Ivemend

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/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/03/2024		PL	
IB/0049/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters	30/03/2023	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).

	and/or limits of the finished product - Other variation B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.				
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/08/2022	29/09/2022	PL	
IA/0047/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.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)	20/06/2022	n/a		
WS/2193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/06/2022	n/a		
II/0045	Update of section 4.8 of the SmPC with the final results from study P045; a non-randomised, single-group, multi-site, open-label study to evaluate the safety and tolerability of consecutive 3-day	23/09/2021	29/09/2022	SmPC and PL	

	intravenous fosaprepitant in paediatric participants scheduled to receive a moderately or highly emetogenic chemotherapy agent/regimen or a chemotherapy agent/regimen not previously tolerated due to vomiting. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and correct the date of the latest renewal in section 9 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/05/2021	29/09/2022	PL	
II/0043	Update of the RMP for IVEMEND to version 5.1 to remove all the safety concerns (important identified risks, important potential risks and missing information), as well as to update data in the post-authorisation exposure (Part II: Module SV) and epidemiology (Part II: Module SI) sections. 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	01/10/2020	n/a		

IB/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2020	23/07/2021	SmPC, Annex II, Labelling and PL	
PSUSA/1471/ 201903	Periodic Safety Update EU Single assessment - fosaprepitant	31/10/2019	n/a		PRAC Recommendation - maintenance
II/0040	Update of sections 4.4 of the SmPC in order to update the safety information related to Infusion Site Reactions (ISR) based on reports of post-marketing experience; the Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to include edits in the SmPC previously and in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/11/2018	16/12/2019	SmPC and PL	Infusion site reactions (ISRs) have been reported with the use of IVEMEND (see section 4.8). The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (e.g., anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy.
T/0039	Transfer of Marketing Authorisation	13/06/2018	23/07/2018	SmPC, Labelling and PL	
II/0037	Extension of Indication to include adolescents, infants, toddlers and children aged 6 months and older for prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 5.0 has also been submitted.	22/03/2018	30/04/2018	SmPC and PL	Please refer to the Scientific Discussion Ivemend EMEA/H/C/000743/II/0037.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0038	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	30/11/2017	n/a		
IA/0036	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	09/06/2017	n/a		
PSUSA/1471/ 201603	Periodic Safety Update EU Single assessment - fosaprepitant	10/11/2016	11/01/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1471/201603.
II/0034/G	This was an application for a group of variations. C.I.4 - Update of sections 5.1 and 5.2 of the SmPC in order to include pharmacodynamic and pharmacokinetic data relevant to the paediatric population. C.I.4 - Update of sections 5.3 of the SmPC in order to include non-clinical data relevant to the paediatric population. The Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0.	15/12/2016	30/01/2018	SmPC and Labelling	Section 5.1 has been updated to reflect the results of the pharmacokinetics in paediatric populations. The pharmacokinetics, safety and tolerability, and exploratory efficacy of intravenous fosaprepitant in paediatric population, administered concomitantly with ondansetron, with or without dexamethasone, were evaluated in a Phase I clinical study (N=34) in paediatric cancer patients receiving moderately or highly emetogenic chemotherapy. However, the efficacy and safety data from this small study do not support a conclusion on the optimal dosing regimen. Further studies evaluating the use of fosaprepitant in paediatric patients are on-going. Section 5.3 on pre-clinical safety data has also been

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				updated to reflect that intravenous administration of fosaprepitant and oral administration of aprepitant reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity (including in vitro tests), and toxicity to reproduction and development. Results for data in juvenile dogs treated with fosaprepitant have been included in the section.
IB/0035/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	30/11/2016	n/a		

	variation 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.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
IA/0033	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		
II/0031	Update of sections 4.8 and 5.1 of the SmPC in order to include data from the clinical study P031. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the QRD template version 9.1 and to make minor editorial changes. Furthermore, the MAH took the opportunity to align section 4.4 of the SmPC (and Package leaflet respectively) for fosaprepitant (Ivemend) with the changes approved through	21/07/2016	11/01/2017	SmPC, Annex II, Labelling and PL	In clinical studies, various formulations of fosaprepitant have been administered to a total of 2,687 individuals including 371 healthy subjects and 2,084 patients with chemotherapy induced nausea and vomiting (CINV). The safety profile of aprepitant was evaluated in approximately 6,500 individuals. In a randomized, parallel, double-blind, placebo-controlled study, IVEMEND 150 mg (N=502) in combination with ondansetron and dexamethasone was compared with

