Alimta

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
IB/0065	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/04/2022		SmPC, Labelling and PL	Update of Sections 4.4 and 4.6 of the SmPC based on the recommended wording provided in the "Report from the CMD(h) meeting held on 20-21 July 2021" concerning duration of contraception following the end of treatment with a genotoxic drug. The PL has been updated accordingly.

[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).

IB/0064/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/02/2022	n/a		
IA/0063/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	19/01/2022	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2022		PL	
PSUSA/2330/ 202102	Periodic Safety Update EU Single assessment - pemetrexed	30/09/2021	n/a		PRAC Recommendation - maintenance
N/0060	Minor change in labelling or package leaflet not	30/09/2020	10/05/2021	PL	

	connected with the SPC (Art. 61.3 Notification)				
WS/1704	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Worksharing to update section 4.8 of the SmPC as requested by CHMP following the assessment of the PSUR covering the period between 05 February 2015 and 04 February 2018. To comply with SmPC guideline and latest QRD update version 10.1, the Alimta and Pemetrexed Lilly SmPCs are updated combining multiple tables of ADRs into one table of ADRs reported in the pivotal registration trials and during the postmarketing period (both clinical trials and spontaneous reporting), organized by SOC with the respective frequency categories. The Package Leaflet is updated accordingly. In addition an updated RMP version 6.1 has been submitted to implement the revised GVP Module V (Rev 2) format as requested by CHMP following the assessment of the PSUR covering the period between 05 February 2015 and 04 February 2018. 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	17/04/2020	10/05/2021	SmPC, Annex II, Labelling and PL	
IB/0059/G	This was an application for a group of variations.	09/04/2020	n/a		

	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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IG/1132	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	14/08/2019	n/a		
IAIN/0056	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	06/02/2019	11/02/2020	SmPC and PL	
PSUSA/2330/201802	Periodic Safety Update EU Single assessment - pemetrexed	18/10/2018	18/12/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2330/201802.
IA/0055	A.7 - Administrative change - Deletion of manufacturing sites	25/06/2018	n/a		
IAIN/0053	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/03/2018	18/12/2018	SmPC, Labelling and PL	
IG/0898	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	12/02/2018	18/12/2018	Annex II	

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0051/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	20/11/2017	n/a		
IB/0050/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a	30/08/2017	n/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.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
IB/0049	C.I.3.z - 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 - Other variation	14/01/2017	06/02/2017	SmPC, Labelling and PL	
IA/0048	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	02/12/2016	n/a		
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	06/02/2017	SmPC, Labelling and PL	
IB/0046	B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	17/12/2015	n/a		
IAIN/0045	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	03/12/2015	n/a		

	manufacturer				
PSUSA/2330/201502	Periodic Safety Update EU Single assessment - pemetrexed	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2330/201502.
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/02/2014	19/11/2015	PL	
IG/0321	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
IAIN/0041/G	This was an application for a group of variations. B.III.2.a.1 - 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 - AS 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	16/07/2013	n/a		
IB/0040/G	This was an application for a group of variations. B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	12/11/2012	15/11/2013	SmPC and PL	

II/0038	Update of sections 4.8 and 5.1 of the SmPC with final efficacy and safety information from the PARAMOUNT study. Sections 4.2 and 4.8 of the SmPC were also updated in order to introduce a minor linguistic change. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	23/10/2012	SmPC	Final Overall Survival (OS) data from the PARAMOUNT study, supporting the use of Alimta in the maintenance treatment of non-squamous non-small cell lung cancer after platinum-based chemotherapy, confirmed preliminary analyses and showed a statistically significant improvement in OS of 2.85 months (13.86 months with Alimta vs 11.01 months with placebo). Safety information in the SmPC was updated, but no new safety signals were identified from the updated information. Finally, the term 'transaminase' was replaced by the term 'aminotransferase' to reflect current nomenclature.
IB/0039	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	14/09/2012	n/a		
II/0037	Update of section 4.8 of the SmPC to add anaphylactic shock as an Adverse Drug Reaction andof section 4.5 of the SmPC to introduce a minor addition to an existing warning on the interaction of pemetrexed with NSAIDs following the assessment of PSUR 9 and RMP v4, respectively. The Package Leaflet is updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 8.1. 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 45/46, or amendments to reflect a Core SPC -	21/06/2012	23/07/2012	SmPC, Annex II and PL	Following rare reports of anaphylactic shock with pemetrexed in the post-marketing setting, the Product Information of Alimta was updated to include this Adverse Drug Reaction. Moreover, the existing warning on avoidance of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) around the time of pemetrexed administration was expanded to recommend that, if concomitant administration of pemetrexed and NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosupression and gastrointestinal toxicity.

