Afinitor

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
IAIN/0092	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	21/11/2024		Annex II and PL	

[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/1758	A.7 - Administrative change - Deletion of manufacturing sites	12/06/2024	n/a		
IG/1724/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/03/2024	n/a		
IB/0088	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	19/10/2023	n/a		
IA/0087/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	17/08/2023	n/a		
IB/0086/G	This was an application for a group of variations.	28/07/2023	n/a		

	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State 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				
WS/2472	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	01/06/2023	n/a		
IB/0084/G	This was an application for a group of variations. B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation 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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	25/11/2022	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation				
IB/0083	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	08/08/2022	n/a		
IG/1520	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	24/06/2022	15/09/2023	SmPC	
IG/1518	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/06/2022	15/09/2023	SmPC and PL	
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
PSUSA/10268 /202103	Periodic Safety Update EU Single assessment - everolimus (indicated for advanced renal cell carcinoma, advanced breast cancer, advanced neuroendocrine tumors (gastrointestinal, lung, pancreatic cancers) (NET)	02/12/2021	n/a		PRAC Recommendation - maintenance

IA/0079/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer 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	18/11/2021	n/a		
II/0076	Update of the SmPC section 4.8 to include Lymphoedema as an adverse drug reaction with the frequency common based on the post-marketing data as requested by the PRAC. 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	28/10/2021	13/06/2022	SmPC and PL	
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2021	13/06/2022	PL	
II/0073	Update of the SmPC section 5.1 based on the results of the analysis of final progression free and overall survival (OS) for study CRAD001T2302. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	13/06/2022	SmPC	SmPC new text The efficacy results for the primary endpoint PFS (independent radiological review) obtained from the final PFS analysis were: Afinitor 11.01 months [95%CI: (9.2, 13.3)]; placebo 3.91 months [95% CI: (3.6, 7.4)]; HR=0.48 [95% CI: 0.35 to 0.67]). The efficacy results for PFS (investigator radiological review) obtained from the final OS analysis were: Afinitor 14.39 months [95%CI:

					(11.24, 17.97)]; placebo 5.45 months [95% CI: (3.71, 7.39)]; HR=0.40 [95% CI: 0.29 to 0.55]). The final overall survival (OS) analysis did not show a statistically significant difference between those patients who received Afinitor or placebo during the blinded treatment period of the study (HR=0.90 [95% CI: 0.66 to 1.22]).
IA/0078	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	08/09/2021	n/a		
WS/2110/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.2.z - Changes in the manufacturing process 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 A.7 - Administrative change - Deletion of manufacturing sites	02/09/2021	n/a		
IB/0075	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/08/2021	n/a		
IAIN/0071/G	This was an application for a group of variations. Replacement of a manufacturer responsible for	27/05/2021	13/06/2022	Annex II and PL	

	importation and/or batch release. 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 A.7 - Administrative change - Deletion of manufacturing sites				
WS/1995	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the Afinitor and Votubia SmPCs to include radiation recall syndrome as an adverse drug reaction observed in the post-marketing phase with unknown frequency (Section 4.8) and a cautionary text regarding radiation therpay complications in 'Special warnings and precautions for use' (Section 4.4). Corresponding changes are also made to the SmPC section 4.5 and package leaflets. Taking the opportunity, the MAH also proposed some editorial changes to harmonize the information in Afinitor and Votubia SmPC (Sections 4.7 and 4.8) and Package leaflet 'Afinitor with food and drink.' Afinitor PI is further updated in compliance with the QRD template version 10.1, while Votubia PI was already updated within the procedure II/061. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	20/05/2021	13/06/2022	SmPC, Annex II, Labelling and PL	SmPC new text Radiation therapy complications Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin injury), including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. Caution should therefore be exercised for the potentiation of radiotherapy toxicity in patients taking everolimus in close temporal relationship with radiation therapy. Additionally, radiation recall syndrome (RRS) has been reported in patients taking everolimus who had received radiation therapy in the past. In the event of RRS, interrupting or stopping everolimus treatment should be considered. For more information, please refer to the Summary of Product Characteristics.

	data				
IB/0070/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	27/01/2021	n/a		

	product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits 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.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.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.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.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.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation 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				
WS/1923	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	29/10/2020	n/a		

	Submission of the Final Clinical Study Report for study CRAD001MIC03 (TOSCA), an international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC), for Votubia. The RMP version 15.0 is submitted to reflect the completion of MEA 14.4 (Votubia) and to remove important safety concerns as recommended by the PRAC (EMEA/H/C/WS1671). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0067/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	09/06/2020	23/07/2021	SmPC	
WS/1777	This was an application for a variation following a worksharing procedure according to Article 20 of	26/03/2020	n/a		

	Commission Regulation (EC) No 1234/2008. B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
IAIN/0066/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	13/02/2020	23/07/2021	Annex II and PL	

	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				
WS/1671	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update the RMP for Afinitor and Votubia to version 14.0 to change the safety concerns, to reflect the completion of pharmacovigilance studies [CRAD001Y2201 (Afinitor II/0058), CRAD001M2304 (Votubia II/0051), CRAD001J2301 (Afinitor II/0051/G), CRAD00W2301 (Afinitor II/0051/G)] and to implement the latest GVP module V rev.2 template; the change has been agreed by the PRAC in the outcome of a PSUR assessment (EMEA/H/C/PSUSA/00010268/201703). 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	03/10/2019	n/a		
IG/1135/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	30/08/2019	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.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				
IG/1100	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		
IG/1099	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		
R/0060	Renewal of the marketing authorisation.	31/01/2019	02/04/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Afinitor in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0058	Update of sections 4.8 and 5.1 of the SmPC to add new safety and efficacy information based on the final report from study CRAD001Y2201, listed as a category 1 study in the RMP. This was a three arm randomised study investigating the combination of everolimus with exemestane versus everolimus alone versus capecitabine in patients with oestrogen receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole. As a consequence of the study completion, Annex II of the Product Information was	20/09/2018	02/04/2019	SmPC and Annex II	The primary objective of the study was to estimate the hazard ratio (HR) of the progression free survival (PFS) for everolimus + exemestane versus everolimus alone. The key secondary objective was to estimate the HR of PFS for everolimus + exemestane versus capecitabine. A total of 309 patients were randomised in a 1:1:1 ratio to the combination of everolimus (10 mg daily) + exemestane (25 mg daily) (n=104), everolimus alone (10 mg daily) (n=103) or capecitabine (1250 mg/m2 dose twice daily for 2 weeks followed by one week rest, 3-week cycle) (n=102). At the time of data cut-off, the median duration

	updated to remove this study. 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				of treatment was 27.5 weeks (range 2.0 165.7) in the everolimus + exemestane arm, 20 weeks (1.3 145.0) in the everolimus arm and 26.7 weeks (1.4 177.1) in the capecitabine arm. The result of the final PFS analysis with 154 PFS events observed based on local investigator assessment showed an estimated HR of 0.74 (90% CI: 0.57, 0.97) in favour of the everolimus + exemestane arm relative to everolimus arm. The median PFS was 8.4 months (90% CI: 6.6, 9.7) and 6.8 months (90% CI: 5.5, 7.2), respectively. For the key secondary endpoint PFS the estimated HR was 1.26 (90% CI: 0.96, 1.66) in favour of capecitabine over the everolimus + exemestane combination arm based on a total of 148 PFS events observed. Results of the secondary endpoint OS were not consistent with the primary endpoint PFS, with a trend observed favouring the everolimus alone arm. The estimated HR was 1.27 (90% CI: 0.95, 1.70) for the comparison of OS in the everolimus alone arm relative to the everolimus + exemestane arm. The estimated HR for the comparison of OS in the everolimus + exemestane combination arm relative to capecitabine arm was 1.33 (90% CI: 0.99, 1.79). With regards to safety, the frequency of pneumonitis was changed from “common” to “very common” and the interstitial lung disease was assigned the frequency “common”.
WS/1324/G	This was an application for a group of variations	13/09/2018	n/a		

	following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.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.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.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.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.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.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.c.1.z - Change in immediate packaging of the AS - Other variation				
IG/0950	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	18/06/2018	n/a		
T/0057	Transfer of Marketing Authorisation	26/03/2018	08/05/2018	SmPC, Labelling and PL	
PSUSA/10268 /201703	Periodic Safety Update EU Single assessment - everolimus (indicated for advanced renal cell carcinoma, advanced breast cancer, advanced neuroendocrine tumors (gastrointestinal, lung, pancreatic cancers) (NET)	26/10/2017	n/a		PRAC Recommendation - maintenance
IG/0829	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	18/08/2017	n/a		

