Renvela

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
T/0066	Transfer of Marketing Authorisation	03/12/2024	19/12/2024	SmPC, Labelling and PL	
IB/0065/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test	20/09/2024	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).

	period/storage period or storage conditions - Change to an approved stability protocol 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.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)				
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2024	19/12/2024	PL	
IB/0063/G	This was an application for a group of variations. 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.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	22/07/2024	n/a		
IAIN/0062	A.1 - Administrative change - Change in the name and/or address of the MAH	16/06/2023	30/08/2023	SmPC, Labelling and PL	
IB/0061	B.II.d.2.d - Change in test procedure for the finished	02/06/2023	n/a		

	product - Other changes to a test procedure (including replacement or addition)				
IB/0060/G	This was an application for a group of variations. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method 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.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 B.II.c.1.c - Change in the specification parameters	04/01/2023	30/08/2023	Annex II and PL	

	and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.g - Change in the specification parameters and/or limits of an excipient - Where there is no monograph in the European/National Ph. for the excipient, a change in specification from in-house to a non-official/third country Ph. 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 arrangements and quality control testing of the FP - Including batch control/testing 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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IB/0059/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	29/07/2022	30/08/2023	SmPC, Annex II and PL	

	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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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 arrangements and quality control testing of the FP - Including batch control/testing 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.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/2697/ 202110	Periodic Safety Update EU Single assessment - sevelamer	10/06/2022	n/a		PRAC Recommendation - maintenance
IA/0058	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/04/2022	n/a		

IA/0057	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/02/2022	n/a		
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/11/2021	30/08/2023	PL	
IA/0054/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	02/09/2021	n/a		
WS/1854	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2020	18/02/2021	SmPC, Labelling and PL	
WS/1775	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	17/04/2020	n/a		Removal of identified or potential risks from the list of safety concerns as these risks are fully characterized and are followed up via routine pharmacovigilance.

	by new additional data to be submitted by the MAH where significant assessment is required 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				
IA/0052	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)	19/03/2020	n/a		
IG/1106	A.7 - Administrative change - Deletion of manufacturing sites	15/01/2020	18/02/2021	SmPC, Labelling and PL	
PSUSA/2697/201810	Periodic Safety Update EU Single assessment - sevelamer	27/06/2019	26/08/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2697/201810.
WS/1560	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	16/05/2019	26/08/2019	SmPC, Labelling and PL	

R/0046	Renewal of the marketing authorisation.	13/12/2018	20/02/2019	SmPC, Annex II, Labelling and PL	
IG/1003	A.1 - Administrative change - Change in the name and/or address of the MAH	20/12/2018	26/08/2019	SmPC, Labelling and PL	
X/0039	Annex I_2.(c) Change or addition of a new strength/potency	26/07/2018	20/09/2018	SmPC, Labelling and PL	
PSUSA/2697/ 201710	Periodic Safety Update EU Single assessment - sevelamer	14/06/2018	n/a		PRAC Recommendation - maintenance
WS/1383	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.f.1.e - Stability of FP - Change to an approved stability protocol	07/06/2018	n/a		
IG/0926/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	06/06/2018	n/a		

II/0043	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/05/2018	n/a		
WS/1332	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 6.6 of the SmPC in order to include the use of food and beverage as an alternative to water for administration of sevelamer carbonate powder for oral suspension. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to revise the Annex A. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	20/09/2018	SmPC and PL	
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/12/2017	20/09/2018	Labelling and PL	
IG/0844	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	22/09/2017	20/09/2018	SmPC, Labelling and PL	
IG/0804/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	26/06/2017	n/a		

	the AS - Minor change in the manufacturing process of the AS 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				
WS/0965	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication for Renvela 1.6 g and 2.4 g powder for oral suspension and Sevelamer carbonate Zentiva 2.4 g powder for oral suspension to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m2) with chronic kidney disease. As a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated in order to add information on posology and safety in paediatric patients and to reflect the results of the paediatric study. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/05/2017	26/06/2017	SmPC and PL	Please refer to the Scientific Discussion of Renvela and Sevelamer carbonate Zentiva EMEA/H/C/WS0965.
PSUSA/2697/ 201610	Periodic Safety Update EU Single assessment - sevelamer	09/06/2017	n/a		PRAC Recommendation - maintenance
PSUSA/2697/ 201510	Periodic Safety Update EU Single assessment - sevelamer	23/06/2016	25/08/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/2697/201510.
WS/0867	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC regarding drug-drug interaction between sevelamer and proton pump inhibitors. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in section 4.8 of the SmPC of Renvela and Sevelamer carbonate Zentiva in order to harmonize the wording for all Sevelamer compounds. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/02/2016	25/08/2016	SmPC and PL	Changes in gastric acidity with acid suppressants may potentially alter the efficacy of sevelamer HCL. During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer hydrochloride.
WS/0803	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	19/11/2015	n/a		
WS/0770	This was an application for a variation following a worksharing procedure according to Article 20 of	01/10/2015	25/08/2016	SmPC and PL	

	Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2697/ 201410	Periodic Safety Update EU Single assessment - sevelamer	11/06/2015	n/a		PRAC Recommendation - maintenance
PSUV/0029	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
IG/0418	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	11/04/2014	n/a		
R/0027	Renewal of the marketing authorisation.	23/01/2014	21/03/2014	SmPC	The CHMP is agreement to renew the Marketing Authorisation Aplication for this product, one additional five-year renewal on the basis of pharmacovigilance grounds is requested by the CHMP. It remains unknown whether in human patients there could be a higher increase of urinary calcium after long-term treatment with sevelamer carbonate as compared to sevelamer hydrochloride. Non-clinical data suggest that long-term sevelamer carbonate may lead to a higher increase in urinary calcium as compared to what is observed with sevelamer hydrochloride. The relevance to humans of tumour formation in the urinary bladder in a rat carcinogenicity study with sevelamer hydrochloride is currently unknown. As the MAH did not perform the requested clinical study to assess this safety topic, an additional 5-year renewal is

					deemed necessary to further evaluate this signal. Since this issue is still outstanding, the CHMP recommends that the MAH is requested to investigate in a new clinical study whether in human patients there could be a higher increase of urinary calcium after long-term treatment with sevelamer carbonate as compared to sevelamer hydrochloride. As a consequence of this outstanding issue, one additional five-year renewal on the basis of pharmacovigilance grounds is required.
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2013	21/03/2014	PL	
IG/0332	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/07/2013	n/a		
IA/0023/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/05/2013	n/a		
IG/0283	C.I.z - Changes (Safety/Efficacy) of Human and	22/03/2013	n/a		

	Veterinary Medicinal Products - Other variation				
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/08/2012	21/03/2014	PL	
IB/0020	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	08/06/2012	n/a		
IB/0019	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	31/05/2012	n/a		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/04/2012	21/03/2014	PL	
IA/0017/G	This was an application for a group of variations. 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.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	28/03/2012	n/a		
WS/0188	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC in order to include precaution information regarding difficulties in	17/11/2011	22/12/2011	SmPC, Annex II, Labelling and PL	The MAH was requested to perform a signal review on Renagel/Renvela for difficulties in swallowing/choking/aspiration due to obstruction of the airways or aspiration of tablet remnants in association with treatment with Renagel/Renvela. A total of seven cases were identified. Four of these patients recovered, for 2 the

	swallowing tablets and section 4.6. In order to add information on fertility. In addition, the list of local representatives in the Package Leaflet has been updated. Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template version 8.0. Minor linguistic corrections have also been made to the Italian Annexes of Renvela. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				outcomes are unknown, and 1 case was fatal (acute MI). In five cases, patients had to be hospitalized/hospitalization was prolonged and/or patients underwent bronchoscopy/endoscopy. The CHMP subsequently identified 12 cases in EudraVigilance on 17 March 2011. The CHMP requested the MAH to perform a cumulative review of cases of possible complications of swallowing Renagel/Renvela tablets, in particular focusing on the MedDRA PTs dysphagia, choking, aspiration, foreign body aspiration and oral administration complication. Swallowing is complex mechanical event, which can be influenced by a great many factors in Chronic Kidney Disease (CKD) patients. It is known for example that these patients often suffer from dysfunctional salivary glands. Furthermore, since hypertension is a frequent co-morbidity in CKD, water retention in the salivary gland's secretory process is not uncommon. Furthermore, concomitant conditions common in CKD patients (e.g. xerostomia, diabetic autonomic neuropathy, GERD and iron deficiency) can affect swallowing. CKD patients are generally also an older population with age related physiological changes such as laryngeal nerve dysfunction contributing to dysphagia and swallowing complications. The MAH performed a number of searches in different media to identify relevant case reports. The MAH's global safety database was queried for adverse events coding to specific Preferred Terms and MedDRA High Level Group Terms. In addition a search of medical literature was performed using Pubmed, OVID, EMBASE, and Biosis to identify any publications discussing choking on or difficulty

					swallowing and sevelamer. In addition, both the Renagel Integrated Summary of Safety submitted with the Renagel MAA and the Renagel and Renvela post-approval safety studies were reviewed. Finally, The FDA Adverse Event Reporting System (AERS) database was also queried. During this query similar data regarding other drugs currently indicated for treatment of hyperphosphatemia in dialysis patients was also retained. The CHMP conclusion is that the MAH has taken adequate action in regards to these sporadic reports of swallowing difficulties by adding a precaution on the use of tablet in swallowing-impaired patients in the product SPC. There are no clinical nor quality related reason as to why Renvela/Renagel should be more difficult to swallow than other similar products.
IG/0122	To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9, to include a change in the major contractual arrangements. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	25/11/2011	n/a		
IG/0116	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	28/10/2011	22/12/2011	Annex II	

	relation to another medicinal product of the same MAH				
IB/0012	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	23/09/2011	n/a		
IA/0013/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/09/2011	n/a		
IB/0010	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	24/08/2011	n/a		
II/0009	C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data. C.I.4 - Variations related to significant modifications	22/07/2010	06/09/2010	SmPC and PL	Update of section 4.6 of the SPC to add information on fertility and to update to section 4.8 of the SPC to add pruritus, rash and intestinal perforation and consequential changes to section 4 of the PL. These proposed changes are to align the Renvela Product Information with the Renagel Product Information. In addition, the MAH has taken the

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				opportunity to update the Product Information to align it with QRD template version 7.3 and to make minor changes to section 5.3 of the SPC and to section 3 of the PL.
IA/0008	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/05/2010	n/a		
IA/0007	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/05/2010	n/a		
IB/0006	IB_33_Minor change in the manufacture of the finished product	27/11/2009	n/a		
IB/0005	IB_33_Minor change in the manufacture of the finished product	05/10/2009	n/a		
IB/0003	IB_17_a_Change in re-test period of the active substance	02/09/2009	n/a		
IA/0004	IA_32_a_Change in batch size of the finished product - up to 10-fold	27/08/2009	n/a		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	31/07/2009	n/a	SmPC, Labelling and PL	
IB/0001	IB_11_c_Change in batch size of active substance or intermediate - more than 10-fold	08/07/2009	n/a		