Kisplyx

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/0058	Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-B61; this is a phase 2, single-arm, open-label clinical trial of pembrolizumab plus lenvatinib in participants with first-line advanced/metastatic non-clear cell Renal Cell Carcinoma (nccRCC). In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/03/2024		SmPC	Additional data are available from the open-label, single-arm, Phase 2 study KEYNOTE-B61 of lenvatinib (20 mg OD) in combination with pembrolizumab (400 mg every 6 weeks) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158), including 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other. The ORR was 50.6% (95% CI (42.6, 58.7)), and the median duration of response was 19.5 months (95% CI 15.3, NR)

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 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 -	05/10/2023	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
II/0055	Update of section 5.1 of the SmPC in order to update efficacy information (OS, PFS, ORR and PFS2) in first-line treatment of patients with advanced renal cell carcinoma treated with Kisplyx in combination with pembrolizumab, based on the final analysis for the overall population and by risk prognosis subgroups from study E7080-G000-307/CLEAR; this is a multicenter, randomized, open-label, phase 3 study comparing the efficacy and safety of lenvatinib in combination with either pembrolizumab or everolimus versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma (RCC). This application was submitted to fulfil the EMA Recommendation (REC) following the assessment of procedure II/0045. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/08/2023		SmPC	Update of section 5.1 to include final analysis (DCO 31 July 2022) of OS, PFS, ORR and DoR from E7080-G000-307/CLEAR. The median PFS for lenvatinib in combination with pembrolizumab was 23.9 months (95% CI: 20.8, 27.7) compared with 9.2 months (95% CI: 6.0, 11.0) for sunitinib, with HR 0.47 (95% CI: 0.38, 0.57; P value <0.0001). For OS, HR was 0.79 (95% CI: 0.63, 0.99; P value 0.0424). The ORR for lenvatinib in combination with pembrolizumab was 71.3% (95% CI: 66.6, 76.0) vs 36.7% (95% CI: 31.7, 41.7) P value <0.0001 for sunitinib. The final OS analysis was not adjusted to account for subsequent therapies, with 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the lenvatinib plus pembrolizumab arm receiving subsequent anti-PD-1/PD-L1 therapy.
IG/1641	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2023		SmPC and PL	
II/0052	Update of section 4.8 of the SmPC based on pooled safety data including results of Study 307, an ongoing, multicenter, randomised, open-label study that is being conducted to compare the efficacy and	14/04/2023		SmPC and PL	

	safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line (1L) treatment in adults with advanced renal cell carcinoma (RCC). The provision of the CSR addresses the post-authorisation measure MEA/FSR 009.3. The Package Leaflet is updated accordingly. An updated RMP version 15.0 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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 data	23/02/2023	17/04/2023	SmPC and PL	
II/0054	Submission of the latest Modelling and Simulation related data (such as PopPK and PK/PD Analyses) following the assessment of procedure II/52 to fulfil	02/02/2023	n/a		Not applicable

	MEA/FSR 008.1, MEA/FSR 007.3 and MEA/FSR 013.2. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
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	17/04/2023	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/0045	Extension of indication to include Kisplyx in combination with pembrolizumab first line treatment of adults with advanced renal cell carcinoma (RCC); as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 13 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to make editorial changes and update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/10/2021	26/11/2021	SmPC and PL	Please refer to Scientific Discussion 'Kisplyx-H-C-4224-II-45'
PSUSA/10380 /202102	Periodic Safety Update EU Single assessment - lenvatinib	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0049	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	13/08/2021	n/a		
II/0048	Submission of the final report from study E7080-G000-211 listed as a category 3 study in the RMP. This is a Multicenter, Randomized, Double-Blind Phase 2 Trial of Lenvatinib (E7080) in subjects with 131 I-Refractory Differentiated Thyroid Cancer to evaluate whether an oral starting dose of 18 mg daily will provide comparable efficacy to a 24 mg	08/07/2021	n/a		

