Siklos

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
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2024		PL	
II/0061	Update of section 4.5 of the SmPC in order to update information regarding the interference with certain Continuous Glucose Monitoring (CGM) sensors, based	27/06/2024		SmPC and PL	SmPC new text Section 4.5 New text is added Interference with Continuous Glucose Monitoring systems

[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).

	on a literature review. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Hydroxycarbamide may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems and may lead to hypoglycemia if sensor glucose results are relied upon to dose insulin. For more information, please refer to the Summary of Product Characteristics.
PSUSA/1692/ 202306	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	11/01/2024	n/a		PRAC Recommendation - maintenance
IA/0060	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	22/12/2023	n/a		
IA/0059	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	30/11/2023	n/a		
T/0057	Transfer of Marketing Authorisation	30/06/2023	26/07/2023	SmPC, Labelling and PL	
IA/0056	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	28/04/2023	n/a		
IAIN/0055	A.1 - Administrative change - Change in the name	27/01/2023	04/04/2023	SmPC,	

	and/or address of the MAH			Labelling and PL	
PSUSA/1692/ 202206	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	12/01/2023	n/a		PRAC Recommendation - maintenance
IA/0053	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	05/09/2022	n/a		
II/0051	C.I.3.b Update of section 5.1 of the SmPC with the available paediatric data from the studies NOHARM and Escort HU according to the PAM-Leg 34. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH	22/04/2022	04/04/2023	SmPC	SmPC new text The MAH has added text section 5.1 to summarize the paediatric data in children < 2 year old from the two randomised placebo-controlled clinical trials (BABY HUG and NOHARM) and subsequent cohort studies providing supporting efficacy and safety data (including data on the maximum tolerated dose). For more information, please refer to the Summary of Product Characteristics.
PSUSA/1692/ 202106	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	13/01/2022	n/a		PRAC Recommendation - maintenance
IB/0049	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	11/11/2021	16/12/2021	SmPC, Labelling and PL	

II/0047	Update of sections 4.8 and 5.1 of the SmPC to include relevant information in paediatric patients based on results from the uncontrolled study ESCORT HU. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Croatia in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.2.and some minor editorial changes are included. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/07/2021	16/12/2021	SmPC and PL	Please refer to Scientific Discussion 'Siklos-H-C-000689-II-0047'
PSUSA/1692/ 202006	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	28/01/2021	28/01/2021	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1692/202006.
II/0045	Update of sections 4.2, 4.4, 4.5, 4.6, 4.8, 4.9 and 5.1 of the SmPC as a consequence of the final study results of the non-interventional cohort study ESCORT-HU (European Sickle Cell Disease Cohort – Hydroxyurea) and harmonisation with other HU products. In addition, Annex II is amended to revise the information on the physician information pack and to add that pharmacists should receive targeted communication on the risk of medication error due to the confusion between the two strengths where both are available. The PIL is updated in accordance with the changes to the SmPC. The RMP (v. 20 revision 1) is updated to reflect the finalisation of the ESCORT-HU study and modifications on the risk minimisation	09/07/2020	27/05/2021	SmPC, Annex II and PL	SmPC new text: Sections 4.2 and 4.4: Additional changes include modification of the neutrophil count threshold requiring modification of treatment, modification of the frequency of blood count monitoring at initiation of treatment and removal of recommendation on continuous follow-up of the growth of treated children and adolescents. Section 4.6 The figures for cases of pregnancy were updated to reflect the data collected in ESCORT-HU without modifying the recommendation. Section 4.8 The figures for cases of undesirable effects were updated to

	measures. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reflect the data collected in ESCORT-HU without modifying the recommendation. Section 4.9 The figures for cases of overdose were updated to reflect the data collected in ESCORT-HU without modifying the recommendation. For more information, please refer to the Summary of Product Characteristics.
IAIN/0046	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	29/05/2020	27/05/2021	Annex II and PL	
PSUSA/1692/ 201906	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	16/01/2020	n/a		PRAC Recommendation - maintenance
IA/0044/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	20/11/2019	n/a		

N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2019	27/05/2021	PL	
IA/0041/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/03/2019	n/a		