WS/1144/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 sections 4.4 and 5.1 of the SmPC in order to include new safety information on stomatitis and its management based on final results from study CRAD001JUS226: a phase II, single arm study of the use of steroid-based mouthwash to prevent stomatitis in postmenopausal women with advanced or metastatic hormone receptor positive breast cancer being treated with everolimus plus exemestane Update of section 4.6 of the SmPC in order to add new information on breast-feeding based on pre-clinical data. The Package Leaflets were updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the Afinitor PI in line with the latest QRD template version 10. 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	29/06/2017	08/05/2018	SmPC, Labelling and PL	Results from a single-arm study in postmenopausal breast cancer patients treated with everolimus plus exemestane suggested that an alcohol-free corticosteroid oral solution, administered as a mouthwash during the initial 8 weeks of treatment when stomatitis mostly occurs, may decrease the incidence and severity of stomatitis. Management of stomatitis may therefore include prophylactic and/or therapeutic use of topical treatments, such as an alcohol-free corticosteroid oral solution as a mouthwash. Furthermore, monitoring for and treatment of fungal infection was recommended, especially in patients being treated with steroid-based medications. The overall safety profile in this study was consistent with that established for everolimus in the oncology and tuberous sclerosis complex settings, with the exception of a slightly increased frequency of oral candidiasis. Based on pre-clinical data suggesting a potential risk of excretion of everolimus in breast milk and considering its elimination half-life, women taking everolimus should not breastfeed during treatment and for 2 weeks after the last dose.
WS/1160	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	18/05/2017	08/05/2018	Annex II	

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0051/G	This was an application for a group of variations. C.I.13 - Submission of the final clinical study report of study RAD001J2301: A randomized phase-III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and paclitaxel, as first line therapy in women with HER2 positive locally advanced or metastatic breast cancer. C.I.13 - Submission of the final clinical study report of study RAD001W2301: A randomized Phase III, double-blind, placebo-controlled multicenter trial of everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer. In addition, the MAH included a report on exposure-response relationship combining data from these two trials. 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	16/03/2017	n/a		

PSUSA/10268 /201603	Periodic Safety Update EU Single assessment - everolimus (indicated for advanced renal cell carcinoma, advanced breast cancer, advanced neuroendocrine tumors (gastrointestinal, lung, pancreatic cancers) (NET)	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0048	Extension of Indication to include a new indication for the treatment of unresectable or metastatic, well-differentiated non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease; as a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 9.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/04/2016	26/05/2016	SmPC, Annex II, Labelling and PL	Please refer to the published Assessment Report Afinitor H-1038-II-48-AR.
IA/0049/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer 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	10/12/2015	n/a		

PSUSA/10268 /201503	Periodic Safety Update EU Single assessment - everolimus (indicated for advanced renal cell carcinoma, advanced breast cancer, advanced neuroendocrine tumors (gastrointestinal, lung, pancreatic cancers) (NET)	08/10/2015	n/a		PRAC Recommendation - maintenance
IB/0045	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	01/07/2015	n/a		
IB/0047/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/06/2015	n/a		
IB/0044/G	This was an application for a group of variations. B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	10/06/2015	n/a		

	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0043/G	This was an application for a group of variations. Update of section 5.1 of the Afinitor SmPC with final overall survival results for Study CRAD001C2324 (RADIANT-3); in addition, an administrative change in the address of the MAH has been also included in the grouped procedure. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	24/02/2016	SmPC, Labelling and PL	

WS/0613/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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.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.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.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	22/01/2015	n/a		

	increase compared to the originally approved batch size B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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 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) 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.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.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 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.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 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.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.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				
PSUV/0039	Periodic Safety Update	23/10/2014	16/12/2014	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0039.
II/0041	This variation concerns the update of the pooled safety data in section 4.8 of the SmPC in line with the revised Core Data Sheet following a review of the expanded safety data from a total of 9 studies related to the approved oncology indications. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to add a sentence to section 4.8 of the SmPC to clarify that angioedema has been reported with and without concomitant use of ACE inhibitors. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	16/12/2014	SmPC and PL	The MAH has submitted new safety data, which expanded the current oncology safety pool with one additional Phase I RCC study (L2101) and included more recent cut-off dates for 3 other studies (CRAD001L2201, CRAD001C2325 RADIANT-2 and CRAD001Y2301 BOLERO-2). Based on the pooling of the expanded safety data from a total of 9 studies, frequencies of a number of already labelled ADRs were adjusted. With the addition of the new safety data, a total of 19 additional new ADR terms appeared in the total list of 971 terms. However, based on a medical assessment, no new terms were identified to be listed in the SmPC. The proposed changes to the SmPC and Package Leaflet are acceptable. The overall benefit / risk balance is not affected by this variation, and remains positive for the approved indications.
II/0038	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	16/12/2014	SmPC	

