EMA/583338/2020

Torisel

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
IB/0080	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2020		SmPC, Annex II, Labelling and PL	
IA/0079	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the	30/04/2020	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	dossier) - Deletion of a supplier				
II/0078	Submission of an updated RMP version 4.0 in order to remove all safety concerns from the RMP in order to comply with the Module V, Risk Management Systems Rev; this includes the removal of all missing information items as well as the 'risk of cardiovascular events in patients with coexisting cardiovascular conditions' and 'reproductive toxicity' as already confirmed in the latest PSUR EMEA/H/C/PSUSA/00002887/201803). 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	16/01/2020	n/a		
IG/1124	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	11/09/2019	n/a		
IA/0075	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	29/07/2019	n/a		
IB/0074	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling	07/02/2019	n/a		

	down to 10-fold				
IB/0073	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/01/2019	09/12/2019	SmPC	
PSUSA/2887/ 201803	Periodic Safety Update EU Single assessment - temsirolimus	31/10/2018	n/a		PRAC Recommendation - maintenance
T/0071	Transfer of Marketing Authorisation	11/07/2018	08/08/2018	SmPC, Labelling and PL	
II/0069	Update of sections 4.2 and 4.3 of the SmPC in relation to hepatic impairment for patients with mantle cell lymphoma (MCL), as requested to be clarified during the renewal procedure (EMEA/H/C/000799/R/0065). In addition, the MAH took the opportunity to make minor editorial changes in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	23/03/2018	SmPC and PL	No dose adjustment is recommended for patients with MCL and mild hepatic impairment. Temsirolimus should not be used in patients with MCL and moderate or severe hepatic impairment, as such use is contra-indicated.
II/0070/G	This was an application for a group of variations. 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	18/01/2018	n/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.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.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.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				
IA/0068	A.7 - Administrative change - Deletion of manufacturing sites	25/09/2017	n/a		
R/0065	Renewal of the marketing authorisation.	18/05/2017	13/07/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Torisel in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0066	Submission of the further analysis of a possible association of corticosteroid (pre-)treatment and frequency and severity of hypersensitivity/infusion reactions in study 3066K1-4438-WW (B1771007), as requested by the CHMP during procedures EMEA/H/C/799/MEA 023.1 and EMEA/H/C/799/MEA 024.1. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/07/2017	n/a		
II/0067	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		
II/0063	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	23/02/2017	13/07/2017	Annex II and PL	

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
II/0064	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	13/07/2017	SmPC and PL	Caution should be exercised when temsirolimus is given concomitantly with ACE inhibitors (e.g. ramipril) and/or calcium channel blockers (e.g. amlodipine). An increased risk of angioneurotic oedema (including delayed reactions occurring two months following initiation of therapy) is possible in patients who receive temsirolimus concomitantly with an ACE inhibitor and/or a calcium channel blocker. An increased incidence of angioneurotic oedema (including delayed reactions occurring two months following initiation of therapy) has been observed in patients who received temsirolimus or other mTOR inhibitors in combination with an ACE inhibitor (e.g. ramipril) and/or a calcium channel blocker (e.g. amlodipine).
PSUSA/2887/ 201503	Periodic Safety Update EU Single assessment - temsirolimus	19/11/2015	14/01/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2887/201503.
II/0062	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/12/2015	12/12/2016	SmPC and Annex II	
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	15/10/2015	PL	
IB/0059/G	This was an application for a group of variations. To extend the due date of the category 1 activity ANX 027.2 - final CSR for study 3066K1-4438-WW.	12/11/2014	15/10/2015	Annex II	

	To extend the due date of the category 1 activity MEA 028, to evaluate the toxic effects of interest [e.g., bleeding, infection-and mucositis-relate events] for study 3066K1-4438-WW (formerly FUM 028) together with a review discussing potential new safety concerns arising from the results. To add a new category 3 activity "Performance of an in vitro CYP3A4/ drug interaction study with both substrates testosterone and midazolam" to the Pharmacovigilance Plan of the RMP. 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				
II/0058	Update of sections 4.5 and 5.2 of the SmPC following the pharmacokinetic (PK) analysis from an in vivo drug-drug interaction (DDI) study between temsirolimus 175mg or 75mg and desipramine. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	15/10/2015	SmPC	In this variation the MAH added clarification pertinent to interactions with other medicines indicating that Torisel is unlikely to affect medicines metabolised by a group of hepatic enzymes, namely CYP2D6.
II/0057	Update of section 4.8 of the SmPC to change the frequency of the adverse reaction interstitial lung	24/10/2013	20/11/2013	SmPC and PL	Interstitial lung disease (ILD) is a known adverse drug reaction for temsirolimus as mentioned in sections 4.4

