Hepcludex

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/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/02/2025	n/a		
II/0031	Extension of indication to include treatment of chronic hepatitis delta virus (HDV) infection in	17/10/2024	25/11/2024	SmPC and PL	Please refer to Scientific Discussion 'Hepcludex-H-C-00004854-II-Var.0031'

[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).

	paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease for Hepcludex, based on a modelling and simulation study and an extrapolation study to evaluate the use of bulevirtide for the treatment of chronic hepatitis D infection in children from 3 to less than 18 years of age. As a consequence, sections 4.1, 4.2, 5.1,5.2 and 6.6 of the SmPC are updated. The Package Leaflet has been updated accordingly. Version 4.1 of the RMP has also been adopted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0034	Update of section 4.8 of the SmPC in order to update safety information based on final results from study MYR204 listed as a category 3 study in the RMP; this is a multicenter, open-label, randomized Phase 2b clinical study to assess efficacy and safety of bulevirtide in combination with pegylated interferon alfa-2a in patients with chronic hepatitis delta. The RMP version 6.0 has also been adopted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/10/2024		SmPC	Bulevirtide treatment alone or in combination with Peg-IFNα was in general well tolerated in participants through 96 weeks of bulevirtide treatment and during 48 weeks of post-treatment follow-up in Study MYR204. The SmPC Section 4.8 has been updated to indicate that there are no data available on the long-term impact (> 96 weeks) of bile salt increase induced by bulevirtide. For more information, please refer to the Summary of Product Characteristics.

IA/0035/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.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) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/09/2024	n/a		
PSUSA/10873 /202401	Periodic Safety Update EU Single assessment - bulevirtide	05/09/2024	n/a		PRAC Recommendation - maintenance
IB/0033/G	This was an application for a group of variations. 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.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.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	14/06/2024	n/a		

PSUSA/10873 /202307	Periodic Safety Update EU Single assessment - bulevirtide	07/03/2024	n/a		PRAC Recommendation - maintenance
IA/0028	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	09/10/2023	n/a		
IA/0029/G	This was an application for a group of variations. 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	05/10/2023	n/a		
PSUSA/10873 /202301	Periodic Safety Update EU Single assessment - bulevirtide	31/08/2023	n/a		PRAC Recommendation - maintenance
II/0019	Update of sections 4.8 and 5.1 of the SmPC in order to update the list of adverse drug reactions (ADRs) and efficacy information based on interim results from study MYR301 listed as a Specific Obligation in the Annex II of the Product Information; this is a Multicenter, Open-label, Randomized Phase III Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta. As a result of this variation, the SmPC, Annex II and	26/04/2023	18/07/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Hepcludex H-C-004854-II-0019'.

	PL are also updated to reflect the completion of the specific obligation and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligations. In addition, the MAH took the opportunity to implement editorial changes in the SmPC. The Package Leaflet is updated accordingly. Version 4.0 of the RMP has also been approved (Study MYR301 was reclassified from a Category 2 to a Category 3 study). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0024	Renewal of the marketing authorisation.	26/04/2023	17/07/2023		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated. Furthermore, the CHMP considered that the Specific Obligation has been fulfilled, therefore there are no remaining grounds for the marketing authorisation to remain conditional and therefore recommends the granting of a standard marketing authorisation not subject to Specific Obligations for Hepcludex.
IA/0027/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	16/06/2023	n/a		

	Replacement/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				
II/0023/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	30/03/2023	17/07/2023	SmPC, Annex II and PL	The SmPC section 6.5 and Annex II has been updated as follows: SmPC section 6.5: The quality of the rubber closure is amended with regards to the alternative chlorobutyl rubber stopper. Annex II: • Section A has been revised to delete the batch release site Lyocontract GmbH., Germany • Section C.1 has been amended to declare "The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months." The revision is an editorial explanatory note only. The PL has been updated accordingly.

