSA/390/201502	Periodic Safety Update EU Single assessment - betaine anhydrous (centrally authorised product only)	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/390/201502.
IA/0021	A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS	30/07/2015	n/a		
IG/0535	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	06/03/2015	n/a		
IB/0018	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	22/12/2014	n/a		
IB/0017	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	07/11/2014	n/a		
IA/0016	A.7 - Administrative change - Deletion of manufacturing sites	23/10/2014	n/a		

PSUV/0015	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0014	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	14/05/2014	n/a		
IA/0013/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	12/03/2014	n/a		
IAIN/0012/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.e.7.b - Change in supplier of packaging	28/02/2014	n/a		

	components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IG/0393	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	20/12/2013	n/a		
IG/0392	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	19/12/2013	06/02/2014	Annex II and PL	
II/0008	The MAH proposed to delete the following condition from the Annex II: Submission of an updated RMP which includes description and timelines of the re-started ROCH registry and of the new E-IMD registry. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/02/2013	06/02/2014	Annex II	Following the assessment of an updated RMP which included: - Description and timelines of the re-started ROCH registry - Description and timelines of the new E-IMD registry the CHMP agreed that the above mentioned obligations have been fulfilled, and therefore recommends their deletion from the Annex II. Both study protocols were found acceptable and minor recommendations were made for an updated RMP and updated study protocols.
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/09/2012	06/02/2014	Labelling and PL	
R/0006	Renewal of the marketing authorisation.	15/12/2011	13/02/2012	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Cystadane remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

					At licensing time the MAH committed to set up a registry (ROCH: Registry for Cystadane - Homocystinuria) to collect more data on safety and efficacy of Cystadane. However, from this registry only limited additional data was gathered. Therefore this registry was stopped to be replaced by another database (E-IMD: European Intoxication type Metabolic Disorders). As from neither this new registry nor the (restarted) old registry any additional data are available yet, the original commitment has been extended, in order to receive and analyse enough data from both registries for granting a renewal with unlimited validity. Therefore, based upon the safety profile of Cystadane, which requires the submission of 1- yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IG/0111	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	27/09/2011	n/a	Annex II	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2011	n/a	PL	
IB/0004	IB_42_a_02_Change in shelf-life of finished product - after first opening	31/07/2008	n/a	SmPC, Labelling and PL	
IB/0003	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	23/11/2007	n/a	SmPC and PL	

IA/0002	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	09/10/2007	n/a	SmPC, Annex II, Labelling and PL	
IA/0001	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	02/05/2007	n/a		