Lenvima

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
WS/2631	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, 4.8, 5.1 and 5.2 of the SmPC for Kisplyx and sections 4.8, 5.1 and 5.2 of the	21/03/2024		SmPC and PL	Efficacy of lenvatinib was assessed but not established in two open-label studies: Study 216, a Phase 1/2 study to determine the safety, tolerability, and antitumour activity of lenvatinib administered in combination with everolimus in paediatric patients with relapsed or refractory solid malignancies and Study 231, a Phase 2 basket study to

[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).

	SmPC for Lenvima, in order to reflect the results of two completed paediatric clinical studies E7080-G000-216 (216) and E7080-G000-231 (231). Study 216 is a Phase 1/2, multicenter, open-label, single arm study of lenvatinib in combination with everolimus in pediatric subjects (and young adults aged ≤21 years) with relapsed or refractory malignant solid tumors. Study 231 is a Phase 2, open-label, multicenter basket study to evaluate the antitumor activity and safety of Lenvatinib in children, adolescents, and young adults with relapsed or refractory solid malignancies. The Package Leaflet for Kisplyx is updated accordingly. The RMP version 16 is acceptable. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				evaluate the antitumour activity and safety of lenvatinib in children, adolescents, and young adults between 2 to ≤21 years of age with relapsed or refractory solid malignancies. Safey and efficacy results of these studies are included in sections 4.2, 4.8, 5.1 and 5.2 of the SmPCs. For more information, please refer to the Summary of Product Characteristics.
II/0053	Submission of interim results from study E7080-M000-508 (STELLAR), listed as a category 3 PASS in the RMP. This is a non-interventional multicentre, observational, phase 4 study to evaluate the safety and tolerability of lenvatinib in patients with advanced or unresectable HCC. Update of section 4.8 of the SmPC to include 'gastrointestinal perforation' as an adverse drug reaction with frequency 'common'. The package leaflet has been updated accordingly. RMP version 15.2 has also been submitted.	30/11/2023	25/01/2024	SmPC and PL	Based on the review of the interim results of the STELLAR study, the CHMP concluded that no new efficacy or safety concerns have been demonstrated for the approved indication of Lenvima in hepatocellular carcinoma. SmPC new text 'Gastrointestinal perforation' has been added to section 4.8 of the SmPC as an adverse drug reaction reported in patients treated with Lenvatinib monotherapy and Lenvatinib in combination with pembrolizumab with frequency 'Common', to align with the information currently provided in other sections of the SmPC.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0050	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies E7080-G000-207 and E7080-G000-230. Study E7080-G000-207 is a multicenter, open-label, Phase 1/2 study of lenvatinib in children and adolescents with refractory or relapsed solid malignancies and young adults with osteosarcoma; Study E7080-G000-230 is a multicenter, open-label, randomized Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents and young adults with Relapsed or Refractory Osteosarcoma (OLIE). The Package Leaflet is updated accordingly. The RMP version 15.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2023	25/01/2024	SmPC and PL	Based on the results from study E7080-G000-207 in children and study E7080-G000-230 in children, adolescents and young adults sections 4.8, 5.1, and 5.2 have been updated. The efficacy and safety of lenvatinib in children were assessed but not established. Currently available data are reported in the SmPC.
WS/2555/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a	05/10/2023	n/a		

	starting material/reagent/intermediate for AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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				
IG/1641	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2023	25/01/2024	SmPC and PL	

II/0049	Update of section 5.1 of the SmPC in order to update the efficacy information of "Endometrial carcinoma" based on the final OS analysis data for the overall population as well as for MMR subgroups from study E7080-G000-309 / KEYNOTE-775. This is a Multicenter, Open-label, Randomized, Phase III study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice in participants with advanced endometrial cancer. In addition, the MAH took the opportunity to implement editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/03/2023	15/05/2023	SmPC	The results from the final OS analysis of Study E7080-G000-309/KEYNOTE-775, with additional 16 months of follow-up, are overall consistent with the data from the first interim analysis submitted to support the approval of the advanced or recurrent endometrial carcinoma indication, in the overall population as well as in pMMR and dMMR subsets. Improvement in OS in Lenvatinib plus pembrolizumab over TPC was consistently observed with the OS HR 0.65 (95% CI: 0.55, 0.77; nominal p<0.0001), with the median OS of 18.7 months versus 11.9 months, respectively. For more information, please refer to the Summary of Product Characteristics.
WS/2312	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update of SmPC sections 4.2 and 6.6 to include the option of administering the capsules as a suspension, including instructions for the administration and preparation of the suspension. The MAH also took the opportunity to include some editorial changes to the SmPC. The package leaflet have been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/02/2023	15/05/2023	SmPC and PL	