	Replacement/addition of a site where batch control/testing takes place B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products				
PSUSA/10873 /202207	Periodic Safety Update EU Single assessment - bulevirtide	16/03/2023	n/a		PRAC Recommendation - maintenance
IA/0025	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/03/2023	n/a		
IB/0022	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/12/2022	n/a		
IA/0021/G	This was an application for a group of variations. 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	25/10/2022	n/a		

	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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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				
II/0014/G	This was an application for a group of variations. 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.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.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	15/09/2022	n/a		

IB/0018	B.II.b.z - Change in manufacture of the Finished Product - Other variation	08/09/2022	n/a		
PSUSA/10873 /202201	Periodic Safety Update EU Single assessment - bulevirtide	01/09/2022	n/a		PRAC Recommendation - maintenance
II/0011	Update of section 4.4 of the SmPC in order to move the warnings for the ADRs 'Increase of bile salts' and 'Administration site reactions' to section 4.8 of the SmPC as additional describing information to the listed PTs , together with the addition of a new ADR: hypersensitivity reactions (including anaphylactic reaction). Further to a safety review based on pooled data from clinical trials and post-marketing experience, editing of existing ADRs in Section 4.8 was also carried out. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring it in line with the EU QRD template v10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	07/07/2022	17/07/2023	SmPC and PL	Following a safety review based on pooled data from clinical trials and post-marketing experience, Section 4.4 and 4.8 of the SmPC have been updated to move the warnings for the ADRs 'Increase of bile salts' and 'Administration site reactions' from Section 4.4 to Section 4.8 of the SmPC. Several PTs in different SOCs from the ADR list in section 4.8. of the SmPC were also updated. Additionally, a new ADR: hypersensitivity reactions (including anaphylactic reaction) was included, together with descriptive text of "eosinophilia" and the update of the frequency of the ADR headache from common to very common, based on the frequency observed in the clinical trial programme. For more information, please refer to the Summary of Product Characteristics.
R/0013	Renewal of the marketing authorisation.	22/04/2022	21/06/2022		
IB/0017/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	02/06/2022	n/a		

	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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				
IA/0016/G	This was an application for a group of variations. 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.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.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	20/04/2022	n/a		
II/0012	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	07/04/2022	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/10873 /202107	Periodic Safety Update EU Single assessment - bulevirtide	10/03/2022	n/a		PRAC Recommendation - maintenance
II/0009/G	This was an application for a group of variations. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	27/01/2022	n/a		
IAIN/0010/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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.2.c.1 - Change to importer, batch release	02/12/2021	21/06/2022	Annex II and PL	

	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				
T/0007	Transfer of Marketing Authorisation	06/08/2021	22/09/2021	SmPC, Labelling and PL	
PSUSA/10873 /202101	Periodic Safety Update EU Single assessment - bulevirtide	02/09/2021	n/a		PRAC Recommendation - maintenance
R/0003	Renewal of the marketing authorisation.	24/06/2021	02/08/2021	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Hepcludex, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. During the annual renewal procedure, it was brought to EMA and the CHMP and the PRAC Rapporteur's attention by the MAH that there was a discrepancy between the PI (Annex II.E) and the RMP referring to the classification category of the additional pharmacovigilance activities. The studies' classification was adequately reflected in the RMP, but not in the PI (Annex II.E) in the list of specific obligations. Therefore, amendments to the list of specific obligations are required, since only the MYR301 study should be classified as category 2 and therefore subject to specific obligation listed in the PI (Annex II.E). As

					requested in the RfSI the MAH has corrected the Annex II.E to include only MYR301 study as Specific Obligation. In addition, milestones of the MYR301 study and MYR-HDV registry have been updated in the RMP version 1.1 dated 17 June 2021. The MAH has also updated the expected completion dates for the studies and further aligned the RMP with the GVP Module V guidance as requested by EMA.
IB/0006/G	This was an application for a group of variations. 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) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/06/2021	02/08/2021	SmPC, Labelling and PL	
IA/0002	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	05/02/2021	n/a		
IB/0001	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)	05/10/2020	02/08/2021	SmPC	