EMEND

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
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/03/2024		PL	
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/08/2022		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).

IA/0067/G	This was an application for a group of variations. 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) 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)	14/06/2022	n/a		
IA/0066/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting	20/10/2021	n/a		

	material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2021		PL	
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/05/2021		PL	
II/0063	Update of the RMP to version 5.1 to remove all the safety concerns (important identified risks, important potential risks and missing information) and information related to both 40 mg and 165 mg	01/10/2020	n/a		

	capsules strengths and the Postoperative Nausea and Vomiting indication (PONV), as well as to update data in the post-authorisation exposure (Part II: Module SV) and epidemiology (Part II: Module SI) sections – following the removal of 2 capsule strengths (40 mg and 165 mg) as well as the removal of the PONV indication as approved in variation IB/0062/G (EC adoption on 19 August 2020). 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				
IB/0062/G	This was an application for a group of variations. C.I.6.b - Change(s) to therapeutic indication(s) - Deletion of a therapeutic indication C.I.7.b - Deletion of - a strength C.I.7.b - Deletion of - a strength	18/06/2020	19/08/2020	SmPC, Annex II, Labelling and PL	
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/11/2019	19/08/2020	PL	
PSUSA/229/201903	Periodic Safety Update EU Single assessment - aprepitant	31/10/2019	n/a		PRAC Recommendation - maintenance
IA/0060/G	This was an application for a group of variations.	26/07/2019	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0058	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	18/12/2018	n/a		
T/0057	Transfer of Marketing Authorisation	20/04/2018	24/05/2018	SmPC, Labelling and PL	
IA/0056	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)	13/03/2018	n/a		
II/0055	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	19/10/2017	SmPC, Labelling and PL	
PSUSA/229/201603	Periodic Safety Update EU Single assessment - aprepitant	27/10/2016	n/a		PRAC Recommendation - maintenance

IA/0054	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	15/09/2016	n/a		
IA/0052	A.7 - Administrative change - Deletion of manufacturing sites	25/04/2016	n/a		
IB/0051/G	This was an application for a group of variations. B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data) 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 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	23/03/2016	17/02/2017	SmPC, Labelling and PL	
X/0049/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.4 - Change(s) in the SPC, Labelling or PL due to	22/10/2015	16/12/2015	SmPC, Annex II, Labelling and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/229/201503	Periodic Safety Update EU Single assessment - aprepitant	08/10/2015	n/a		PRAC Recommendation - maintenance
IA/0048/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	08/12/2014	n/a		
PSUV/0044	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/09/2014	16/12/2015	PL	
IB/0046	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	03/09/2014	n/a		
IB/0045/G	This was an application for a group of variations. 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.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	01/09/2014	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold 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.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				
PSUV/0042	Periodic Safety Update	24/10/2013	18/12/2013	SmPC, Annex II and PL	Please refer to Emend-H-C-000527-PSUV-0042: EPAR - Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation. In addition, the MAH took the opportunity to update the product information according to the latest QRD template.
IG/0366	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	08/11/2013	n/a		
N/0041	Inclusion of an additional local representative of the MAH for Croatia. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/07/2013	18/12/2013	PL	

WS/0354	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 5.1 of the SmPC to reflect the recently approved safety dose restriction for ondansetron 32 mg IV. Additionally, the product information has been updated in accordance with the latest QRD template and the list of local representatives in the package leaflet was updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	22/03/2013	SmPC, Annex II and PL	Based on the results from a recent clinical trial with ondansetron (5-HT3 receptor antagonist) and concerns about prolongation of the QT interval at a single IV dose of 32 mg section 5.1 of the SmPC has been updated to reflect that the ondansetron IV dose used concomitantly in clinical trials with aprepitant may no longer be the currently recommended dose. Furthermore references to the dose of ondansetron were removed from 4.2 referring the prescribing physician to the respective package insert for the selected co-administered 5-HT3 antagonist.
IB/0038	"Alignment of the EMEND PI to the PI of IVEMEND R/018. This realignment includes updates of section 4.4, 4.5 and 4.6 of the SmPC and corresponding sections of the PL. The Applicant also updated the local representatives contact details in the PL for the following countries: Malta, The Netherlands, Poland, Iceland and Italy." C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/12/2012	22/03/2013	SmPC, Annex II and PL	
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
IB/0036/G	This was an application for a group of variations.	23/04/2012	n/a		