	data				
IG/1493/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	12/04/2022	n/a		
WS/2235	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 of Lenvima and Kisplyx in order to add colitis to the list of ADRs with frequency uncommon for monotherapy/ combination with everolimus and common for combination with pembrolizumab, following PRAC Signal assessment of colitis with lenvatinib (EPITT no: 19691). The Package Leaflets are updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/04/2022	15/05/2023	SmPC and PL	The table in Module 8b of the EPAR will be updated as follows: Scope Please refer to the Recommendations section above Summary Not applicable
II/0042	Extension of indication to include lenvatinib in combination with pembrolizumab for the treatment of adult patients with advanced endometrial carcinoma (EC) who have disease progression following prior systemic therapy in any setting and	14/10/2021	26/11/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Lenvima H/C/003727/II/0042'

	are not candidates for curative surgery or radiation; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.1 of the RMP has also been agreed. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC, Annex II and to update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.2. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10380 /202102	Periodic Safety Update EU Single assessment - lenvatinib	30/09/2021	n/a		PRAC Recommendation - maintenance
II/0045	Submission of CSR of the Phase 2 multicentre, randomized, double-blind, non-inferiority trial in Subjects with 131I-Refractory Differentiated Thyroid Cancer to evaluate whether an oral starting dose of 18 mg daily will provide comparable efficacy to a 24 mg starting dose with an improved safety profile (study E7080-G000-211) in fulfilment of the MEA 005.5. The RMP version 12.3 is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	n/a		
IG/1370	A.6 - Administrative change - Change in ATC	17/03/2021	26/11/2021	SmPC and	

	Code/ATC Vet Code			Annex II	
IG/1366/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	04/03/2021	26/11/2021	Annex II and PL	
IA/0040	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	08/02/2021	n/a		
WS/1976	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13-Submission of the final nonclinical (pharmacokinetic) study report: XT205008 on the Inhibitory potential of uridine 5´-diphosphoglucuronosyltransferase UGT- 2B17 in human liver microsomes. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/01/2021	n/a		
WS/1861/G	This was an application for a group of variations following a worksharing procedure according to	10/12/2020	26/11/2021	SmPC	Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of peripheral oedema,

	Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC following the submission of the final clinical study report (CSR) for Study E7080-G000-201 (Study 201) - To evaluate the long-term safety of lenvatinib in Medullary and Iodine-131 Refractory, Unresectable differentiated thyroid carcinoma (DTC), Stratified by Histology (MEA 001 for Lenvima; from initial MAA for Kisplyx). Submission of the final CSR for Study E7080-G000-303 (Study 303) - To evaluate long-term safety of lenvatinib in patients with RR-DTC (radioiodine refractory differentiated thyroid cancer) in a randomized, double-blind, placebo-controlled Phase 3 study (MEA 004 for Lenvima; MEA 002 for Kisplyx). Submission of an updated integrated summary of safety (ISS) including data from DTC subjects in Studies 201, 303 and E7080-J081-208 (Study 208) - the latter study was to determine the long-term safety profile of lenvatinib in Japanese patients with advanced thyroid cancer (Kisplyx REC from Study 208 variation (procedure EMEA/H/C/003727/II/0008) for Lenvima). The RMP version 12 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				hypertension, fatigue, PPE, proteinuria, stomatitis, thrombocytopenia, and myalgia; while Caucasian patients had a higher incidence of diarrhoea, weight decreased, nausea, vomiting, constipation, asthenia, abdominal pain, pain in extremity, and dry mouth. A larger proportion of Asian patients had a lenvatinib dose reduction compared to Caucasian patients the median time to first dose reduction and the average daily dose taken were lower in Asian than in Caucasian patients.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10380 /202002	Periodic Safety Update EU Single assessment - lenvatinib	17/09/2020	18/11/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10380/202002.
II/0035/G	This was an application for a group of variations. -Submission of non-clinical final report from study M14014: Antiproliferative Activities of Lenvatinib Mesilate and Sorafenib Tosylate in VEGF-Stimulated Growth of HUVECs (human umbilical vein endothelial cells), relevant to the license's approved indications of differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC) which were conducted since the approval of the initial Marketing Authorisation Application. -Submission of non-clinical final report from study M13015: Antiangiogenic Activity of Lenvatinib Mesilate and Sorafenib Tosylate in Human Papillary Thyroid Cancer Cell Line K1 Xenografts in Mice, relevant to the license's approved indications of differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC) which were conducted since the approval of the initial Marketing Authorisation Application.	16/07/2020	n/a		

