CRYSVITA

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/0038	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	27/02/2024		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).

II/0035/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.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is	30/11/2023		SmPC, Labelling and PL	

	an integrated part of the primary packaging				
IB/0037	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	17/11/2023	n/a		
PSUSA/10669 /202302	Periodic Safety Update EU Single assessment - burosumab	28/09/2023	n/a		PRAC Recommendation - maintenance
IAIN/0036	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	06/07/2023		SmPC and PL	
PSUSA/10669 /202208	Periodic Safety Update EU Single assessment - burosumab	16/03/2023	n/a		PRAC Recommendation - maintenance
R/0031	Renewal of the marketing authorisation.	13/10/2022	13/10/2022		The Commission Decision for II/0028 (see below) was issued on 21/09/2022. As the outcome of that procedure concluded with the granting of a MAH no longer subject to Specific Obligations for Crysvita, there was no longer any regulatory need to continue with the ongoing renewal procedure R/0031 after the date of that Commission Decision. Hence, the procedure for R/0031 was stopped and as a consequence did not proceed to a CHMP opinion and Commission Decision. The dates 13/10/2022 and 13/10/2022 to the left are arbitrarily chosen and do not correspond with any actual regulatory outcome.

PSUSA/10669 /202202	Periodic Safety Update EU Single assessment - burosumab	29/09/2022	n/a		PRAC Recommendation - maintenance
II/0028	Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of the adverse drug reactions, to split immunogenicity data into paediatric and adult populations and to update clinical efficacy in paediatric patients, upon request by the CHMP following the assessment of PAM procedures P46/006 and P46/007 and type II variations II/04 and II/10/G, based on the final results from studies UX023-CL201, UX023-CL205 and UX023-CL301. The Package Leaflet was updated accordingly. As a consequence of the provision of the final CSR for study UX023-CL205, the last remaining specific obligation was deleted from the Annex II. This was an open-label, phase 2 study undertaken to assess the safety, pharmacodynamics, and efficacy of KRN23 in paediatric patients between 1 and 4 years old with X-linked Hypophosphataemia (XLH). With the fulfilment of this specific obligation the MAH is requesting for the Crysvita MA to no longer be subject to specific obligations. The RMP version 5.0 was agreed. 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	21/07/2022	21/09/2022	SmPC, Annex II, Labelling and PL	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, as all Specific Obligations have been fulfilled, there are no remaining grounds for the marketing authorisations to remain conditional and therefore recommends the granting of the MA no longer subject to Specific Obligations for Crysvita. For more information, please refer to the Summary of Product Characteristics. Please refer to Scientific Discussion ‘Crysvita-H-C-4275-II-28’

IB/0032	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	15/09/2022	n/a		
II/0023	Extension of indication to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in children and adolescents aged 1 to 17 years and in adults, based on data from two ongoing open-label clinical studies, UX023T-CL201 and KRN23-002, in adults with TIO (144-week data and 88-week data are available, respectively). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. An updated RMP version 6.0 was agreed during the procedure. The MAH also applied for one additional year of market protection. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/06/2022	25/07/2022	SmPC and PL	Please refer to Scientific Discussion 'Crysvita-H-C-4275-II-23'
IA/0030	A.7 - Administrative change - Deletion of manufacturing sites	16/05/2022	n/a		
R/0026	Renewal of the marketing authorisation.	14/10/2021	06/01/2022		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 CRYSVITA, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IA/0027/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	03/12/2021	25/07/2022	Annex II and PL	
PSUSA/10669 /202102	Periodic Safety Update EU Single assessment - burosumab	30/09/2021	n/a		PRAC Recommendation - maintenance
IB/0024	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	10/05/2021	n/a		
II/0021	Update of section 4.2 of the SmPC in order to modify administration instructions to include the option of self/carer-administration based on results from two Phase 3 interventional clinical safety and efficacy studies; Study KRN23-003 in paediatric patients (final study report) and Study KRN23-004 in adult patients (interim report). The Package Leaflet has	06/05/2021	06/01/2022	SmPC, Labelling and PL	For some patients, self/carer-administration may be suitable. Once no immediate dose modifications are anticipated, the administration can be performed by an individual who has been trained in injection techniques. The first self-administered dose after drug initiation or dose change should be conducted under the supervision of a healthcare professional. Clinical monitoring of the patient,

	been updated accordingly and a new section with instructions for use has been added at the end. In addition, the MAH took the opportunity to implement editorial changes in the SmPC, labelling and Package Leaflet. The updated RMP version 3.1 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				including monitoring of phosphate levels, must continue as required. A detailed 'Instructions for Use' section intended for the patient is provided at the end of the Package Leaflet. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10669 /202008	Periodic Safety Update EU Single assessment - burosumab	11/03/2021	n/a		PRAC Recommendation - maintenance
II/0017	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	18/02/2021	n/a		
IB/0022	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	15/01/2021	n/a		
R/0019	Renewal of the marketing authorisation.	15/10/2020	11/01/2021		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 CRYSVITA, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10669 /202002	Periodic Safety Update EU Single assessment - burosumab	01/10/2020	n/a		PRAC Recommendation - maintenance
II/0010/G	This was an application for a group of variations. Extension of Indication to include treatment of adults with X-linked hypophosphataemia (XLH), and modification of the currently approved indication in children and adolescents, by removing the qualification 'with growing skeletons', in order to include treatment in children and adolescents with closed epiphyseal growth plates. The application provides new week-48 data from Study UX023-CL304; a randomized, double-blind, placebo-controlled, phase 3 study with open-label extension to assess the efficacy and safety of KRN23 in adults with XLH. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated and the Package Leaflet has been updated in accordance. Furthermore, the annexes are brought in line with the latest QRD template version 10.1. The updated RMP version 2.1 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/07/2020	30/09/2020	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Crysvita-H-C-4275-II-10-G'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0018	Update of section 4.8 of the SmPC to include the new ADR 'blood phosphorous increased', which includes the terms blood phosphorus increased and hyperphosphataemia, with a frequency of 'not known' based on post-marketing data. In addition, the MAH took the opportunity to implement some editorial changes in SmPC section 4.8 and to include an age qualifier for the paediatric population (>1 year of age) for clarity. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2020	11/01/2021	SmPC and PL	n/a
IA/0015	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	11/05/2020	n/a		
PSUSA/10669 /201908	Periodic Safety Update EU Single assessment - burosumab	12/03/2020	n/a		PRAC Recommendation - maintenance
II/0007/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	20/02/2020	30/09/2020	SmPC	

	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol				
R/0009	Renewal of the marketing authorisation.	17/10/2019	16/12/2019		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 CRYSVITA, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0004	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC, to reflect the results of Study UX023-CL301, a phase III study undertaken to further assess the efficacy, safety and pharmacodynamics in paediatric patients aged 1-12 years with X-linked Hypophosphataemia (XLH). The provision of the final CSR addresses Specific Obligation 2 (ANX 002). The Package Leaflet and Annex II have been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC to increase readability. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/10/2019	16/12/2019	SmPC and PL	The submission of the results of study UX23-CL301 confirms the results from the paediatric phase 2-studies, the safety profile being similar and no new safety issues being identified. The SmPC section 4.2 was updated in terms of the recommended starting dose. Section 4.3 and other several sections of the SmPC clarify that it is the active form of vitamin-D that is contraindicated. The summary of the safety profile in section 4.8 was also updated to reflect the adverse events confirmed during the clinical study and section 5.1 is now reflecting the data from the submitted Phase 3 study. The pharmacokinetic data support the change in section 5.2 that following multiple dose administration to paediatric subjects, a plateau is reached for serum concentration of burosumab by 8 weeks after initiation of treatment. For more information, please refer to the Summary of Product

					Characteristics.
IAIN/0014/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 including batch control/testing	27/11/2019	30/09/2020	Annex II and PL	
IA/0012/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.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)	20/11/2019	30/09/2020	Annex II	
IAIN/0011	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing	31/10/2019	30/09/2020	Annex II	

	authorisation, including the RMP - Implementation of wording agreed by the competent authority				
PSUSA/10669 /201902	Periodic Safety Update EU Single assessment - burosumab	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0008/G	This was an application for a group of variations. B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	24/07/2019	n/a		
IB/0006	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	24/06/2019	n/a		
PSUSA/10669 /201808	Periodic Safety Update EU Single assessment - burosumab	14/03/2019	n/a		PRAC Recommendation - maintenance
R/0002	Renewal of the marketing authorisation.	15/11/2018	17/01/2019		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 CRYSVITA, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
T/0001	Transfer of Marketing Authorisation	20/07/2018	17/09/2018	SmPC, Labelling and PL	