	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.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation 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)				
IB/0035	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2012	10/10/2012	SmPC and PL	Alignment of the EMEND 165 mg PI to the PI of the other approved strengths of EMEND in line with the outcome of procedures II/029 and WS/180. This realignment includes the update of sections 4.8 and 6.5 of the SmPC and corresponding section of the PL. The MAH also updated the contact details in section 6 of the PL for EMEND 165 mg for the following countries: Greece, Hungary, Netherlands, Portugal, Latvia and Lithuania.
WS/0180	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 4.8 of the SmPC regarding "toxic	17/11/2011	19/12/2011	SmPC and PL	Following the review of post-marketing safety reports of cases of Stevens-Johnson syndrome/toxic epidermal necrolysis, the work-sharing application proposed to update section 4.8 of the SmPC for Emend and Ivemend by adding

	epidermal necrolysis". The PIL is being updated accordingly. Furthermore, the MAH implemented the new QRD template v8 and a correction of a misleading reference is made in section 4.4 of the Ivemend SmPC. The list of local representatives is updated in section 6 of the PIL for both products. For Ivemend, Annex IIA is also being updated to align with information in Module 3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the term “toxic epidermal necrolysis”.
X/0028	Annex I_2.(c) Change or addition of a new strength/potency	22/09/2011	28/11/2011	SmPC, Annex II, Labelling and PL	
II/0029	Alignment of Emend PI with Ivemend 115 mg and 150 mg PI agreed in previous procedures. Furthermore, section 4.8 of the SmPC is updated in line with the QRD template (7.3.1). The PIL is revised accordingly and the list of local representatives being updated. The DDPS and RMP information in Annex II is being modified. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	24/10/2011	SmPC, Annex II and PL	Fosaprepitant, the active ingredient in Ivemend, is a prodrug of aprepitant that is rapidly converted to aprepitant in vivo. As the pharmacologic activity of fosaprepitant is attributed to aprepitant, modifications introduced in the product information (PI) for Ivemend are also in many instances relevant for Emend. With the present variation, the MAH has aligned the PI for Emend with relevant modifications to the Ivemend PI recently approved in variation procedures II/009 and II/012, respectively.
IG/0112	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of	11/10/2011	n/a		

	the pharmacovigilance system				
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/07/2011	n/a	PL	
IA/0027	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	14/01/2011	n/a		
IG/0027/G	This was an application for a group of variations. C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	10/11/2010	n/a	Annex II	
N/0025	The MAH amended the immediate packaging (Annex IIIA) of the 2-day treatment pack. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2010	n/a	Labelling	
IG/0008	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)	09/06/2010	n/a		

II/0024	Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/11/2009	12/01/2010	SmPC, Labelling and PL	Update of SPC sections 4.8 and 5.1 based on the safety and efficacy data from clinical study P130 (prevention of MEC-induced nausea and vomiting in a patient population with a variety of tumour types who were treated with a range of MEC agents). In SPC section 4.8 the number of patients in clinical trials and the combined data from studies P071 and P130 was updated for all strengths. The table presenting the adverse reactions observed in either highly emetogenic chemotherapy or moderately emetogenic chemotherapy studies in patients treated with the aprepitant regimen and at a greater incidence than with standard therapy was amended with the following adverse reactions with a frequency of "uncommon" under the respective System Organ Class: palpitation, somnolence and malaise, abdominal distension, faeces hard, neutropenic colitis, rash pruritic, muscular weakness, chills, gait disturbance, neutrophil count decreased and cardiovascular disorder. Furthermore, SPC section 5.1 for the 80mg and 125mg strengths was updated with efficacy data from clinical study P130. The package leaflet has been updated accordingly. In addition, section 4 of the package leaflet has been revised in order to improve the readability following a CHMP comment raised with a recently finalised variation procedure. Furthermore, the MAH took the opportunity to amend the labelling of the 125/80mg trifold pack as well as to insert the latest renewal date in the SPC.
II/0023	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the version number of the	25/06/2009	31/07/2009	Annex II	The MAH updated its DDPS and submitted therefore this Type II variation. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils

	DDPS. In addition, in Annex II the version number of the RMP (version 2.1) has been updated following finalisation of the follow-up measure RMP028. Update of DDPS (Pharmacovigilance)				the requirements and is considered acceptable.
II/0022	Update of SPC sections 4.4 and 4.5 regarding interaction with tolbutamide and oral contraceptives for the 40mg hard capsule based on two clinical pharmacology studies. In addition, SPC section 4.5 and PL section 2 have been revised as requested by CHMP with FUM026 of the EMEND renewal in order to simplify the text and increase readability. In this context, also in SPC section 4.4 an existing warning regarding concomitant orally administered active substances that are metabolised through CYP3A4 has been amended with a list of active substances with a narrow therapeutic range for the 80mg and 125mg strengths as well as the list of active substances that inhibit CYP3A4 activity for all strengths. Moreover, additional changes have been implemented in the Package Leaflet including an update to the list of local representatives. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	31/07/2009	SmPC and PL	SPC sections 4.4 and 4.5 have been updated based on two new interaction studies evaluating the effect of a 40mg single aprepitant oral dose. One study evaluated the effect over time on tolbutamide and one study the effect on an oral contraceptive. In the tolbutamide study the time course and magnitude of the induction, when assessed as the change over time from baseline, was similar as previously observed for the 3-day CINV regimen. However, the parallel placebo group also displayed a time dependent change. Hence, the overall placebo-corrected change was considerably smaller. However, given the unexpected results in the placebo group in the new study, it seems more appropriate to evaluate the inductive effect of Emend 40mg based on the change from baseline in the aprepitant group. Based on that, aprepitant 40mg single dose is a moderate inducer of CYP2C9 resulting in about 30% reduction in tolbutamide exposure. Also the oral contraceptive study suggests an inductive effect of a single 40mg aprepitant dose. The ethinyl estradiol AUC was decreased by 29% on Day 4 after aprepitant administration and trough concentrations were decreased up to 37%. This is less than the 64% decreased in ethinyl estradiol trough concentrations for the 3-day CINV regimen, but still suggest clinically relevant induction.

					In addition, for all strengths the statement regarding concomitant administration with active substances that inhibit CYP3A4 activity has been amended in SPC sections 4.4 and 4.5 with "itraconazol, voriconazol, posaconazol, nefazodone"; "ritonavir" was replaced by "protease inhibitors". Furthermore, for the 80 and 125mg strengths in SPC section 4.4 the existing warning regarding active substances concomitant orally administered active substances that are metabolised primarily through CYP3A4 has been amended. A list of CYP3A4 substrates with narrow therapeutic margin and where caution may be needed in case of a 2-3 fold increase in exposure over 3 days as could be expec
IA/0021	IA_09_Deletion of manufacturing site	10/11/2008	n/a		
R/0020	Renewal of the marketing authorisation.	24/07/2008	22/09/2008	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Emend continues to be favourable. Adverse event of special interest will be further monitored by the MAH on a continuing basis. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
IA/0019	IA_05_Change in the name and/or address of a manufacturer of the finished product	21/04/2008	n/a		

IA/0018	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/04/2008	n/a		
II/0017	The variation concerns an update of the SPC on the concomitant use of EMEND and vinorelbine. Section 4.4 and 4.5 of the 80 and 125 mg SPC and section 6 of the PL have been updated. Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	28/02/2007	SmPC, Annex II and PL	
IA/0016	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	01/08/2006	n/a		
X/0015	Annex I_2.(c) Change or addition of a new strength/potency	23/03/2006	29/05/2006	SmPC, Annex II, Labelling and PL	
II/0014	Extension of Indication	23/03/2006	29/05/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion document: Emend-H-527-II-14
II/0011	Update of Summary of Product Characteristics	15/09/2005	07/11/2005	SmPC	
II/0012	Change(s) to the manufacturing process for the active substance	15/09/2005	23/09/2005		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/07/2005	07/11/2005	PL	
II/0010	Update of the SPC section 4.5 to reflect the result of a clinical study showing that aprepitant had no	16/03/2005	28/04/2005	SmPC	

	significant effect on any of the pharmacokinetic parameters (AUC, maximum plasma concentration, time of maximum plasma concentration, half-life) of hydrodolasetron (the active metabolite of dolasetron). Update of Summary of Product Characteristics				
II/0009	Additional indication: "Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy". Extension of Indication	16/03/2005	28/04/2005	SmPC and PL	Please refer to the Scientific Discussion document: Emend-H-527-II-09
II/0006	Update of the SPC sections 4.4 and 4.5 to add pharmacokinetic data regarding the interaction with oral contraceptives. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	30/03/2005	SmPC and PL	
IB/0008	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	27/10/2004	n/a	SmPC and PL	
II/0005	Update of the SPC section 4.5 on the concomitant use of EMEND and docetaxel. Update of Summary of Product Characteristics	16/09/2004	25/10/2004	SmPC	
IB/0007	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	08/09/2004	n/a		

N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2004	n/a	Labelling and PL	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/06/2004	n/a	PL	
IB/0002	IB_33_Minor change in the manufacture of the finished product	14/04/2004	n/a		
IB/0001	The MAH applied for the extension of shelf life of the finished product to 3 years. The MAH also took the opportunity to update the package leaflet for the telephone number of the German local representative and the full address of the Islandic local representatives. IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	14/04/2004	n/a	SmPC and PL	