	disease (ILD) further to the request of the CHMP (LEG 031.1). In addition, the MAH took the opportunity to make minor corrections to the Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				'Special warnings and precautions for use' and section 4.8 'Undesirable effects' of the SmPC. Further to the assessment of safety data from a cumulative review on ILD (LEG 031.1), the MAH was requested in May 2013 to submit a variation to update the SmPC with the correct frequency for this adverse drug reaction. A review of the pooled dataset from studies 3066K1-304 and 3066K1-305 (n=321) described a total of 16 ILD reports (5%) and 6 (1.9%) Grade 3-4 events. Section 4.8 of the SmPC has been revised to reflect these frequencies.
IB/0056/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.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.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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters	22/08/2013	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.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.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.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/0055	Update of section 4.4 of the SmPC to add a warning on Pneumocystis jiroveci pneumonia (PCP) and	27/06/2013	20/11/2013	SmPC, Annex	Section 4.4 and 4.8 of the SmPC have been updated to include cases of Pneumocystis jiroveci pneumonia (PCP),

	section 4.8 of the SmPC to include PCP with the frequency of rare, based on a safety review conducted by the Marketing Authorisation Holder. The Package Leaflet (PL) has been updated accordingly. The PL has also been updated to add the Croatian local representative. Furthermore the MAH took the opportunity to align the product information to the QRD template (version 9). Lastly, the MAH made some modifications to the ADR pooled table in section 4.8 of the SmPC for correctness. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II and PL	some with fatal outcomes, that have been reported in patients who received temsirolimus, many of whom also received corticosteroids or other immunosuppressive agents. Prophylaxis of Pneumocystis jiroveci pneumonia (PCP) should be considered for patients who require concomitant use of corticosteroids or other immunosuppressive agents based upon current standard of care.
IAIN/0054	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	18/02/2013	20/11/2013	Annex II and PL	
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0052	Update of sections 4.5 and 5.2 of the SmPC with regards to drug-drug interactions with lenalidomide, a P-glycoprotein substrate, further to the request of the CHMP in responses to PSUR 6. The MAH has also taken the opportunity to introduce some	15/11/2012	20/11/2013	SmPC and PL	In vitro data on drug-drug interactions between temsirolimus and medicinal products that are P-glycoprotein substrates are currently reflected in the product information of Torisel. The effect of P-gp inhibition by temsirolimus has not been investigated in a clinical

	modifications to sections 6.4 and 6.6 of the SmPC for clarity and consistency. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				drug-drug interaction study, however recent preliminary data from a phase 1 study of combined lenalidomide (dose of 25 mg) and temsirolimus (dose of 20 mg) seemed to support the in vitro findings and suggested an increased risk of adverse events. Hence, the product information of Torisel has been updated to reflect this information. When temsirolimus is co administered with medications which are P-gp substrates (e.g. digoxin, vincristine, colchicine, dabigatran, lenalidomide, and paclitaxel) close monitoring for adverse events related to the co-administered drugs should be observed. The CHMP considered the changes to the product information do not affect the current benefit-risk balance of Torisel which continues to be positive.
A20/0051	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the CHMP further to the concerns raised during a Good Clinical Practice inspection on the conduct of bio-analytical studies by the Cetero Research facilities (Houston, USA), to assess the impact thereof on the risk-benefit balance of Torisel and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.	19/07/2012	24/09/2012		Please refer to the assessment report : EMEA/H/C/891/A-20/0019
R/0047	Renewal of the marketing authorisation.	19/07/2012	20/09/2012	SmPC, Annex II, Labelling and PL	Based on the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the risk-benefit balance of Torisel for the first-line treatment of adult patients with advanced renal

					cell carcinoma (RCC) who have at least three of six prognostic risk factors and for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL) remains positive but considers that its safety profile is to be closely monitored for the following reasons: • The MAH should provide the results of an ongoing post-marketing study in Mantle Cell Lymphoma to address whether similar efficacy can be achieved with a less toxic dose regimen. • The MAH should continue to closely monitor and address several safety concerns in the next PSURs, including incidence and frequency of interstitial lung disease (ILD) evaluating in particular ILD in Japanese and East Asiatic populations, fatal respiratory events, cardiac events, cases observed in children, off-label use, safety in children and cases of palmar-plantar erythrodysaesthesia. Therefore, based upon the safety profile of Torisel, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IA/0050	A.7 - Administrative change - Deletion of manufacturing sites	19/07/2012	n/a		
IG/0169/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	08/06/2012	n/a		

	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				
A20/0045	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	16/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/799/A-20/0045
IA/0048	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	07/05/2012	n/a		
IB/0046	A.7 - Administrative change - Deletion of manufacturing sites	21/03/2012	n/a		
IB/0042	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	19/12/2011	n/a		
IB/0041	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	18/11/2011	n/a		