PSUSA/1692/201806	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	17/01/2019	n/a		PRAC Recommendation - maintenance
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2018	27/05/2021	PL	
IA/0038	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/05/2018	02/08/2018	SmPC and PL	
IB/0036	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	02/03/2018	n/a		
PSUSA/1692/201706	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	11/01/2018	n/a		PRAC Recommendation - maintenance
IB/0035/G	This was an application for a group of variations. B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings B.II.a.1.b - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in scoring/break lines intended to divide into equal doses B.II.a.2.a - Change in the shape or dimensions of the	17/11/2017	02/08/2018	SmPC, Labelling and PL	

	pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IAIN/0033	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	15/09/2017	02/08/2018	SmPC and PL	
IAIN/0032/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	04/08/2017	02/08/2018	SmPC, Labelling and PL	
II/0031/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological	18/05/2017	n/a		

	product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
R/0030	Renewal of the marketing authorisation.	23/02/2017	24/04/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Siklos in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation, with unlimited validity.
PSUSA/1692/ 201606	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	12/01/2017	n/a		PRAC Recommendation - maintenance
PSUSA/1692/ 201506	Periodic Safety Update EU Single assessment - hydroxycarbamide (for centrally authorised product only)	14/01/2016	n/a		PRAC Recommendation - maintenance
IAIN/0026	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	11/08/2015	n/a		
PSUV/0025	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
N/0024	Minor change in labelling or package leaflet not	14/07/2014	24/04/2017	PL	

	connected with the SPC (Art. 61.3 Notification)				
PSUV/0020	Periodic Safety Update	20/02/2014	23/04/2014	SmPC and PL	The frequency of azoospermia and oligospermia in the SmPC/PL should be changed from "very rare" to "very common". The proposed changes to sections 4.6 and 4.8 of the SmPC and the leaflet are detailed in Annex 1 of the appended assessment report. However, a further update to the SmPC might be needed, if final study results become available in 2014.
IB/0023	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	25/02/2014	n/a		
IAIN/0022	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities	20/02/2014	n/a		
IA/0021/G	This was an application for a group of variations. B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	19/02/2014	n/a		

	relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
IB/0019	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	12/10/2012	23/04/2014	SmPC	
R/0018	Renewal of the marketing authorisation.	19/04/2012	28/06/2012	SmPC	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Siklos continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Siklos, subject to the conditions and obligations as laid down in Annex II to the Opinion. The CHMP recommends that the renewal be granted for a further 5 years. The MAH is requested to submit yearly PSURs unless otherwise specified by the CHMP.
IA/0017/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	26/01/2012	10/05/2012	Annex II and PL	

	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IB/0015	- to replace the manufacturing site for the finished product 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	07/06/2011	n/a		
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2011	n/a	Labelling and PL	The MAH applied to delete some not legally required information in Annex IIIA, in order to accommodate the space problem raised by the trilingual labels. In addition,

					the Braille mentioned in the outer carton will be embossed in lower cases. Finally, additional minor linguistic changes have been proposed for DE, EL, ES, FR, MT, NL, PT and SK languages.
IA/0016/G	This was an application for a group of variations. B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings 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 site 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 currently approved batch size	11/05/2011	n/a	SmPC and PL	
X/0005	Annex I_2.(c) Change or addition of a new strength/potency	18/11/2010	28/02/2011	SmPC, Labelling and PL	
IA/0013	B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	19/11/2010	n/a	Annex II and PL	
IA/0012/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur.	26/10/2010	n/a		

	Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
IA/0009	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	09/09/2010	n/a		
IB/0008/G	This was an application for a group of variations. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product 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 site	21/07/2010	n/a	SmPC, Labelling and PL	
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/05/2010	n/a	PL	

IA/0006	IA_01_Change in the name and/or address of the marketing authorisation holder	27/01/2010	n/a	SmPC, Labelling and PL	
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	05/05/2009	n/a		
IA/0002	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	05/05/2009	n/a		
II/0001	Update of Detailed Description of the Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)	30/05/2008	07/07/2008	SmPC, Annex II and Labelling	The MAH applied to update the Detailed Description of the Pharmacovigilance System further to a change in the management of the pharmacovigilance and of the Qualified Person for Pharmacovigilance (QPPV). Consequently, a new version of the risk Management plan has been issued to be signed by the new QPPV. Annex II has been updated using standard text and including the new version numbers of these documents. The marketing authorisation number was included in Annexes I and IIIA, as well as the date of first authorisation in Annex I.