Kyprolis

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
PSUSA/10448 /202307	Periodic Safety Update EU Single assessment - carfilzomib	08/02/2024	n/a		PRAC Recommendation - maintenance
II/0058	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/12/2023		SmPC	

[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).

PSUSA/10448 /202207	Periodic Safety Update EU Single assessment - carfilzomib	09/02/2023	n/a		PRAC Recommendation - maintenance
IA/0057	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	21/12/2022	n/a		
IB/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/11/2022	n/a		
IA/0055/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	03/10/2022	n/a		
II/0051/G	This was an application for a group of variations. A.6 The ATC code of the product is updated C.I.4, Update of section 4.2 of the SmPC in order to modify administration instructions of daratumumab when Kyprolis is dosed in combination with daratumumab and dexamethasone, based on results from efficacy and safety studies MMY2040 (ongoing phase 2), MMY1001 (completed phase 1b) and CANDOR (ongoing phase 3). are recommended for approval.	24/02/2022	01/04/2022	SmPC	The table in Module 8b of the EPAR will be updated as follows: Scope Please refer to the Recommendations section above Summary SmPC new text: in section 4.2 the tables are updated with the posology instructions of daratumumab subcutaneous administration and the following text is added: "Alternatively, daratumumab can be given subcutaneously at a dose of 1800 mg on days 1, 8, 15 and 22 of cycle 1 and days 1, 8, 15 and 22 of cycle 2, then every 2 weeks for

	Amendments to the marketing authorisation In view of the data submitted with the group of variations, amendments to Annex(es) I are recommended. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression Refer to the daratumumab summary of product characteristics for additional information regarding the use of the subcutaneous formulation". For more information, please refer to the Summary of Product Characteristics.
IA/0053	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	18/03/2022	n/a		
PSUSA/10448 /202107	Periodic Safety Update EU Single assessment - carfilzomib	10/02/2022	n/a		PRAC Recommendation - maintenance
PSUSA/10448 /202007	Periodic Safety Update EU Single assessment - carfilzomib	25/02/2021	16/04/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10448/202007.
II/0050/G	This was an application for a group of variations. B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.e.1.a.3 - Change in immediate packaging of the	09/04/2021	n/a		

	finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products				
II/0045	Extension of existing indication to include combination of Kyprolis with daratumumab and dexamethasone; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 12.0 of the RMP has also been submitted. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	12/11/2020	17/12/2020	SmPC and PL	Please refer to Scientific Discussion Kyprolis-H-C-003790-II-0045
PSUSA/10448 /202001	Periodic Safety Update EU Single assessment - carfilzomib	03/09/2020	n/a		PRAC Recommendation - maintenance
IB/0048	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	28/07/2020	n/a		
R/0044	Renewal of the marketing authorisation.	30/04/2020	25/06/2020	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Kyprolis in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Excipients information relevant to sodium and cyclodextrin content in the Product Information were updated, in line

					with latest version of Guideline EMA/CHMP/302620/2017.
IA/0046	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	23/04/2020	n/a		
II/0043	Update of section 4.8 of the SmPC in order to include cardiomyopathy as a new adverse drug reaction with uncommon frequency following a signal evaluation triggered by a request from the Therapeutic Goods Administration (TGA) Australian authority. The RMP version 11.0 has also been submitted. In addition, the MAH took the opportunity to make some 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	17/04/2020	25/06/2020	SmPC	
II/0040	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	28/11/2019	n/a		
IA/0042/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	15/11/2019	n/a		

	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				
PSUSA/10448 /201901	Periodic Safety Update EU Single assessment - carfilzomib	19/09/2019	14/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10448/201901.
IA/0041	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	10/10/2019	n/a		
II/0038	Update of section 6.6 of the SmPC with information regarding the handling and preparation of Kyprolis. Labelling and PL are updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/09/2019	14/11/2019	SmPC and PL	Carfilzomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Kyprolis. Use of gloves and other protective equipment is recommended.
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/05/2019	14/11/2019	PL	
PSUSA/10448 /201807	Periodic Safety Update EU Single assessment - carfilzomib	28/02/2019	26/04/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10448/201807.
IB/0035	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	12/04/2019	n/a		

	or addition) for the AS or a starting material/intermediate				
II/0034	Update of the RMP (v.10.1) for Kyprolis to align with the revised guideline GVP Module V (Revision 2), resulting in the reclassification and removal of a number of identified and potential risks and missing information. 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	11/04/2019	n/a		
IB/0033/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	04/04/2019	n/a		