IB/0040/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	01/07/2014	n/a		
R/0036	Renewal of the marketing authorisation.	20/03/2014	16/05/2014	SmPC, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of post-authorisation measures and having confirmed the positive benefit/risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of Afinitor, subject to the Conditions as laid down in Annex II to the Opinion. The CHMP recommends that one additional five-year renewal be required based on pharmacovigilance grounds.
II/0030	Update of section 4.8 of the SmPC based on the pooled safety database from eight clinical studies. A specific subsection for older people has also been introduced. Consequential changes have been introduced in section 4.4 of the SmPC. The PL was updated accordingly. In addition, the MAH took the opportunity to make an administrative change in section 5 of the PL. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD	21/11/2013	16/05/2014	SmPC and PL	The MAH undertook a review of the safety database by pooling together the safety data from the 3 randomized trials C2324, C2325, and C2240 as well as 4 open-label supportive Phase II studies (related to the approved indications) with a total number of patients of 2406 having received Afinitor in the approved indications. The frequency of the adverse reactions has been updated in section 4.8 of the SmPC. As a result, the following ADRs have been shifted down in frequency category: thrombocytopenia,

	template version 9. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				conjunctivitis, pure red cell aplasia, hypertriglyceridaemia, pulmonary embolism, haemoptysis, dry skin, nail disorder, pyrexia, non-cardiac chest pain, cough, dyspnoea, acute respiratory distress syndrome, angioedema, impaired wound healing. Newly listed ADRs have also been introduced: increased daytime urination, pancytopenia, menstruation irregular, amenorrhea have a frequency of "uncommon", herpes zoster is presented in a footnote to infections (uncommon) and glossitis and glossodynia have been included as footnote to stomatitis (uncommon). Section 4.4 of the SmPC was also revised in line with the Votubia SmPC.
IA/0037	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	28/10/2013	n/a		
II/0032	Update of section 4.5 of the SmPC in order to update the safety information on the interaction of Afinitor with moderate CYP3A4/PgP inhibitors. The requested variation proposed amendments to the Summary of Product Characteristics. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	16/05/2014	SmPC	Following a review of the SmPC, the MAH provided additional clarification concerning the use of CYP3A4 inhibitors and inducers. These included additional information on the wash-out periods following discontinuation of co-administration of moderate CYP3A4/PgP inhibitors and potent CYP3A4 inducers, refinement of the wording in the table of interactions and, following approval of procedure X-17-G, correction in the second dose reduction with co-administration of moderate CYP3A4/PgP inhibitors of 2.5mg daily instead of 5mg every other day. The changes to section 4.5 of the SmPC were not the result from any safety issues.
IAIN/0034	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure	22/10/2013	16/05/2014	SmPC and PL	

	concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority				
IAIN/0035/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	18/10/2013	n/a		
II/0033	Update of section 5.2 of the SmPC in order to clarify the dose adjustments for hepatic impaired patients based on the results of two studies X2102 and	25/07/2013	16/05/2014	SmPC	Following the assessment of the variation X-17-G based on two clinical trials, X2102 and A2303, section 5.2 of the SmPC has been updated in order to clarify the dose

	A2303. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				adjustments for hepatic impaired patients.
II/0031	Update of sections 4.6 and 5.3 of the SmPC with information related to the female fertility based on the clinical and nonclinical experience with Afinitor. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet with the addition of the Croatian representative and to amend contact details for the representative of the Netherlands. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	16/05/2014	SmPC, Annex II and PL	Based on the search in the MAH's safety database using MedDRA SMQ (broad) "fertility disorders" and the HLT "female gonadal function disorders" within the clinical and nonclinical experience with everolimus, sections 4.6 and 5.3 have been updated with information related to the female fertility.
II/0023/G	This was an application for a group of variations. Update of sections 4.2 and 4.4 of the SmPC with additional clarification on dose recommendations to manage the most commonly occurring adverse events. In addition, sections 4.6 and 4.8 in the SmPC have been updated to include information on	25/04/2013	27/05/2013	SmPC, Annex II and PL	Many of the most commonly occurring adverse drug reactions (ADR) with Afinitor require dose interruption or reduction and can be managed with supportive treatment. A more detailed guidance around the management of common ADRs is already available in the everolimus clinical study protocols for dose adjustments based on ADR severity as well as supportive ADR treatment and based on