	procedure EMEA/H/C/000527/X/0049/G for aprepitant (Emend). Moreover, the updated RMP version 4.0 has been submitted as part of this application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				ondansetron and dexamethasone alone (control regimen) (N=498) in patients receiving a moderately emetogenic chemotherapy regimen. The fosaprepitant regimen consisted of fosaprepitant 150 mg on Day 1 in combination with oral ondansetron 8 mg for 2 doses and oral dexamethasone 12 mg. On Days 2 and 3, patients in the fosaprepitant group received placebo for ondansetron every 12 hours. The control regimen consisted of fosaprepitant placebo 150 mg IV on Day 1 in combination with oral ondansetron 8 mg for 2 doses and oral dexamethasone 20 mg. On Days 2 and 3, patients in the control group received 8 mg oral ondansetron every 12 hours. Fosaprepitant placebo and dexamethasone placebo (on Day 1) were used to maintain blinding. The efficacy of fosaprepitant was evaluated based on the primary and secondary endpoints and was shown to be superior to the control regimen with regard to complete response in the delayed and overall phases.
II/0030/G	This was an application for a group of variations. B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	04/02/2016	n/a		

	in the manufacturing process B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
PSUSA/1471/ 201503	Periodic Safety Update EU Single assessment - fosaprepitant	08/10/2015	n/a		PRAC Recommendation - maintenance
IA/0028	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)	19/02/2015	n/a		
IB/0027	B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	27/01/2015	n/a		
PSUV/0025	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/09/2014	11/01/2017	PL	
II/0024	Change in the quantitative composition of the finished product. B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product	25/04/2014	n/a		

PSUV/0022	Periodic Safety Update	24/10/2013	20/12/2013	SmPC, Annex II and PL	Please refer to Ivemend-H-C-000743-PSUV-0022: 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/0021	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	20/12/2013	PL	Inclusion of an additional local representative of the MAH for Croatia.
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.

R/0018	Renewal of the marketing authorisation.	20/09/2012	12/11/2012	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 Ivemend continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Ivemend continues to be favourable in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults and in the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.
IAIN/0019	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/10/2012	n/a		
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 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.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article	17/11/2011	22/12/2011	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 the term “toxic epidermal necrolysis”.

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
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 the pharmacovigilance system	11/10/2011	n/a		
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/07/2011	22/12/2011	PL	
II/0012	Update of section 4.8 of the SmPC based on the pooling of data from 4 studies of aprepitant and to align it with the recommendations from the latest SmPC guideline (Sept. 2009) and QRD/MedDRA templates. Relevant sections of the Package Leaflet are updated accordingly. Furthermore, the list of local representatives has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	14/06/2011	SmPC and PL	The MAH has revised the text in the side effects sections of the Company Core Data Sheets (CCDS) and the SmPC for aprepitant and fosaprepitant. The prior versions of the CCDS and the SmPC included adverse drug reaction (ADR) terms based on a separate analyses of the pivotal clinical efficacy/safety studies conducted with aprepitant in patients treated with highly emetogenic chemotherapy (HEC; Protocols 052 and 054) pooled and moderately emetogenic chemotherapy (MEC: Protocols 072 and 130) pooled, as the studies were submitted in separate labelling supplements. This analysis is based on the pooling of adverse experience data from 4 double-blind, randomized, parallel-group studies of aprepitant for prevention of chemotherapy-induced nausea and vomiting (CINV) that included 2808 patients who received highly emetogenic chemotherapy -HEC- (1094 patients) or moderately emetogenic chemotherapy -MEC- (1714) for the treatment of cancer.