	of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
II/0030	Update of section 4.4 of the SmPC in order to include a warning of the increased risk of cardiac failure in Asian patients treated with carfilzomib based on postmarketing experience and three phase 3 randomized-controlled studies (CLARION-Study 2011-003; ENDEAVOR-Study 20130398 and A.R.R.O.W.-Study 20140355). In addition, the Marketing authorisation holder (MAH) took the opportunity to propose few minor typographical changes to SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to	20/09/2018	22/11/2018	SmPC	Cardiac failure is an important risk associated to carfilzomib, which is already described in the SmPC. During an analysis subgroup of study CLARION, a signal of a higher incidence of cardiac failure was identified in Chinese patients treated with carfilzomib compared to the overall study population. As a result of the signal, a review of the frequency of cardiac failure reported in carfilzomib clinical trials was performed. A trend towards a higher incidence of cardiac failure in Asian subjects treated with carfilzomib was reported compared to non-Asian subjects in the ENDEAVOR, CLARION and ARROW clinical trials. Thus, the exisiting warning in section 4.4 of the SmPC is updated to

	new quality, preclinical, clinical or pharmacovigilance data				reflect that the risk of cardiac failure is also increased in Asian patients.
PSUSA/10448 /201801	Periodic Safety Update EU Single assessment - carfilzomib	06/09/2018	n/a		PRAC Recommendation - maintenance
IG/0946	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	04/06/2018	22/11/2018	PL	
II/0025	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	22/11/2018	SmPC and PL	A pre-planned overall survival (OS) analysis was performed after 246 deaths in the Kyprolis, lenalidomide and dexamethasone (KRd) arm and 267 deaths in the lenalidomide and dexamethasone (Rd) arm. The median follow-up was approximately 67 months. A statistically significant advantage in OS was observed in patients in the KRd arm compared to patients in the Rd arm. Patients in the KRd arm had a 21% reduction in the risk of death compared with those in the Rd arm (HR = 0.79; 95% CI: 0.67, 0.95; p value = 0.0045). The median OS improved by 7.9 months in patients in the KRd arm compared with those in the Rd arm (see sections 5.1 of the SmPC for further details). Based on the safety data obtained, section 4.8. of the SmPC Undesirable effects has been updated.
PSUSA/10448 /201707	Periodic Safety Update EU Single assessment - carfilzomib	22/02/2018	19/04/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10448/201707.
IB/0026/G	This was an application for a group of variations. 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of	27/03/2018	n/a		

	the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the 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.a - Change in test procedure for AS or				

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0017/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	19/04/2018	SmPC, Labelling and PL	Results from the 2nd interim analysis of overall survival (OS) for the ENDEAVOR study confirm previous findings and provide a statistically significant and clinically relevant result. The study thus met the objective for OS, and therefore the ENDEAVOR Overall Survival 2nd interim analysis CSR (53.4% data maturity) is considered the final OS analysis. Section 5.1 of SmPC has been updated to reflect this analysis of OS (2nd IA). Results in terms of the secondary endpoint of peripheral neuropathy (incidence of grade 2 of higher peripheral neuropathy) continue showing a clinically relevant reduction of events. Regarding safety, updated data confirm previous findings. The slightly higher rates of adverse events are consistent with the longer treatment exposure and no safety concerns have been identified. Section 4.4 is updated to reflect that some of the acute renal failure events had been fatal. Changes regarding hypertension control prior to starting treatment and routinely evaluated while on carfilzomib were added in view of the number of hypertension adverse events reported. From the updated data available from ENDEAVOR study and pooled safety data analysis, frequencies in the tabulated list of adverse reactions in section 4.8 have been updated according to the new data available. Additionally, changes in line with the MedRA terms were made for some adverse reactions. Overall the summary of safety profile is

					updated to reflect that serious adverse reactions include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischaemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory failure, pulmonary hypertension, dyspnoea, hypertension including hypertensive crises, acute kidney injury, tumour lysis syndrome, infusion related reaction, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopenia, hepatic failure, PRES, thrombotic microangiopathy and TTP/HUS. In clinical studies with Kyprolis, cardiac toxicity and dyspnoea typically occurred early in the course of Kyprolis therapy. The most common adverse reactions (occurring in > 20% of subjects) were: anaemia, fatigue, thrombocytopenia, nausea, diarrhoea, pyrexia, dyspnoea, respiratory tract infection, cough and neutropenia. Overall the CHMP considered acceptable to update the product information.
II/0022/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	14/12/2017	n/a		