	Change(s) with new additional data submitted by the MAH				
IB/0036/G	This was an application for a group of variations. 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) B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	16/12/2011	23/07/2012	SmPC	
II/0033	Extension of the existing indication in the maintenance treatment of Non Small-Cell Lung Cancer (NSCLC) other than squamous cell histology after first line chemotherapy. Pemetrexed can be given as maintenance therapy after first line platinum-based chemotherapy including a pemetrexed/platinum combination. Sections 4.1, 4.8 and 5.1 of the SmPC were updated. The Package Leaflet was updated accordingly and minor editorial changes were made to the SmPC, Annex II and PL. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/09/2011	24/10/2011	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Alimta-H-C-564-II-0033-Assessment Report-Variation'
II/0035/G	This was an application for a group of variations. to register an new container closure system, for Alimta 500 mg, alternate to the currently approved	20/10/2011	20/10/2011		

	container closure system. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products				
IA/0034	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 relation to another medicinal product of the same MAH	23/02/2011	n/a		
II/0031/G	This was an application for a group of variations. Update of section 4.8 of the SmPC with the addition of Stevens Johnson syndrome, toxic epidermal necrolysis, haemolytic anaemia and sepsis in follow-up to PSUR 8; corresponding changes were made to the Package Leaflet. Sections 4.4, 4.5 and 5.2 of the SmPC were also updated regarding third space fluid, pemetrexed interaction with NSAIDs and pharmacokinetic information on secretion, respectively. The MAH took the opportunity to delete the version number of the DDPS and update the version number of the RMP in Annex II, to update the PI according to the current SmPC Guideline (September 2009) and QRD template (version 7.3.1)	16/12/2010	27/01/2011	SmPC, Annex II and PL	Bullous conditions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as sepsis and haemolytic anaemia have been reported in patients receiving pemetrexed and the causal association with pemetrexed has not been excluded. Moreover, third-space fluid (e.g. pleural effusion or ascites) does not seem to affect the pharmacokinetics of permetrexed and drainage of such fluid may not be necessary prior to pemetrexed administration. Finally, the administration of NSAIDs with long half-lives (such as ibuprofen) in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of and at least 2 days after pemetrexed administration.

	and to introduce a minor editorial change and update the list of local representatives in the Package Leaflet. 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 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IB/0032	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	14/12/2010	n/a		
II/0028/G	This was an application for a group of variations. to introduce changes to all steps of the manufacturing process for Alimta 500 mg as a result of a new production area in the existing manufacturing site and to introduce changes in the IPC for Alimta 500 mg. B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	24/06/2010	14/07/2010		

	B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product				
II/0029/G	This was an application for a group of variations. Group of variations: to introduce new container closure system and to delete a non relevant specification on the stopper and seal. B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	22/04/2010	03/05/2010		
IA/0030	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	23/03/2010	n/a		

	in the manufacture of the AS				
IB/0027	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)	24/02/2010	n/a	SmPC	
II/0023	Addition of an alternative manufacturing site for Alimta 500 mg powder for concentrate for solution for infusion. Quality changes	17/12/2009	12/01/2010		
IB/0024	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	24/11/2009	n/a		
IA/0026	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	09/11/2009	n/a		
IA/0025	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	09/11/2009	n/a		
R/0018	Renewal of the marketing authorisation.	25/06/2009	21/09/2009	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of the 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 Alimta continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. The MAH will continue to submit PSURs annually until otherwise specified by the CHMP.

					During the procedure, the CHMP requested the MAH to update section 4.8 of the SPC with regard to the ADR "esophagitis /radiation oesophagitis". Oesophagitis/ radiation oesophagitis has been uncommonly reported during clinical trials with pemetrexed.
IB/0022	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	30/07/2009	n/a		
IB/0021	IB_33_Minor change in the manufacture of the finished product IA_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	08/07/2009	n/a		
II/0015	Extension of Indication This type II variation concerns an extension of indication to include monotherapy maintenance treatment of locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. Sections 4.1, 4.8 and 5.1 of the SPC have been updated and the Package Leaflet has been updated accordingly. Further, the MAH has updated annex IIB to include the version number of the latest Risk Management Plan (version 2.1) agreed with the CHMP.	29/05/2009	02/07/2009	SmPC, Annex II and PL	Please refer to the Scientific discussion EMEA/H/C/000564/II/0015.