	-Submission of non-clinical final report from study M13016: Antiangiogenic Activity of Lenvatinib Mesilate and Sorafenib Tosylate in Human Follicular Thyroid Cancer Cell Line RO82-W-1 Xenografts in Mice, relevant to the license's approved indications of differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC) which were conducted since the approval of the initial Marketing Authorisation Application. -Submission of non-clinical final report from study W-20140845: Antiangiogenic Activity of Lenvatinib Mesilate and Sorafenib Tosylate in bFGF-Induced Matrigel Plug Assay in Athymic Mice, relevant to the license's approved indications of differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC) which were conducted since the approval of the initial Marketing Authorisation Application. -Submission of non-clinical final report from study on the Immuno-modulatory Activity of Lenvatinib Contributes to Antitumor Activity in the Hep1-6 Hepatocellular Carcinoma Model, relevant to the license's approved indications of differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC) which were conducted since the approval of the initial Marketing Authorisation Application. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				

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IG/1263	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	24/06/2020	18/11/2020	Annex II and PL	
IG/1260/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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	24/06/2020	18/11/2020	SmPC, Labelling and PL	

IG/1253/G	This was an application for a group of variations. 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.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	20/05/2020	n/a		
R/0031	Renewal of the marketing authorisation.	26/03/2020	20/05/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Lenvima in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/1240/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/05/2020	n/a		
IB/0030/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished	04/10/2019	20/05/2020	SmPC, Labelling and	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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 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			PL	
IAIN/0029	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	18/09/2019	20/05/2020	SmPC and PL	
IG/1144	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	05/09/2019	n/a		
PSUSA/10380 /201902	Periodic Safety Update EU Single assessment - lenvatinib	05/09/2019	n/a		PRAC Recommendation - maintenance

IG/1118	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)	05/07/2019	n/a		
WS/1607	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 5.2 of the SmPC based on the results of Study E7080-A001- 010, a Multicenter Phase 0 Study in Healthy Subjects and Subjects with Either Hepatic or Renal Impairment to Obtain Plasma for Assessment of in Vitro Lenvatinib Protein Binding. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	20/05/2020	SmPC	Plasma protein binding in plasma from hepatically or renally impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed.
T/0024	Transfer of Marketing Authorisation	17/01/2019	07/02/2019	SmPC, Labelling and PL	
IG/1054	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	11/01/2019	n/a		
IG/1045	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	11/01/2019	07/02/2019	Annex II and	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing			PL	
WS/1445	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.1.g - Change in the specification parameters and/or limits of an excipient - Where there is no monograph in the European/National Ph. for the excipient, a change in specification from in-house to a non-official/third country Ph.	13/12/2018	n/a		
IG/0998/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 B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/11/2018	n/a		
WS/1444	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 4.4 and 4.8 of the SmPC to amend the existing warnings on proteinuria and non-gastro-intestianl fistula and to add pneumothorax	25/10/2018	07/02/2019	SmPC and PL	Cases of nephrotic syndrome have been reported in patients using lenvatinib. In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung

	and nephrotic syndrome as new adverse drug reactions (ADRs) with uncommon frequency. The PL is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				metastases may also increase the risk of pneumothorax.
WS/1446	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	04/10/2018	n/a		
WS/1416	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	13/09/2018	n/a		
WS/1396	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC to include that there is no significant drug-drug interaction risk with	13/09/2018	07/02/2019	SmPC	A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in the presence of lenvatinib. No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.

	midazolam, based on the results of study E7080-A001-109 (A Phase 1 Study to determine DDI of lenvatinib and midazolam, a cytochrome P450 3A4 (CYP3A4) substrate, in subjects with advanced solid tumors). The RMP is updated (version 10.4) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10380 /201802	Periodic Safety Update EU Single assessment - lenvatinib	06/09/2018	n/a		PRAC Recommendation - maintenance
II/0011/G	This was an application for a group of variations. Extension of indication to include treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy; consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, section 4.2 of the SmPC is being updated to add that the product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include the unique identifier. The RMP was updated (version 10.6). The Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to	28/06/2018	20/08/2018	SmPC, Labelling and PL	Please refer to the Scientific Discussion Lenvima EMEA/H/C/003727/II/0011/G.

