Constella

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
PSUSA/10025 /202408	Periodic Safety Update EU Single assessment - linaclotide	13/03/2025	n/a		PRAC Recommendation - maintenance
II/0063	Update of section 4.4 of the SmPC in order to remove the statement relating to guanylate cyclase-C (GCC) receptor expression in the paediatric	05/09/2024		SmPC, Annex II, Labelling and PL	Update of section 4.4 of the SmPC in order to remove the statement relating to guanylate cyclase-C (GCC) receptor expression in the paediatric population based on

[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).

	population based on final results from study MCP-103-311; this is a non-interventional clinical research study to characterize GCC mRNA expression in duodenal and colonic mucosal biopsies in children aged 0 to 17 years. In addition, the MAH took the opportunity to introduce minor editorial changes to the Product Information and to bring it in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Final results from study MCP-103-311, a non-interventional clinical research study to characterize GCC mRNA expression in duodenal and colonic mucosal biopsies in children aged 0 to 17 years, have been submitted. As a consequence, section 4.4 of the SmPC has been updated to remove the information regarding the paediatric population.
IAIN/0064	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	26/08/2024		Annex II and PL	
IB/0062	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/06/2024	n/a		
PSUSA/10025 /202308	Periodic Safety Update EU Single assessment - linaclotide	11/04/2024	n/a		PRAC Recommendation - maintenance
IAIN/0061/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved	05/04/2024	n/a		

	manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
PSUSA/10025 /202208	Periodic Safety Update EU Single assessment - linaclotide	16/03/2023	n/a		PRAC Recommendation - maintenance
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/07/2022		PL	
T/0057	Transfer of Marketing Authorisation	29/04/2022	07/06/2022	SmPC, Labelling and PL	
PSUSA/10025 /202108	Periodic Safety Update EU Single assessment - linaclotide	07/04/2022		SmPC and PL	PRAC Recommendation - maintenance
IA/0055	A.7 - Administrative change - Deletion of manufacturing sites	27/05/2021	n/a		
IB/0054/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.a.3.b.6 - Changes in the composition (excipients) of the finished product - Other excipients - Replacement of a single excipient with a	19/05/2021	22/09/2021	SmPC and PL	The product information was updated to add 'Polyethylene glycol' in section 6.1 of the Summary of Product Characteristics and section 6 of the Package Leaflet. In addition the German local representative was updated in the package leaflet.

	comparable excipient with the same functional characteristics and at a similar level				
II/0053	Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on intestinal perforation and to add gastrointestinal perforation to the list of adverse drug reactions (ADRs) with frequency rare as requested by the PRAC in procedure EMEA/H/C/002490/LEG/015, 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.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	09/04/2021	22/09/2021	SmPC and PL	Of the provided 13 ICSR forms of the cumulative cases of intestinal perforation seven were considered possibly related to linaclotide, for one case a causal relationship could not be excluded but data were lacking for a proper assessment, four were not assessable due to lack of information, and for two cases it was not quite clear whether they are cases at all as it was uncertain if intestinal perforation happened at all under treatment. It was considered that linaclotide, due to its mechanism of action inducing movement of the intestine and based on the course of the events which, in some of the provided case reports, suggested a temporal relation could be a trigger for intestinal perforation in patients with localized or diffuse weakness of the intestinal wall. These patients should be advised to seek immediate medical care in case of severe, persistent or worsening abdominal pain and linaclotide should be discontinued if these symptoms occur. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10025 /202008	Periodic Safety Update EU Single assessment - linaclotide	09/04/2021	n/a		PRAC Recommendation - maintenance
IB/0051	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	12/10/2020	n/a		
II/0049	Update of section 4.6 of the SmP based on the final results of Lactation study 1915-7/LIN-PK-01 listed as	04/09/2020	22/09/2021	SmPC and PL	In Study LIN-PK-01 linaclotide and its active metabolite (MM-419447) were below the quantitation limit in the

	a category 3 study in the RMP; this is a an open-label, multiple-dose, milk-only lactation study in lactating women receiving linaclotide therapeutically. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				breast milk of lactating women studied. Given the minimal/negligible oral bioavailability of linaclotide, the large molecular size of linaclotide and its metabolite it is reasonable to conclude, that breastfed infants do not receive linaclotide or its metabolite through breast milk and therefore, no pharmacological activity of linaclotide and its metabolite are expected in breastfed infants. Constella can be used during breast-feeding.
IB/0050	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/08/2020	n/a		
IB/0048	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/06/2020	n/a		
PSUSA/10025 /201908	Periodic Safety Update EU Single assessment - linaclotide	26/03/2020	02/06/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10025/201908.
IB/0046/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	07/05/2020	n/a		

