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
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		

[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).

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 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	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

	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				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 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	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

	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				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 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	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. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/09/2017	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	01/06/2017	07/03/2018	SmPC	

	of the finished product - As packaged for sale (supported by real time data)				
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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	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 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.