	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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.z - Change in the specification parameters and/or limits of the finished product - Other variation				
II/0020	B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	23/11/2017	n/a		
PSUSA/10448 /201701	Periodic Safety Update EU Single assessment - carfilzomib	14/09/2017	15/11/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10448/201701.
IG/0853	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	10/11/2017	19/04/2018	Annex II and PL	
IB/0023	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	31/10/2017	n/a		
IA/0019/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	11/08/2017	n/a		

	manufacturing sites 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				
IB/0016/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.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	02/08/2017	n/a		
IA/0015	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	23/06/2017	n/a		
IB/0014	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/05/2017	n/a		
IA/0013/G	This was an application for a group of variations.	05/05/2017	n/a		

	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0010	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	n/a		
IAIN/0011	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/03/2017	15/11/2017	Annex II and PL	
PSUSA/10448 /201607	Periodic Safety Update EU Single assessment - carfilzomib	09/02/2017	n/a		PRAC Recommendation - maintenance
II/0007/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	10/11/2016	12/12/2016	SmPC	The Marketing Authorisation Holder has submitted information on a dedicated renal impairment study (Study CFZ001) conducted in subjects with relapsed multiple myeloma and on a dedicated hepatic impairment study

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(Study CFZ002) conducted in subjects with relapsed or progressive advanced malignancies (solid tumours or hematologic malignancies).
IB/0008	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/11/2016	12/12/2016	SmPC and PL	
PSUSA/10448 /201601	Periodic Safety Update EU Single assessment - carfilzomib	02/09/2016	n/a		PRAC Recommendation - maintenance
II/0006/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 B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	04/08/2016	12/12/2016	SmPC, Labelling and PL	

	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products				
II/0001/G	This was an application for a group of variations. Extension of Indication to include new indication for Kyprolis to be used with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) is updated in accordance. In addition, the Marketing authorisation holder (MAH) updated section 6.6 of the SmPC to include the option to administer Kyprolis in a 100 mL	26/05/2016	29/06/2016	SmPC and PL	Please refer to the published Assessment Report Kyprolis H-3790-II-01-G-AR.

	intravenous bag containing 5% glucose solution for injection in line with the extension of indication part of this variation. Furthermore the MAH took the opportunity to include some editorial changes and harmonisations in the PI and to update the information of local representatives for Croatia and Cyprus. C.I.4 - Change(s) in the SPC, Labelling or PL due to 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				
II/0004/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to add information on haemorrhagic events and update of sections 4.4 and 4.6 of the SmPC in order to add information on venous thrombolic events; the Package Leaflet and RMP are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the RMP with the request to better characterize infections in patients with relapsed / refractory multiple myeloma requested during MAA review. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	29/06/2016	SmPC and PL	Cases of haemorrhage (e.g. gastrointestinal, pulmonary and intracranial haemorrhage) have been reported in patients treated with Kyprolis, often associated with thrombocytopenia. Some of these events have been fatal. Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received Kyprolis. Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimisze all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia). Caution should be used in the concomitant administration of other agents that may increase the risk of thrombosis (e.g. erythropoietic agents or hormone replacement therapy). Patients and physicians

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, haemoptysis, arm or leg swelling or pain. Thromboprophylaxis should be considered based on an individual benefit/risk assessment.
II/0002/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to update information on the potential for carfilzomib to inhibit UGT1A1 and UGT2B7 based on study 121863. In addition, the Marketing authorisation holder (MAH) submitted two other in-vitro drug-drug interaction (DDI) studies (121856 and 121939) on major metabolites M14, M15 and M16 to address their inhibitory and induction effects on CYP. Furthermore the MAH took the occasion to introduce an editorial change to section 4.5 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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	25/02/2016	29/06/2016	SmPC	In vitro, carfilzomib inhibits OATP1B1 with an IC50 = 2.01 whereas it is unknown whether carfilzomib may or not inhibit other transporters OATP1B3, OAT1, OAT3, OCT2 and BSEP, at the systemic level. Carfilzomib does not inhibit human UGT2B7 but inhibits human UGT1A1 with an IC50 of 5.5 µM. Nonetheless, considering the fast elimination of carfilzomib, notably a rapid decline in systemic concentration 5 minutes after the end of infusion, the risk of clinically relevant interactions with substrates of OATP1B1 and UGT1A1 is probably low.
IB/0003	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	23/02/2016	n/a		

	material/intermediate/reagent - Other variation				