RAVICTI

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/0049/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.2.c.2 - Change to importer, batch release	17/02/2025		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).

	arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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				
PSUSA/10454 /202401	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	03/10/2024	n/a		PRAC Recommendation - maintenance
IB/0047	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)	13/02/2024	23/01/2025	SmPC	
IA/0046/G	This was an application for a group of variations. 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.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	24/07/2023	n/a		
IA/0045	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	10/02/2023	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0044	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/02/2023	n/a		
IAIN/0043	A.1 - Administrative change - Change in the name and/or address of the MAH	19/10/2022	04/10/2023	SmPC, Labelling and PL	
IB/0040/G	This was an application for a group of variations. B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - 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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	09/03/2022	n/a		
IA/0042/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	08/02/2022	n/a		
IB/0041	B.II.d.1.z - Change in the specification parameters	07/02/2022	n/a		

	and/or limits of the finished product - Other variation				
II/0038/G	This was an application for a group of variations. Group of variations consisting of: - Submission of the final study report, HPN-100-014 non-interventional registry study "Long-Term Registry of Patients with Urea Cycle Disorders (UCDs) conducted in the US". - An update to the RMP (version 7.3) submitted and agreed to remove the important potential risk of carcinogenicity. The update to the RMP is based on the review of new and available data including the study report for HPN-100-014 and a new toxicological expert examination of pre-clinical carcinogenicity findings as well as a cumulative review of literature and post marketing data. In accordance with the proposed changes to the RMP, the requested waiving of the Annex II imposed condition related to the non-interventional post authorisation safety study (PASS), "European Post-Authorization Registry for RAVICTI® (glycerol phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)" is agreed but this PASS agreed to be discontinued is retained in the RMP as a category 3 PASS until final PASS results submission. The SmPC and Package Leaflet have been updated to delete the information on additional monitoring (including the black triangle).	16/12/2021	05/05/2022	SmPC, Annex II and PL	Following submission of new data, the CHMP agreed that the uncertainties to be evaluated in the imposed non-interventional post-authorisation safety study (PASS) for Ravicti have been adequately addressed. For more information, please refer to the Summary of Product Characteristics.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/10454 /202101	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	02/09/2021	n/a		PRAC Recommendation - maintenance
IB/0037/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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 B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site A.7 - Administrative change - Deletion of manufacturing sites	28/04/2021	05/05/2022	SmPC, Annex II, Labelling and PL	

IB/0036/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	13/01/2021	n/a		
PSUSA/10454 /202001	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	03/09/2020	n/a		PRAC Recommendation - maintenance
R/0034	Renewal of the marketing authorisation.	25/06/2020	25/08/2020	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 RAVICTI in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IAIN/0033	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	17/12/2019	n/a		
IB/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/09/2019	n/a		
IAIN/0032/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	18/09/2019	25/08/2020	Annex II and PL	

	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				
PSUSA/10454 /201901	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0031	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	21/08/2019	25/08/2020	SmPC, Labelling and PL	
IB/0030	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	19/08/2019	n/a		
IA/0029/G	This was an application for a group of variations. 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 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)	28/06/2019	n/a		
T/0026	Transfer of Marketing Authorisation	03/05/2019	06/06/2019	SmPC,	

				Labelling and PL	
IAIN/0025/G	This was an application for a group of variations. 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 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	03/05/2019	06/06/2019	Annex II and PL	
II/0024	B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions	31/01/2019	n/a		
II/0019	Extension of indication to include in the authorised indication the new paediatric population from 0 to 2 months for RAVICTI based on the final results from study HPN-100-009, an Open Label Study of the Safety, Efficacy and Pharmacokinetics of Glycerol Phenylbutyrate in Pediatric Subjects under Two Years of Age with Urea Cycle Disorders (UCDs); as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) -	15/11/2018	18/12/2018	SmPC and PL	Please refer to Scientific Discussion 'Ravicti-H-C-3822-II-19'

	Addition of a new therapeutic indication or modification of an approved one				
II/0023	Update of section 5.1 of the SmPC in order to update the efficacy and safety information based on study HPN-100-011, a non randomised, open-label safety extension study on the long term use of HPN-100 in Urea Cycle Disorders. In addition, QRD changes are made in the labelling related to the addition of section 17 and 18 and in line with the QRD template version 10.0 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	18/10/2018	18/12/2018	SmPC and Labelling	An open-label, long-term study (Study 5) was conducted to assess ammonia control in paediatric patients with UCD. The study enrolled a total of 45 paediatric patients between the ages of 1 and 17 years with UCD who had completed Study 2 and the safety extensions of Studies 3 and 4. The length of study participation ranged from 0.2 to 5.9 years. Venous ammonia levels were monitored at a minimum of every 6 months. Mean venous ammonia values in paediatric patients in Study 5 were within normal limits during long-term (24 months) treatment with glycerol phenylbutyrate (range: 15-25 micromol/L). Of the 45 paediatric patients participating in the open-label treatment with glycerol phenylbutyrate, 11 patients (24%) reported a total of 22 hyperammonemic crises.
PSUSA/10454 /201711	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0021	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/05/2018	18/12/2018	SmPC and PL	
IA/0020/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) B.I.b.2.a - Change in test procedure for AS or	11/04/2018	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0017	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	27/02/2018	12/04/2018	SmPC, Labelling and PL	
PSUSA/10454 /201705	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	11/01/2018	n/a		PRAC Recommendation - maintenance
IA/0016	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	19/10/2017	n/a		
IA/0015/G	This was an application for a group of variations. A.z - Administrative change - Other variation 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/09/2017	n/a		

	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products				
IB/0013	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/08/2017	n/a		
IB/0012/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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	20/06/2017	n/a		
PSUSA/10454 /201611	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	09/06/2017	n/a		PRAC Recommendation - maintenance
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/05/2017	12/04/2018	Labelling	
IAIN/0010/G	This was an application for a group of variations. 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	03/05/2017	12/04/2018	Annex II and PL	

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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.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 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				
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/03/2017	12/04/2018	Labelling and PL	
PSUSA/10454 /201605	Periodic Safety Update EU Single assessment - glycerol phenylbutyrate	12/01/2017	n/a		PRAC Recommendation - maintenance
IB/0007	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	11/01/2017	16/02/2017	SmPC	
II/0004	Update of SmPC section 4.5 based on the final clinical study report for the Drug/Drug Interaction study HPN-100-027.	12/05/2016	16/02/2017	SmPC	The effects of glycerol phenylbutyrate on cytochrome P450 (CYP) 2C9 isoenzyme and potential for interaction with celecoxib has been studied in humans with no evidence of

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				an interaction observed.
IB/0005	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	31/03/2016	n/a		
IB/0003	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/03/2016	16/02/2017	SmPC, Annex II, Labelling and PL	
IAIN/0002	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	01/03/2016	n/a		
T/0001	Transfer of Marketing Authorisation	04/02/2016	24/02/2016	SmPC, Labelling and PL	