	new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0966/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.III.2.a.2 - 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 - Excipient/AS starting material	16/07/2018	n/a		
WS/1363	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/06/2018	20/08/2018	SmPC and PL	Serious complications of poorly controlled hypertension, including aortic dissection, have been reported with the use of lenvatinib. No formal studies of the effect of lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving lenvatinib. Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of lenvatinib following a major surgical procedure. Therefore, the decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.
PSUSA/10380 /201708	Periodic Safety Update EU Single assessment - lenvatinib	08/03/2018	n/a		PRAC Recommendation - maintenance

II/0008	Submission of the final Clinical Study Report for Study E78080-J081-208; a phase 2 study of lenvatinib in subjects with advanced thyroid cancer. The provision of the report addresses MEA 003. An updated RMP version 10.1 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/10/2017	n/a		n/a
PSUSA/10380 /201702	Periodic Safety Update EU Single assessment - lenvatinib	01/09/2017	n/a		PRAC Recommendation - maintenance
WS/1161	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	01/06/2017	21/09/2017	SmPC	
WS/1123	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 to add the adverse events "cholecystitis" with frequency common, and the adverse events "pancreatitis", "amylase Increased" and "lipase increased" with	23/03/2017	21/09/2017	SmPC, Labelling and PL	Serious but not lethal acalculous cholecystitis have occurred in clinical trials and have been reported in post marketing experience in association with lenvatinib dosage. All subjects were managed using dose interruption as recommended in the protocol and there were no dose reductions or treatment discontinuations as a result of events of cholecystitis. During the clinical trials the overall frequency of cholecystitis including cholecystitis with

	frequencies uncommon, common and common, respectively. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to implement a correction to section 5.2 of the SmPC for both products and to combine the Kisplyx SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				gallstones was "common", i.e., it occurred in between 1/100 and 1/10 of the patients. The table 4 of the section 4.8 of the SmPC is updated accordingly. Serious pancreatitis and pancreatitis related events (lipase increased and amylase increased) were observed in clinical trials and in post marketing experience in association with lenvatinib dosage, the majority being associated with the 24 mg daily dose. All subjects were managed using dose interruption, dose reduction and discontinuations (0.3% of all subjects) as recommended in the protocol. During the clinical trials pancreatitis occurred at a frequency of 0.9% and high grade pancreatitis at a frequency of 0.7%. Lipase and amylase elevations were reported at frequencies of 3.8% and 2% respectively with high grade frequencies of 2.1% and 1.1% respectively. Amylase and lipase elevations are frequently reported with Tyrosine Kinase Inhibitors and may result from a class effect. The table 4 of section 4.8 of the SmPC is updated accordingly. No case of death has been linked to lenvatinib regimen.
PSUSA/10380 /201608	Periodic Safety Update EU Single assessment - lenvatinib	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0004	Update of sections 4.2, 4.4 and 4.8 of the SmPC to amend the already existing information on haemorrhage and fistula formation. The package leaflet is updated accordingly. Minor changes were made throughout the product information and changes were made in line with the product information of Kisplyx. The SmPCs of the 4mg and 10mg strengths were combined in line with the latest QRD template (version 10).	15/09/2016	21/09/2017	SmPC, Labelling and PL	Serious tumour related bleeds, including fatal haemorrhagic events have occurred in clinical trials and have been reported in post marketing experience (see section 4.8, Description of selected adverse reactions). In post marketing surveillance, serious and fatal carotid artery haemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in DTC or other tumour types. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumour shrinkage and fistula formation, e.g. tracheo-oesophageal fistulae. Cases of fatal intracranial haemorrhage have been reported in some patients with or without brain metastases. Bleeding in sites other than the brain (e.g. trachea, intra-abdominal, lung) has also been reported. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (for more information, please refer to the SmPC). Patients may be at increased risk for the development of fistulae when treated with lenvatinib. Cases of fistula formation or enlargement that involve other areas of the body than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae). Prior surgery and radiotherapy may be contributing risk factors. Lenvatinib should not be started in patients with fistula to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula (see section 4.2); limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. Lenvatinib may adversely affect the wound healing process as other agents of the same class.
PSUSA/10380 /201602	Periodic Safety Update EU Single assessment - lenvatinib	02/09/2016	n/a		PRAC Recommendation - maintenance

PSUSA/10380 /201508	Periodic Safety Update EU Single assessment - lenvatinib	17/03/2016	n/a		PRAC Recommendation - maintenance
IB/0003/G	This was an application for a group of variations. 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 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.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	14/01/2016	n/a		
IA/0001	A.7 - Administrative change - Deletion of manufacturing sites	30/10/2015	n/a		