	amenorrhea. The Package Leaflet was updated accordingly. Furthermore, the MAH took the opportunity to make minor changes to the SmPC. Finally, the PI is being brought in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				this section 4.2 of the SmPC has been updated to include a table on dose recommendations. In addition, in clinical trials and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhoea (secondary amenorrhoea and other menstrual irregularities). Sections 4.6 and 4.8 in the SmPC have been updated to include information on amenorrhea.
IB/0029/G	This was an application for a group of variations. B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	14/05/2013	n/a		

	procedure B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
X/0017/G	This was an application for a group of variations. Update of the Product Information (PI) for Afinitor based on the results of study X2102 in hepatically impaired patients and to apply for a new dosage strength of Afinitor 2.5 mg tablets to accommodate for the revised dosing recommendations in such patients. Sections 4.2, 4.4 and 5.2 of the SmPC were updated and the package leaflet was updated accordingly. Section 6.4 of the SmPC, Labelling and Package Leaflet were also updated regarding storage conditions. In addition, the MAH took the opportunity to make minor editorial amendments in the SmPC and to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 8.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data Annex I_2.(c) Change or addition of a new strength/potency	18/10/2012	18/12/2012	SmPC, Annex II, Labelling and PL	Study X2102 was a Phase I study to assess the pharmacokinetics of everolimus in subjects with mild, moderate and severe hepatic impairment. Based on the geometric mean ratio (90% CI) of AUC(0-inf), the doses required to adjust the exposure to subjects of normal hepatic function in subjects of mild, moderate, and severe hepatic impairment were 6.25 mg (4.7 – 8.3 mg), 3.07 mg (2.4 – 4.0 mg), and 2.75 mg (2.1 –3.7 mg), respectively. The newly proposed recommended starting dose for patients with mild, moderate and severe hepatic impairment is 7.5, 5, and 2.5 mg daily, respectively. Moreover, in patients with severe hepatic impairment, Afinitor should only be used if the potential benefit outweighs the risk. Finally, Afinitor tablets should not be stored at temperatures above 25oC.
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IB/0026/G	This was an application for a group of variations.	14/12/2012	n/a		

	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	17/08/2012	n/a		
II/0020	Extension of indication to include Afinitor for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. Consequently the sections 4.1, 4.5, 4.8 and 5.1 of the SmPC were updated in order to include changes in the indication. Section 4.6 was updated to align with wording in the SmPC for Votubia and minor editorial changes were made to section 5.3 to revise the wording to correlate exposure in rats in a male fertility study and clinical exposure. The Package Leaflet is updated accordingly. The Risk Management Plan and the Package Leaflet were	21/06/2012	23/07/2012	SmPC, Annex II and PL	Please refer to the Scientific Discussion H-1038-VAR-II-20-en

	updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0015	The scope of this type II variation is to amend the product information for Afinitor based on the results of study X2301 with an update of sections 4.4 and 4.5 of the SmPC to revise the information on the precaution for administration of Afinitor in combination with oral CYP3A4 substrates and update of the information on interaction of everolimus with CYP3A4, respectively. There were no changes to the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	19/03/2012	SmPC	The results from study X2301 showed that co-administration of everolimus with midazolam resulted in an increase in plasma concentration-time curve of 20-25% and an increase in peak concentration of 25-30% for hydroxy midazolam and midazolam. The increases in exposure and peak concentration were most likely attributed to pre-systemic drug interaction at the level of the intestinal wall. The inhibitory effect of everolimus on CYP3A4 substrates was considered weak and a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates was not expected.
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	22/02/2012	n/a		

IA/0021/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	16/12/2011	n/a		
II/0014	To update the product information for Afinitor with Deep Vein Thrombosis (DVT) as an adverse drug reaction. Changes are as follows: to include deep vein thrombosis as an uncommon adverse drug reaction in section 4.8 of the Summary of Product Characteristics (SmPC) and as an uncommon side effect in Section 4 of the Package Leaflet (PL). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	22/11/2011	SmPC and PL	From the MAH's clinical database, a total of 26 cases were identified with suspected relationship between everolimus administration and events of deep vein thrombosis reported in clinical studies and in post-marketing spontaneous reports. Of these, 16 cases originated from the renal cell carcinoma and pancreatic neuroendocrine tumour studies. The observed frequency of deep vein thrombosis events was between 0.5 and 1.6 % in the pooled databases for renal cell carcinoma and NET respectively. For post-marketing, a total of 3 cases of deep vein thrombosis were reported corresponding to 3400 patient years. The inclusion of deep vein thrombosis in the safety information was endorsed. The ADR has been added to the corresponding table in section 4.8 of the SmPC with the frequency of 'uncommon'. Section 4 of the Package Leaflet has been updated accordingly.
II/0010/G	This was an application for a group of variations.	22/09/2011	22/09/2011		

	- Addition of a new active substance manufacturing site. - Replacement of a site responsible for quality control and in-process control. - Substantial changes to the manufacturing process of the active substance. - Downscaling of the manufacturing process. - Deletion of a non-significant in-process test. - Addition of mixture specifications for a solvent. - Addition of specification for a raw material. - Tightening of specification limits for a starting material. - Deletion of a non-significant parameter. - Minor widening of specification of a reagent. - Deletion of non-significant specification parameters for an excipient. - Tightening of specification limits for an excipient. - Addition of a new specification parameter for an excipient. - Addition of the specification parameters for an excipient. - Addition of the specification parameters for an excipient. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - Other variation B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling 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.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.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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.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) 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) 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) 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) 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) 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)				
II/0008	Extension of indication Extension of indication to include 'Afinitor is indicated for the treatment of unresectable or metastatic, well-	21/07/2011	24/08/2011	SmPC, Annex II and PL	Please refer to Scientific discussion Affinitor-H-C-1038-II-08

	or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease'. Consequently, sections 4.1, 4.4, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics and the Package Leaflet have been updated. The Risk Management Plan statement in Annex II has been updated to the new template. The MAH also took the opportunity to update the product information in line with the QRD template (version 7.3.1) and to make minor corrections. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	11/07/2011	n/a		
II/0009/G	This was an application for a group of variations. C.I.4 - Variations related to significant modifications	14/04/2011	14/06/2011	SmPC, Annex II and PL	

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of	21/12/2010	n/a	Annex II	

	the pharmacovigilance system				
IB/0007/G	This was an application for a group of variations. to update the list of manufacturing sites involved in the manufacture of the AS and implement many minor amendments in the AS manufacturing process. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling 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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting	26/07/2010	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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				
II/0005	Within the finished product specifiction: to raise the authorised content limit for an already identified degradation product and to add a test parameter specification for a newly identified degradation product; finished product shelf life is updated accordingly based on the initially registered stability data. Opportunity is taken to submit updated validation reports. Quality changes	18/03/2010	27/04/2010	SmPC	
II/0006	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to include information regarding reported cases of hepatitis B reactivation based on the review of a signal	18/02/2010	30/03/2010	SmPC, Annex II and PL	A signal of a HBV reactivation with a fatal outcome in an ongoing clinical study prompted a review of the safety database for cases of HBV reactivation. The review detected 2 reports of HBV reactivation in patients treated

	prompted by a fatal outcome during an ongoing clinical study. The Package Leaflet has been updated accordingly. Section 4.5 of the SmPC has been updated to include corticosteroids as a drug class of the CYP3A4 inducers. In section 4.4 of the SmPC, a sentence regarding the occurrence of hyperglycaemia in patients who had abnormal fasting glucose was removed based on data from the pivotal phase 3 trial C2240. Frequencies of adverse events have been corrected in the PL in line with the SmPC. Furthermore, the MAH updated the list of local representatives in the Package Leaflet. The MAH also took the opportunity to update the SmPC in line with QRDv7.3 and to include other minor editorial changes. Update of Summary of Product Characteristics and Package Leaflet				with Afinitor with suspected causality and serious outcome. In addition one case of acute hepatic failure with suspected causality was identified. Therefore sections 4.4 and 4.8 of the SmPC were updated. The PL was amended accordingly. Furthermore, section 4.5 of the SmPC was updated to include the interaction with corticosteroids as a drug class of CYP3A4 inducers and a sentence regarding the occurrence of hyperglycaemia in patients who had abnormal fasting glucose was removed from section 4.4 based on the data from the pivotal phase 3 trial C2240. Finally, the frequency of adverse event in the PL for "high blood sugar" and "coughing up blood" was corrected in line with the information available in the SmPC.
II/0004	Update of the Detailed Description of the Pharmacovigilance system (DDPS) to version 8.0, including a change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number of the agreed DDPS. Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	30/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
IA/0003	To add a new site for primary and secondary packaging	03/12/2009	n/a		

	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms				
IB/0002	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	15/10/2009	15/10/2009	SmPC, Labelling and PL	
IB/0001	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	15/10/2009	15/10/2009	SmPC, Labelling and PL	