IA/0043	A.7 - Administrative change - Deletion of manufacturing sites	18/11/2011	n/a		
IA/0040	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	07/11/2011	n/a		
T/0039	Transfer of Marketing Authorisation from Wyeth Europa Ltd to Pfizer Limited. Transfer of Marketing Authorisation	15/08/2011	02/09/2011	SmPC, Labelling and PL	n/a
IB/0037	B.II.e.4.z - Change in shape or dimensions of the container or closure (immediate packaging) - Other variation	26/08/2011	n/a		
IB/0036/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.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	13/07/2011	n/a		
IA/0038	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	07/07/2011	n/a		

	procedure				
II/0032	Update of SmPC sections 4.4 and 5.2 regarding the treatment of patients with hepatic impairment, in particular with respect to an increased rate of fatal events observed in patients with moderate to severe hepatic impairment as well as reflecting the results of a phase I study for mild to moderate hepatic impaired patients. The MAH also took the opportunity to include a correction to SmPC section 4.2 as well as in the labelling. The list of local representatives in the Package Leaflet (PL) has also been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	23/06/2011	SmPC, Labelling and PL	Temsirolimus should be used with caution when treating patients with hepatic impairment; use of temsirolimus in patients with mantle cell lymphoma with moderate or severe hepatic impairment is not recommended. In an open-label, dose-escalation phase I study in 110 subjects with advanced malignancies and either normal or impaired hepatic function, concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. Assessment of AST and bilirubin levels is recommended before initiation of temsirolimus and periodically after. An increased rate of fatal events was observed in patients with moderate and severe hepatic impairment. The fatal events included those due to progression of disease; however a causal relationship cannot be excluded. Based on the phase I study, no dose adjustment of temsirolimus is recommended for renal cell carcinoma (RCC) patients with baseline platelet counts 100x109/l and mild to moderate hepatic impairment (total bilirubin up to 3 times upper limit of normal [ULN] with any abnormality of AST, or as defined by Child-Pugh Class A or B). For patients with RCC and severe hepatic impairment (total bilirubin > 3 times ULN with any abnormality of AST, or as defined by Child-Pugh Class C), the recommended dose for patients who have baseline platelets 100 x 109/l is 10 mg IV once a week infused over a 30-60 minute period.
IA/0035/G	This was an application for a group of variations.	19/04/2011	n/a		

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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)				
WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	n/a		
IB/0034	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)	03/03/2011	n/a	SmPC	
II/0031	Update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 with information based on the results of a Phsae I/II safety and exploratory PK study in paediatric subjects with relapsed/refractory solid tumours in line with FUM 007. The Package Leaflet (PL) has been updated accordingly. The MAH also took the opportunity to update the List of Local Representatives in the PL as well as to remove the DDPS version number from Annex II. C.I.4 - Variations related to significant modifications	16/12/2010	24/01/2011	SmPC, Annex II and PL	In the paediatric population, clearance of temsirolimus was lower and exposure (AUC) was higher than in adults. In contrast, exposure to sirolimus was commensurately reduced in paediatric patients, such that the net exposure as measured by the sum of temsirolimus and sirolimus AUCs (AUCsum) was comparable to that for adults. In a phase 1/2 safety and exploratory efficacy study, 71 patients (59 patients, aged from 1 to 17 years, and 12 patients, aged from 18 to 21 years) received temsirolimus as a 60-minute IV infusion once weekly in three-week cycles. In part 1, 14 patients aged from 1 to 17 years with

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				advanced recurrent/refractory solid tumours received temsirolimus at doses ranging from 10 mg/m2 to 150 mg/m2. In part 2, 45 patients aged from 1 to 17 years with recurrent/relapsed rhabdomyosarcoma, neuroblastoma, or high grade glioma were administered temsirolimus at a weekly dose of 75 mg/m2. Adverse events were generally similar to those observed in adults. Temsirolimus was found to be ineffective in paediatric patients with neuroblastoma, rhabdomyosarcoma, and high-grade glioma (n = 52). For subjects with neuroblastoma, the objective response rate was 5.3% (95% CI: 0.1%, 26.0%). After 12 weeks of treatment, no response was observed in subjects with rhabdomyosarcoma or high-grade glioma. None of the 3 cohorts met the criterion for advancing to the second stage of the Simon 2 stage design. The adverse reactions reported by the highest percentage of patients were haematologic (anaemia, leukopaenia, neutropaenia, and thrombocytopaenia), metabolic (hypercholesterolaemia, hyperlipaemia, hyperglycaemia, increase of serum aspartate amino transferase [AST] and serum alanine aminotransferase [ALT] plasma levels), and digestive (mucositis, stomatitis, nausea, and vomiting).
IB/0033	The purpose of this variation is to modify the expression of the strength of the medicinal product throughout the Product Information in order to improve clarity with respect to the content of the pack and the instructions for dilution and administration and prevent/avoid medication errors. C.I.z - Changes (Safety/Efficacy) of Human and	15/12/2010	n/a	SmPC, Labelling and PL	