	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.7 - Administrative change - Deletion of manufacturing sites 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.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0045/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.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	30/04/2020	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites 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 B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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 B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised 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.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.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				
IA/0047	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)	23/04/2020	n/a		
II/0043	Submission of the final report from study "Linaclotide Utilization Study in Selected European Populations" listed as a category 3 study in the RMP. This is a rug Utilisation Study (DUS) addressing the following safety concerns: - The potential for off-label use and abuse/excessive use - Extent of use in pregnancy and lactation, and male patients - Assess the extent of off-label use and the extent of use in males and in pregnant females C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/03/2020	n/a		In the study the potential off-label use in patients diagnosed with IBS was high with regard to abuse or excessive use in two of the three countries. On the other hand, the majority of patients either switched or discontinued treatment. Discontinuation occurred mainly after the first prescription and discontinuation might be a consequence of diarrhoea development. Accordingly, no additional risk minimisation measures are recommended at this point in time due to the self-limiting (trial and error) nature of the off-label use. The study results indicate that linaclotide is prescribed only very rarely to pregnant women (< 0.5% in all countries) and with regard to lactation it was not possible to identify cases, as there are no diagnostic codes specific for this in use. Males accounted for 13.7%, 14.3% and 18.9% users in the UK, Spain, and Sweden respectively. The gender distribution of linaclotide users appears to match the clinical trials.
IB/0042	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/04/2019	n/a		

IAIN/0041	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	10/04/2019	n/a		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/03/2019	02/06/2020	PL	
PSUSA/10025 /201808	Periodic Safety Update EU Single assessment - linaclotide	14/03/2019	n/a		PRAC Recommendation - maintenance
IA/0038	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	23/08/2018	n/a		
IB/0037/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.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	17/04/2018	07/06/2018	Annex II and PL	
PSUSA/10025 /201708	Periodic Safety Update EU Single assessment - linaclotide	08/03/2018	n/a		PRAC Recommendation - maintenance

IAIN/0036	A.1 - Administrative change - Change in the name and/or address of the MAH	21/12/2017	07/06/2018	SmPC, Labelling and PL	
IA/0034	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	15/09/2017	n/a		
R/0032	Renewal of the marketing authorisation.	22/06/2017	28/08/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Constella in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0033	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	05/07/2017	07/06/2018	SmPC	
PSUSA/10025 /201608	Periodic Safety Update EU Single assessment - linaclotide	09/03/2017	n/a		PRAC Recommendation - maintenance
IB/0031	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	16/02/2017	n/a		
II/0028	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	27/10/2016	n/a		
N/0029	Update of the package leaflet to remove the telephone number of the Marketing Authorisation Holder in Section 6. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2016	11/04/2017	PL	

IB/0027	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	25/08/2016	11/04/2017	SmPC, Labelling and PL	
IB/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/06/2016	n/a		
PSUSA/10025 /201508	Periodic Safety Update EU Single assessment - linaclotide	01/04/2016	26/05/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10025/201508.
IAIN/0025/G	This was an application for a group of variations. A.z - Administrative change - Other variation A.1 - Administrative change - Change in the name and/or address of the MAH	22/04/2016	11/04/2017	SmPC, Labelling and PL	
T/0024	Transfer of Marketing Authorisation	20/01/2016	22/02/2016	SmPC, Labelling and PL	
II/0021	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	22/02/2016	SmPC, Annex II and PL	
IB/0022/G	This was an application for a group of variations. 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	10/04/2015	n/a		

	data 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 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				
II/0017	Introduction of a new manufacturer of the active substance that is supported by an ASMF B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	26/03/2015	n/a		
PSUSA/10025 /201408	Periodic Safety Update EU Single assessment - linaclotide	12/03/2015	n/a		PRAC Recommendation - maintenance
IA/0018	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	11/12/2014	n/a		
PSUV/0016	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0013/G	This was an application for a group of variations. This was an application for a group of variations: Addition of a manufacturing site for the finished product including primary and secondary packaging, batch control/testing. Furthermore, a change in the	24/07/2014	n/a		

	batch size of the finished product, minor changes in the manufacturing process of the finished product and a change in the specification parameters and/or limits of the finished product. 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.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.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.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological				

	product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue				
IB/0014/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/07/2014	n/a		
PSUV/0010	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
IAIN/0015	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/05/2014	16/03/2015	Annex II and PL	
IB/0011	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)	14/03/2014	16/03/2015	SmPC	
IA/0012	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/03/2014	n/a		
PSUV/0009	Periodic Safety Update	18/12/2013	20/02/2014	SmPC and PL	Please refer to Constella-H-C-2490-PSUV-0009 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IB/0008/G	This was an application for a group of variations.	08/01/2014	n/a		

	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 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 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 B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue				
IA/0007	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	22/11/2013	20/02/2014	SmPC	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2013	20/02/2014	PL	
II/0003/G	This was an application for a group of variations. Group of a type II variation to introduce a new manufacturer of the active substance and a subsequent type IA variation to introduce a new residual solvents testing site.	19/09/2013	n/a		

	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF 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				
IAIN/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/08/2013	20/02/2014	SmPC and PL	
IA/0004/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	06/06/2013	n/a		
IB/0002/G	This was an application for a group of variations. 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	04/04/2013	n/a		

	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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites				
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/03/2013	20/02/2014	PL	