II/0009	Update of the Ivemend 115 mg product information to include relevant changes from the recently approved new 150 mg strength. In addition, minor editorial amendments are made in section 4.2 of the SmPC and section 6 of the PIL (list of local representatives). The DDPS version number and date are deleted from Annex II. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/02/2011	18/03/2011	SmPC, Annex II, Labelling and PL	The MAH has introduced changes to the product information for Ivemend 115 mg to align it with the wording agreed for the recently approved 150 mg strength presentation. As the 115 mg formulation is part of the 3-day regimen including administration of oral aprepitant, while Ivemend 150 mg is for single-dose administration, the wording from the 150 mg strength was not in all cases relevant for the 115 mg presentation. The MAH has provided appropriate justifications for the relevance of the proposed changes.
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	
IA/0011/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture 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)	26/10/2010	n/a		

IA/0010	A.3 - Administrative change - Change in name of the AS	26/10/2010	n/a	SmPC, Labelling and PL	
X/0006	X-3-iii_Addition of new strength	24/06/2010	31/08/2010	SmPC, Labelling and PL	
IA/0008/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture 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)	06/08/2010	n/a		
II/0007	Update of SPC sections 4.4 and 4.8 with safety information from study P017L1 and to add information related to post-marketing experience on immediate hypersensitivity reactions with fosaprepitant. Section 4 of the Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	26/03/2010	SmPC and PL	Post-marketing safety reports received by the MAH indicate a possible relationship between hypersensitivity reactions in patients administered fosaprepitant 115 mg. Since market introduction of fosaprepitant (cumulative data from market introduction on 26-Mar-2003 through 30-Jun-2009), 26 reports of hypersensitivity reactions were identified in which onset occurred on Day 1, thereof 12 reports in which the event or events occurred within a few minutes of initiation of administration suggesting an immediate hypersensitivity reaction. The most commonly reported adverse events were flushing, erythema and dyspnoea. Section 4.4 of the SPC has therefore been amended to

					include a specific warning of hypersensitivity reactions that may occur during intravenous administration of fosaprepitant. In addition, this type II variation updated sections 4.8 of the SPC of fosaprepitant 115 mg based on safety data from study P017L1. Although this study evaluated fosaprepitant 150 mg single intravenous dose for the prevention of highly emetogenic chemotherapy induced nausea and vomiting, the safety findings in P017L1 were considered relevant for the approved 115 mg dosage strength as it represents a robust safety data set for fosaprepitant and adds to the understanding of the safety profile of this substance. Overall, the benefit-risk assessment for Ivemend 115 mg remains favourable and the proposed changes to the SPC, reflecting study data and post marketing experience, are considered approvable.
II/0005	Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	23/12/2009	SmPC and PL	Update of SPC sections 4.8 and 5.1 based on the safety and efficacy data for aprepitant 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. 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 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.
II/0004	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the version number and date of the 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 RMP012. Update of DDPS (Pharmacovigilance)	25/06/2009	29/07/2009	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 the requirements and is considered acceptable.
II/0003	Update of SPC section 4.8 regarding hypersensitivity reactions as reported for aprepitant (EMEND) postmarketing. In addition, revision of SPC section 4.5 and PL section 2 has been proposed by the MAH as requested by CHMP with FUM026 of the EMEND renewal procedure 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	25/06/2009	29/07/2009	SmPC and PL	SPC section 4.8 has been updated based on spontaneous reports that indicate a possible relationship between aprepitant and hypersensitivity reactions, including anaphylactic reaction, urticaria, pruritus and rash. In many cases there is a close temporal relationship between administration of aprepitant and development of adverse events. Although postmarketing reports for these adverse events have not been received for fosaprepitant since marketing of Ivemend, the MAH proposed to add a postmarketing section also to Ivemend since fosaprepitant is rapidly converted to aprepitant after intravenous

	amended with a list of active substances with a narrow therapeutic range as well as the list of active substances that inhibit CYP3A4 activity. The Package Leaflet has been updated accordingly. Furthermore, the MAH took the opportunity to preform changes throughout the Product Information to align it with the QRD revisions agreed for EMEND during the Renewal procedure and to update the list of local representatives in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet				administration. Furthermore, 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 expected during co-administration of the 3 day CINV regimen, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine has been added. In addition, 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". Moreover, in SPC section 4.5 a statement has been added informing that during the 3 day CINV regimen, a transient moderate increase followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g. cyclosporine, tacrolimus, everolimus and sirolimus) is expected. Given the short duration of the 3-day regimen and the time-dependent limited changes in exposure, dose reduction of the immunosuppressants is not recommended during the 3 days of co-administration with Ivemend/EMEND. The package leaflet has been updated accordingly.
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/05/2008	n/a	Labelling	

IA/0001	IA_06_a_Change in ATC code: Medicinal products for human use	07/05/2008	n/a	SmPC	