	Extension of Indication				
IA/0020	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	10/06/2009	n/a		
II/0016	The Marketing Authorisation Holder applied to replace the volatiles specifications in the active substance specification with the addition of process control parameters for volatiles content in two steps of the manufacture for the active substance. Quality changes	19/03/2009	25/03/2009		
IA/0017	IA_28_Change in any part of primary packaging material not in contact with finished product	22/01/2009	n/a		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	06/01/2009	SmPC and PL	This type II variation concerns an update of section 4.8 of the SPC, upon request by the CHMP following the assessment of the 6th PSUR, with information regarding the ADRs 'peripheral ischaemia' and 'oedema'. Uncommon cases of oedema have been reported in patients treated with pemetrexed and cases of peripheral ischemia leading sometimes to extremity necrosis have been reported. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SPC and to update the contact details in the list of local representatives in the Package Leaflet.
IB/0013	IB_10_Minor change in the manufacturing process of the active substance	18/06/2008	n/a		

II/0009	Extension of Indication	21/02/2008	08/04/2008	SmPC, Annex II and PL	This type II variation concerns an Extension of Indication to include 1st line treatment in combination with cisplatin of patients with locally advanced or metastatic Non Small Cell Lung Cancer other than predominantly squamous cell histology. In addition, the existing 2nd line monotherpay indication has been amended accordingly. Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC have been updated and the Package Leaflet has been updated accordingly. Further, the Marketing Authorisation Holder (MAH) has updated annex IIB to include a reference to the Pharmacovigilance system (version 2.0) and the Risk Management Plan (version 1.2) agreed with the CHMP. In addition, the MAH took the opportunity to make a minor change to section 4.5 of the SPC regarding concomitant use with yellow fever vaccine and to make minor editorial changes to the SPC and Package Leaflet. Please refer to Scientific Discussion EMEA-H-C-564-II-09
II/0012	Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	22/01/2008	SmPC and PL	This type II variation concerns an update of sections 4.4 and 4.8 of the SPC with information regarding 'radiation recall phenomenon' and was submitted by the Marketing Authorisation Holder upon request by the CHMP following the assessment of the 5th PSUR. The Package Leaflet has been updated accordingly. Radiation recall is a skin rash like severe sunburn, which can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation. Cases of radiation recall have been reported for Alimta in patients who received radiotherapy weeks or years previously.

IB/0011	IB_10_Minor change in the manufacturing process of the active substance	28/11/2007	n/a		
IB/0010	IB_10_Minor change in the manufacturing process of the active substance	28/11/2007	n/a		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	31/10/2007	SmPC and PL	The MAH has applied for a type II variation, upon request by the CHMP following the assessment of the 4th PSUR, to update sections 4.4 and 4.8 of the SPC with information regarding the ADR 'radiation pneumonitis' and section 4.8 of the SPC with information regarding the ADRs 'colitis' and 'interstitial pneumonitis'. The Package Leaflet has been updated accordingly. During post marketing surveillance, cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising agents. In clinical trials, cases of colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) have been reported uncommonly in patients treated with pemetrexed. In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed.
II/0007	New presentation(s)	20/09/2007	31/10/2007	SmPC, Labelling and PL	The MAH applied to add a 100 mg vial presentation and took the opportunity to introduce a combined Package Leaflet.

II/0006	Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	14/03/2007	SmPC and PL	The MAH applied for a Type II variation, upon request by the CHMP following the assessment of `DNR 014', to update section 5.3 of the SPC with the results of a non-clinical study as follows: `In a study conducted in beagle dog by intravenous bolus injection for 9 months, testicular findings (degeneration/necrosis of the seminiferous epithelium) have been observed.' In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.
II/0004	Update of Summary of Product Characteristics, Labelling and Package Leaflet	14/12/2006	26/01/2007	SmPC, Annex II, Labelling and PL	The Marketing Authorisation Holder (MAH) applied for a type II variation, upon request by CHMP following the assessment of the 3rd PSUR, to update sections 4.4 and 4.8 of the SPC to include information regarding acute renal failure. Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Further, the MAH has made an editorial change in section 4.2 and a minor amendment to the warning regarding yellow fever vaccine in section 4.4 for increased clarity. Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines (except yellow fever which is contraindicated) is not recommended.

					In addition, the MAH took the opportunity to revise the Annexes in line with the latest QRD template and to include the local representatives of BUL and ROM in the Package Leaflet.
IA/0005	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	27/10/2006	n/a		
IB/0003	IB_10_Minor change in the manufacturing process of the active substance	20/03/2006	n/a		
II/0002	Update of Summary of Product Characteristics and Package Leaflet	14/12/2005	30/01/2006	SmPC and PL	The MAH applied, upon request by the CHMP following the assessment of the 1st PSUR, to update sections 4.4, 4.8 and 4.9 of the Summary of Product Characteristics with the following information: "Pancytopenia" has been uncommonly reported during clinical trials with pemetrexed. During post marketing surveillance, rare cases of "colitis" have been reported in patients treated with pemetrexed. Further, "sensory polyneuropathy" has been reported following overdose. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives.