Votubia

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/0090	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	04/12/2024		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).

PSUSA/1343/202403	Periodic Safety Update EU Single assessment - everolimus (indicated for astrocytoma (SEGA), renal angiomyolipoma, refractory seizures)	28/11/2024	n/a		PRAC Recommendation - maintenance
II/0089	Submission of the final report from study CRAD001M2305 listed as a category 3 study in the RMP. This is an interventional PASS study to monitor the growth and development of paediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT). The RMP version 16.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/09/2024	n/a		Not applicable
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/0085	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/10/2023	n/a		
IB/0083/G	This was an application for a group of variations.	20/09/2023	n/a		

	B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation 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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
IA/0084/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	17/08/2023	n/a		

	(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)				
IB/0082/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	28/07/2023	n/a		
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/0080/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.3.z - Change in the manufacturing process of the finished or intermediate 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 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.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	18/11/2022	n/a		
IB/0079	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	29/07/2022	n/a		

IG/1520	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	24/06/2022	19/06/2023	SmPC	
IG/1518	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/06/2022	19/06/2023	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/1343/ 202103	Periodic Safety Update EU Single assessment - everolimus (indicated for astrocytoma (SEGA), renal angiomyolipoma, refractory seizures)	02/12/2021	n/a		PRAC Recommendation - maintenance
IA/0075/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	23/11/2021	n/a		
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2021	21/06/2022	PL	
IA/0074	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	10/09/2021	n/a		

	the product information				
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		
IAIN/0070/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	03/06/2021	21/06/2022	Annex II and PL	
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	20/05/2021	21/06/2022	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

	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 data				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.
IB/0069/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.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	08/01/2021	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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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				
II/0061	Update of sections 4.2, 5.1, and 5.2 of the SmPC based on results from a modelling and simulation study of patients from 6 months to less than 2 years of age whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/07/2020	25/08/2020	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0061'
R/0065	Renewal of the marketing authorisation.	28/05/2020	23/07/2020	PL	
IB/0066/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of	26/06/2020	n/a		

	the finished or intermediate product - Other variation B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation				
WS/1777	This was an application for a variation following a worksharing procedure according to Article 20 of 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	26/03/2020	n/a		
IAIN/0064/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.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)	22/01/2020	23/07/2020	Annex II and PL	

	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.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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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 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 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 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				
IB/0062/G	This was an application for a group of variations. 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.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/11/2019	n/a		
WS/1671	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	03/10/2019	n/a		

	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				
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 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	30/08/2019	n/a		

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		
PSUSA/1343/ 201803	Periodic Safety Update EU Single assessment - everolimus (indicated for astrocytoma (SEGA), renal angiomyolipoma, refractory seizures)	31/10/2018	n/a		PRAC Recommendation - maintenance
WS/1324/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.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 -	13/09/2018	n/a		

	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				
II/0055	Submission of the final report from the non-interventional study CRAD001MIC03, listed as a category 3 study in the RMP. This is an international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/09/2018	n/a		

II/0051	Update of sections 4.8 (all pharmaceutical forms) and 5.1 (dispersible tablets only) of the SmPC in order to update the safety and efficacy information based on final results from study CRAD001M2304, listed as a category 3 study in the RMP; this is a three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/07/2018	12/06/2019	SmPC and PL	Based on the results of a post-extension phase of study CRAD001M2304, the frequency category of the adverse drug reaction (ADR) "hypertension" has been upgraded from common to very common and the listed ADR "diarrhoea" has newly been added also under the most frequent grade 3-4 ADRS (with incidence ≥1%). In addition, figures indicating impact of early discontinued patients on response rate over time were also updated. These updates did not influence the benefit-risk balance of the product, which remains positive.
IAIN/0056/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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/07/2018	n/a		
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/0052	Transfer of Marketing Authorisation	16/05/2018	07/06/2018	SmPC, Labelling and PL	
X/0045	Annex I_2.(c) Change or addition of a new strength/potency	22/03/2018	31/05/2018	SmPC, Labelling and PL	
IB/0048/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.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	05/01/2018	n/a		
IB/0049	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	20/11/2017	n/a		
IB/0047/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	16/10/2017	31/05/2018	SmPC, Labelling and PL	
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	18/08/2017	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0044	Update of sections 4.2, 4.4 and 4.8 of the SmPC for Votubia 2.5 mg, 5 mg and 10 mg tablets and 2 mg, 3 mg and 5 mg dispersible tablets in order to reflect on data from study CRAD001M2304, in particular to revise dosing recommendations for patients with hepatic impairment, to update the warning related to infections, to include "sepsis" as an adverse drug reaction with the frequency "uncommon" and to revise frequencies of the following adverse drug reactions: "pharyngitis" ["common" to "very common"], "pneumonitis" ["uncommon" to "common"] and "rash" ["common" to "very common]". In addition, the subsection on Paediatric population in section 4.8 of the SmPC was updated based on results from study CRAD001M2304. Furthermore, sections 5.1 and 5.2 of the SmPC for Votubia 2 mg, 3 mg and 5 mg dispersible tablets was updated to add new information on pharmacodynamic and pharmacokinetic properties based on results from study CRAD001M2304. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/06/2017	26/07/2017	SmPC and PL	Based on the results from study CRAD001M2304, the CHMP considered that dose adjustments should be recommended in patients ≥18 years of age with hepatic impairment. In particular, in patients with moderate hepatic impairment (Child Pugh B): 50% of the recommended starting dose calculated based on BSA should be administered. In patients with severe hepatic impairment (Child Pugh C), Votubia is only recommended if the desired benefit outweighs the risk. In this case, 25% of the dose calculated based on BSA must not be exceeded. Some infections affecting patients treated with Votubia were severe, e.g. leading to sepsis, including septic shock. The CHMP considered that this information should be highlighted in the Product Information as a warning and signs of serious infections (fever, chills, rapid breathing and heart rate, rash, and possibly confusion and disorientation) should be presented in the Package Leaflet. Frequency of other adverse drug reactions (pharyngitis, pneumonitis and rash) was also updated based on the available study data. With regards to clinical efficacy, reduction in seizure frequency was sustained over an evaluation period of approximately 2 years. Based on a sensitivity analysis considering patients who prematurely discontinued Votubia as non-responders, response rates of 38.8% and 41.0% were observed at Week 54 and Week 102, respectively. Minor amendments were introduced with regards to information on pharmacokinetics based on the study results.

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	31/05/2018	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	31/05/2018	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/0041	Extension of Indication to include adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC) for Votubia 2 mg, 3 mg and 5 mg dispersible tablets. Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC were updated in parallel based on the results from the pivotal study. In addition, sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 were also updated for the 2.5 mg, 5 mg and 10 mg tablets to reflect on data relevant to these formulations. The Package Leaflet was updated in accordance. Furthermore, the PI was brought in line with the latest QRD template version 10. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/12/2016	27/01/2017	SmPC, Labelling and PL	Please refer to the Scientific Discussion Votubia EMEA/H/C/002311/II/0041.
II/0039	Update of sections 4.2 and 4.8 (for dispersible tablets) and sections 4.2, 4.8 and 5.1 (for tablets) of the SmPC in order to update the safety and efficacy information with the data from the final CSR comprising the extension phase of study M2302 in fulfilment of PAM (ANX 027). The Annex II and Package Leaflet are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the	25/02/2016	27/01/2017	SmPC, Annex II, Labelling and PL	In the pivotal study conducted to evaluate the efficacy and safety of Votubia in patients with TSC plus renal angiomyolipoma, patients initially treated with placebo were allowed to cross over to everolimus at the time of angiomyolipoma progression and upon recognition that treatment with everolimus was superior to treatment with placebo. At the time of the final analysis (4 years following the last patient randomisation), the median duration of

	opportunity to make minor editorial changes in the SmPC and to make few updates in the PI in order to align with Afinitor PI. Furthermore, the MAH took the opportunity to bring the PI in line with the latest QRD template version 9.1. Moreover, the revised RMP version 11.0 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				exposure to everolimus was 204.1 weeks (range 2 to 278). The angiomyolipoma best overall response rate had increased to 58.0% (95% CI: 48.3, 67.3), with a rate of stable disease of 30.4%. Similar improvements were seen in terms of reduction in angiomyolipoma volume, median time to angiomyolipoma progression, skin lesion response rate and SEGA response rate (based on an exploratory analysis in patients who also had SEGA). Among patients treated with everolimus during the study, no cases of angiomyolipoma-related nephrectomy and only one case of renal embolisation were reported. For more information, please refer to the Summary of Product Characteristics.
IA/0040	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		
II/0038	Update of sections 4.2 and 5.2 of the SmPC in order to define an appropriate initial dose for patients below the age of 3 years following requested additional simulations and Literature searches analysis. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/10/2015	10/12/2015	SmPC and PL	The recommended starting dose for Votubia for the treatment of patients with SEGA is 4.5 mg/m2. A higher starting dose of 7 mg/m2 is recommended for patients 1 to less than 3 years of age based on pharmacokinetic simulations.
II/0034	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update product information after completion of long-term follow up on duration of responses and	24/09/2015	16/11/2015	SmPC, Annex II and PL	Clinical study results did not show an impact of Votubia on growth and pubertal development. The long-term follow-up of patients randomised to everolimus and patients

	time to progression for study M2301. The Package Leaflet is updated accordingly. The data submitted fulfils the specific obligation SOB 024 and the Conditional Marketing Authorisation is switched to a Marketing Authorisation not subject to specific obligations. Votubia is also removed from the European list of additionally monitored medicines. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				randomised to placebo who thereafter crossed over to everolimus demonstrated durable responses. The most frequent adverse reactions (incidence ≥1/10 and suspected by the investigator to be related to treatment) from the pooled safety data are (in decreasing order): stomatitis, amenorrhoea, upper respiratory tract infections, hypercholesterolaemia, nasopharyngitis, menstruation irregular, acne, sinusitis, otitis media and pneumonia. The most frequent grade 3 4 adverse reactions (incidence ≥1%) were stomatitis, amenorrhoea, pneumonia, neutropenia, pyrexia, gastroenteritis viral and cellulitis.
PSUSA/1343/ 201503	Periodic Safety Update EU Single assessment - everolimus (indicated for astrocytoma (SEGA), renal angiomyolipoma, refractory seizures)	08/10/2015	n/a		PRAC Recommendation - maintenance
R/0033	Renewal of the marketing authorisation.	21/05/2015	28/07/2015		
IB/0035	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/0036/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.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	29/05/2015	n/a		

	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/0030/G	This was an application for a group of variations. Update of SmPC section 5.2 to provide information regarding the effect of food on the pharmacokinetics of the Votubia dispersible tablets based on Study X2114. Further, the MAH took the opportunity to implement editorial changes in the SmPC. Update of SmPC section 4.5 to provide a recommendation to consider a washout period following discontinuation of concomitant moderate CYP3A4/PgP inhibitors and potent CYP3A4 inducers, and to align the corticosteroid inducer-classification with the approved Afinitor SmPC (pursuant to variation II-32) 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	26/02/2015	28/07/2015	SmPC	In healthy subjects taking a single 9 mg dose (3 x 3 mg) of Votubia dispersible tablets in suspension, high fat meals reduced AUC by 11.7% and the peak blood concentration Cmax by 59.8%. Light fat meals reduced AUC by 29.5% and Cmax by 50.2%. Food, however, had no apparent effect on the post absorption phase concentration time profile 24 hours post-dose of either dosage form.

IAIN/0032	A.1 - Administrative change - Change in the name and/or address of the MAH	10/02/2015	28/07/2015	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	22/01/2015	n/a		

	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.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/0025	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/0025.
IA/0031/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)	12/12/2014	n/a		
II/0028	Update of the efficacy data in section 5.1 of the SmPC (5-year analysis) based on the CSR for study CRAD001C2485, an open-label study of everolimus in patients with SEGA associated with TSC. The CSR is provided in accordance with Article 46 and is part of the post-authorisation measure ANX 016.	23/10/2014	16/12/2014	SmPC	As part of the present application, the MAH has provided the final clinical study report (5-year analysis) for Study CRAD001C2485; a prospective, open-label, single-arm phase II study of everolimus in patients with SEGA. Twenty-eight evaluable patients with a confirmed diagnosis of TS and evidence of serial SEGA growth were recruited in

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				this study. All 28 patients were analyzed for efficacy and safety analyses. The primary efficacy endpoint was the change from baseline in the volume of the primary SEGA lesion at 6 months after the start of treatment (or at the last available assessment if a patient ended treatment prior to this time point) as determined by central radiology review. As exploratory analysis, magnetic resonance spectroscopy data for reduction of SEGA volume was collected at Month 6, and then at 6-monthly intervals. Patients (median age 11 years) were typical of the broad population of patients with SEGA associated with TS. 78,5% of the patients were less than 18 years of age at baseline. The primary SEGA volume was reduced by a median of 0.83 cm3 (range: 0.06 to 6.25; n=27) at Month 6 relative to baseline ($p < 0.001$). Results from the longer-term extension phase follow-up per independent central review show that the effect of everolimus on reducing SEGA volume is maintained at Month 60 with a median reduction in primary SEGA volume of 0.50 cm3 (range: -0.74 to 9.84; n=23) with 14 patients (60.9%) experiencing reductions of ≥ 30% relative to baseline and 12 patients (52.2%) experiencing reductions of ≥ 50%. Similar reductions were observed at Month 6 and sustained over time when assessed per local review. Median reduction in primary SEGA volume at Month 60 per local investigator assessment was 0.90 cm3 (range: -1.50 to 4.90), with 69.6% and 39.1% of patients experiencing reductions of ≥ 30% and ≥ 50%, respectively. As per local review, five patients (21.7%) had a % increase, as compared to two patients (8.7%) at the same time point per independent

					central review. Of the 26 patients with a ≥ 30% reduction in primary SEGA volume at any time point per central review, two patients met the definition for progression (i.e., an increase from nadir of ≥ 25% to a value greater than baseline) at a later time point. Median duration from first response (≥ 30% reduction in primary SEGA volume) to progression or last radiological assessment was 56.74 months (range: 5.7 to 77.1 months) per central review (n=26). Similar results were obtained for local review. Of the 23 patients with a ≥ 50% reduction in primary SEGA volume at any time point as per central review, one patient met the definition for progression (i.e., an increase from nadir of ≥ 25% to a value greater than baseline) at a later time point. Median duration from first response (≥ 50% reduction in primary SEGA volume) to progression or last radiological assessment was 53.91 months (range: 0 to 77.1 months) per central review (n=23). Similar results were obtained for local review. Among the 28 patients included in this study, SEGA progressions were observed in a total of three patients (10.7%) as per central review and in seven patients (25.0%) as per local review. With reference to safety, total exposure to everolimus in patients with TSC-associated SEGA amounted to 145.5 patient- years. The median duration of exposure to everolimus was 67.8 months (range: 4.7 to 83.2 months). 24 of the 28 patients (85.7%) were exposed to everolimus treatment for a period of at least 57 months. The median dose intensity was 5.04 mg/m2/day, with a range of 2.0 to

					10.5 mg/m2/day. The mean dose intensity was higher than the planned dosage (3 mg/m2/day). Dose interruptions, reductions and/or increases were required by all patients. A majority of patients had at least 2 dose reductions or interruptions (27 patients; 96.4%). Dose interruptions were primarily attributable to AEs (26 patients; 92.9%). Dose reductions were reported in 22 patients (78.6%), and were primarily due to protocol requirements (19 patients; 67.9%). Dose increases were primarily attributable to protocol requirements (28 patients; 100%). There were no AEs that led to study drug discontinuation. All patients experienced at least one AE suspected to be related to study drug. The most frequently reported AEs suspected to be related to study drug (in at least 30% patients), by PT were upper respiratory tract infection, cellulitis, gastroenteritis, stomatitis, mouth ulceration, sinusitis, otitis media and nasopharyngitis. Most AEs suspected to be related to study drug were considered by the Investigator to be grade 1 (mild) or grade 2 (moderate) in intensity. There were no grade 4 AEs suspected to be related to study drug. The most frequently reported grade 3 AEs by PT were cellulitis, pneumonia, sinusitis and stomatitis (2 patients each; 7.1%). The frequency of AEs suspected to be related to study drug reduced over the study period. One patient died during the study due to epilepsy. The Investigator did not suspect a relationship between the event and the study medication. Of the total number of AEs observed in the study, 32.1% AEs were considered SAEs, mostly of the SOC Infections and infestations. One patient experienced two SAEs in the

					sixth year on everolimus – cellulitis and abscess in limb, which were grade 3 in severity. In conclusion, no new safety concerns have been raised with the final (5-year) analysis. The benefit / risk balance is not affected by this variation, and remains positive for the approved indications.
II/0021	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/10/2014	n/a		
II/0027	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 safety data from studies CRAD001M2301, CRAD001M2302 and CRAD001C2485. The Package Leaflet has been updated accordingly. 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 and PL	The MAH has submitted a report on longer-term observations in the TSC safety pool of 3 ongoing trials in TSC (C2485, M2301, and 2302) with a data lock point of 31 March 2014. With this method, the MAH has identified a new ADR (mild to moderate lymphoedema), and the MAH has also taken the opportunity to update section 4.8 of the SmPC in order to reflect safety according to an approximately 1-year longer exposure of TSC patients to Votubia in ongoing clinical trials. The changes to the SmPC and Package Leaflet are acceptable. The benefit / risk balance is not affected by this variation, and remains positive for the approved indications.
R/0024	Renewal of the marketing authorisation.	22/05/2014	18/07/2014	SmPC and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations 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 annual renewal of the conditional MA for Votubia, subject to

					the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IB/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/07/2014	n/a		
II/0020	Update of sections 4.2 and 5.2 of the SmPC further to the pharmacokinetic sub-study results from the pivotal trial CRAD001M2301 investigating the pharmacokinetics in the paediatric population (MEA 017). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/06/2014	16/12/2014	SmPC	Limited data in patients <3 years of age (n=13) indicate that BSA normalised clearance is about two fold higher in patients with low BSA (BSA of 0.556 m2) than in adults. Therefore it is assumed that steady state could be reached earlier in patients <3 years of age Consequently, for patients <3 years of age, trough concentrations should be monitored at least 1 week after start of treatment or after any change in dose or pharmaceutical form.
PSUV/0022	Periodic Safety Update	25/04/2014	19/06/2014	SmPC and PL	Update of section 4.4 and 4.5 of the SmPC to add a warning on angioedema following the co-administration of everolimus and angiotensin converting enzyme inhibitors (ACEi). The Package leaflet was updated accordingly. Please refer to: Votubia-H-C-2311-PSUV-0022 EPAR - Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IA/0023	A.7 - Administrative change - Deletion of manufacturing sites	11/02/2014	n/a		
II/0019	Update of Section 5.2 of the SmPC to clarify that the dose adjustments for hepatic impairment patients was based on results of two studies conducted in patients with impaired hepatic function relative to subjects with normal hepatic function.	21/11/2013	19/06/2014	SmPC	Following the assessment of the variation for Afinitor II-33, the section 5.2 of the SmPC was clarified that the dose adjustments for hepatic impairment patients was based on results of two clinical trials, X2102 and A2303.

	The requested variation proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
X/0008/G	This was an application for a group of variations. Extension of indication to include treatment of patients < 3 years of age with TSC who have SEGA. In addition, the SmPC was updated based on efficacy and safety data from the pivotal Study M2301 and longer-term follow-up from the Study C2485 for the SEGA paediatric population. A revised starting dose from 3 mg/m2 to 4.5 mg/m2 for patients with TSC who have SEGA has also been included. The SmPC was modified in sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2. The Package Leaflet and Labelling were updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The requested group of variations proposed amendments to the SmP, Annex II, Labelling and Package Leaflet. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/09/2013	15/11/2013	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion "H-2311-VAR-X-08/G-en".

II/0016/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC with the pooled safety data based on three studies (CRAD001C2485, CRAD001M2301, CRAD001M2302), update of sections 4.6 and 5.3 of the SmPC with information related to female fertility based on the clinical and nonclinical experience with everolimus and update of sections 4.4 and 4.5 of the SmPC with regard to the potential interaction of Votubia with CYP3A4/5 substrates based on the results of X2103 study. In addition, the MAH took the opportunity to propose minor further changes to the SmPC. The package Leaflet was updated accordingly. The requested group of variations 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 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	19/09/2013	15/11/2013	SmPC and PL	As requested by the CHMP, the MAH performed an analysis of the pooled safety data from the three studies in TSC-SEGA patients (CRAD001C2485, CRAD001M2301, CRAD001M2302). The reassessment lead to changes in section 4.8, where new ADRs have been listed as common (pharyngitis streptococcal, lymphopenia, urinary tract infection, pharyngitis, cellulitis, pneumonia, gastroenteritis viral, epistaxis, oral pain) and uncommon (bronchitis viral, blood follicle stimulation hormone increased). In addition, other ADRs are no longer listed (agitation, conjunctivitis, convulsion, and gait disturbance) since they have been reassessed as either related to underlying condition or not listed in the double blind phase of the two randomised studies. The terms "haemorrhage" has been listed by individual the preferred terms epistaxis (1.7%)", "menorrhagia (1.2%)", and "vaginal haemorrhage (1.2%) with frequencies above 1%. Other changes include a new section on elderly patients, addition of "sepsis" as an example of infection which has had occasional fatal outcome and the splitting of "blood glucose" and "blood lipids" for better readability. Based on the outcome of the variation for Afinitor EMEA/H/C/1038/II/15, the MAH included a warning on the co-administration of Votubia with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions, in particular, with midazolam which resulted in a 25% increase in midazolam Cmax and a 30% increase in midazolam AUC(0-inf). Reanalysis of the non-clinical data showed that female fertility may be affected by treatment with everolimus by increasing loss of implantation.
N/0018	Minor change in labelling or package leaflet not	07/08/2013	15/11/2013	PL	

	connected with the SPC (Art. 61.3 Notification)				
IA/0017/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	29/07/2013	n/a		
R/0015	Renewal of the marketing authorisation.	25/04/2013	17/07/2013	Annex II	
IB/0014/G	This was an application for a group of variations. 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	25/01/2013	n/a		
IB/0012	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	19/12/2012	15/07/2013	SmPC, Labelling and PL	
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0011/G	This was an application for a group of variations.	07/11/2012	n/a		

	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.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/0004	Extension of indication to include Votubia for the treatment of "adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume."Consequently the sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated in order to include changes related to the indication. The Package Leaflet was updated accordingly. The requested variation proposed amendments to the SmPC 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	20/09/2012	31/10/2012	SmPC and PL	Please refer to Scientific Discussion "H-2311-VAR-II-04-en"
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance	17/08/2012	n/a		

	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				
R/0005	Renewal of the marketing authorisation.	24/05/2012	26/07/2012	SmPC and Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations 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 the conditional MA for Votubia, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IAIN/0006	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	29/06/2012	n/a		
II/0002	Update of sections 4.2, 4.4, and 5.2 of the SmPC in order to update the safety information based on the results of study CRAD001X2102 which investigated the effect of everolimus in hepatically impaired patients (Child Pugh A-C) and dose adjustment according to grade. Section 4.2 was updated to include dosing recommendations for hepatically impaired patients, section 4.4 to advise on the precaution of the administration of Votubia in	24/05/2012	28/06/2012	SmPC	The safety, tolerability and pharmacokinetics of Votubia were evaluated in a single oral dose study of everolimus in 34 adult subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively. Dose adjustment was recommended for adult patients with hepatic impairment.

	hepatically impaired patients, and section 5.2 to include the key results of the pharmacokinetic study of everolimus in subjects with impaired hepatic function. No changes have been proposed for 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				However, Votubia was not recommended in adults with severe hepatic impairment and in children of less than 18 years of age with any grade of hepatic impairment.
II/0001	To update the product information for Votubia 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	15/12/2011	06/02/2012	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 net 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.
IA/0003/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	16/12/2011	n/a		

	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				