	starting dose, but have a better safety profile. The RMP version 12.3 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				
R/0043	Renewal of the marketing authorisation.	22/04/2021	17/06/2021	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Kisplyx in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0041	Update of section 4.5 of the SmPC in order to update the drug-drug interaction with everolimus based on data from study 221, a single-arm, multicenter, Phase 2 trial to evaluate the safety and efficacy of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic nccRCC who have not received any chemotherapy for advanced disease. (MEA 008.1). The RMP version 12.1 is submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/03/2021	17/06/2021	SmPC	Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances. Additionally, in patients with RCC the pharmacokinetics of lenvatinib was not significantly affected by concomitant everolimus. 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. Additionally, in patients with RCC the pharmacokinetics of everolimus was not significantly affected by concomitant lenvatinib. No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.
IG/1370	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	17/03/2021	17/06/2021	SmPC and Annex II	
IG/1366/G	This was an application for a group of variations.	04/03/2021	17/06/2021	Annex II and	

	A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites			PL	
II/0042	Submission of the final Clinical Study Report for Study E7080-G000-218. Study 218 is a randomized, open-label (formerly double-blind), Phase 2 trial to assess safety and efficacy of Lenvatinib at two different starting doses (18 mg vs 14 mg QD) in combination with Everolimus (5 mg QD) in Renal Cell Carcinoma following one prior VEGF-Targeted treatment. (MEA 007.3). The RMP 12.2 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	11/02/2021	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	14/01/2021	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0039/G	This was an application for a group of variations. C.I.13. Submission of a nonclinical (primary pharmacodynamics) study report-M14014 on the Antiproliferative Activities of Lenvatinib Mesilate and Sorafenib Tosylate in VEGF-Stimulated Growth of HUVECs. C.I.13. Submission of a nonclinical (primary pharmacodynamics) study report-W-20140845 on the Antiangiogenic Activity of Lenvatinib Mesilate and Sorafenib Tosylate in bFGF-Induced Matrigel Plug Assay in Athymic Mice. 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	14/01/2021	n/a		
WS/1861/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. 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	10/12/2020	17/06/2021	SmPC	Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of peripheral oedema, 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

	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 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				Caucasian patients the median time to first dose reduction and the average daily dose taken were lower in Asian than in Caucasian patients.

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	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/07/2020	n/a		
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	20/05/2020	n/a		

	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				
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		
II/0030	Submission of an updated RMP version 11.3 to reflect changes related to the category 3 study E7080-G000-307. The protocol for study E7080-G000-307 has been updated to version 06, dated 10 September 2019, to include an interim analysis for profession-free survival and overall survival and the due dates for the interim and final analysis have been adjusted. 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	16/01/2020	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
IB/0028/G	This was an application for a group of variations. 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.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	04/10/2019	25/06/2020	SmPC, Labelling and 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	25/06/2020	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	05/09/2019	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/10380 /201902	Periodic Safety Update EU Single assessment - lenvatinib	05/09/2019	n/a		PRAC Recommendation - maintenance
II/0024	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	05/09/2019	n/a		
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	27/06/2019	25/06/2020	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.

	data				
T/0022	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 - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	11/01/2019	07/02/2019	Annex II and 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	26/11/2018	n/a		

	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				
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 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	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 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	13/09/2018	n/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				
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 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	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.
PSUSA/10380 /201802	Periodic Safety Update EU Single assessment - lenvatinib	06/09/2018	n/a		PRAC Recommendation - maintenance
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	16/07/2018	n/a		

	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				
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	07/02/2019	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
IB/0009	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/01/2018	n/a		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/11/2017	07/03/2018	PL	
II/0004	Submission of full report regarding pharmacodynamic results (secondary endpoint) from Study E7080-G000-205.	28/09/2017	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
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	07/03/2018	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 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.	23/03/2017	07/03/2018	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 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

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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/0001	Update of sections 4.2, 4.4 and 4.8 of the SmPC to add a warning on "haemorrhage" and posology recommendations and a warning on "non-gastrointestinal fistula" in line with what was approved for Lenvima. The package leaflet is updated accordingly. In addition, the format of the EU authorisation numbers is corrected throughout the product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	27/02/2017	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. 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 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, 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.