	Veterinary Medicinal Products - Other variation				
II/0027	Update of SmPC section 4.8 with the term "rhabdomyolisis" as adverse reaction under post-marketing experience. Section 4 of the PL has been revised accordingly. In addition, the MAH took the opportunity to perform two numerical corrections in SmPC sections 4.4 and 5.2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	05/11/2010	SmPC and PL	Following a company's safety database search 3 reports of rhabdomyolysis were identified. It was concluded that there is reasonable suspicion of a causal relationship between the administration of temsirolimus and the occurrence of rhabdomyolysis. As a consequence, the term "rhabdomyolysis" has been added as an adverse reaction under post-marketing experience to SmPC section 4.8. Information in this regard has also been added to section 4 of the package leaflet under side effects for which frequency has not been determined.
IB/0029	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/10/2010	n/a		
IA/0030	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/09/2010	n/a		
IA/0028	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/09/2010	n/a		
IB/0025	B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/	14/07/2010	n/a		

	immunological medicinal products				
II/0016	Update of SPC section 4.4 to amend the existing warning on Interstitial lung disease with guidance on screening and monitoring for potential cases. Furthermore, update of SPC section 4.8 to add "Stevens-Johnson syndrome" as an adverse drug reaction in the postmarketing section. In addition, update of SPC sections 4.4 and 4.7 to reflect the ethanol amount related to the higher starting dose of 175mg in MCL patients. The package leaflet has been updated accordingly. The MAH took also the opportunity to revise the Product Information in accordance with the latest QRD template version as well as to update the list of Local Representatives in 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	20/05/2010	02/07/2010	SmPC, Annex II and PL	A more specific guidance on screening and monitoring for potential cases of ILD has been added to SPC section 4.4 following a retrospective radiological review of chest CT scans from the pivotal study (3066K1-304-WW) supporting the RCC indication. An independent review of radiographic images and an Advisory Board review of cases of ILD from study 3066K1-2217-AP (a phase 2 open-label study of temsirolimus in patients with advanced RCC) were also conducted. There have been cases of non-specific interstitial pneumonitis, including fatal reports, occurring in patients who received weekly intravenous TORISEL. Some patients were asymptomatic or had minimal symptoms with pneumonitis detected on computed tomography scan or chest radiograph. It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of TORISEL therapy. Periodical follow-up assessments may be considered. It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms. and patients should be advised to report promptly any new or worsening respiratory symptoms. If clinically significant respiratory symptoms develop, consider withholding TORISEL administration until after recovery of symptoms and improvement of radiographic findings related to pneumonitis. Empiric treatment with corticosteroids and/or antibiotics may be considered. Furthermore, in response to the receipt of spontaneous reports of Stevens-Johnson syndrome coincident with the administration of temsirolimus, the MAH conducted a

					focused review of this topic. Two reports described patients who experienced Stevens-Johnson syndrome. Since the reports of Stevens-Johnson syndrome were spontaneous cases, an estimated frequency for this event cannot be determined and the adverse drug reaction has been added under post-marketing experience in SPC section 4.8. Information has been added to SPC section 4.4 and 4.7 that patients
IB/0022	To add a new In Process Test (IPC) for Torisel Diluent. B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	01/07/2010	n/a		
IB/0026	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	29/06/2010	n/a		
IA/0024	To replace Wyeth Research site (Barwell Lane, Gosport Hampshire, PO 13 0AU UK) by Wyeth Medica Ireland Ltd (Newbridge WMI, County Kildare, Republic of Ireland) for testing oxidative/hydrolysis degradants by HPLC/MS. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing	28/04/2010	n/a		

	takes place				
IA/0021	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	23/04/2010	n/a	Annex II	
IA/0020	C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	23/04/2010	n/a	Annex II	
IA/0019	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	23/04/2010	n/a	Annex II	
IA/0018	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	23/04/2010	n/a	Annex II	
IA/0017	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	23/04/2010	n/a	Annex II	
IA/0023	To replace a site where quality control tests for the active substance take 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	19/04/2010	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
II/0015	Update of sections 4.5 and 5.2 of the Summary of Product Characteristics to reflect the results of in vitro CYP iso-enzymes and P-gp inhibition studies as well as the results of an in vivo study on the elimination of temsirolimus in the faeces, further to the request of the CHMP following the assessment of follow-up measures (FUM 008, 009, 010 and 011). The MAH also took the opportunity to update the list of local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	25/01/2010	SmPC and PL	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) made the commitments: * To provide CYP2B6 and 2E1-mediated in vitro inhibition data (FUM 008), * To provide updated results of the ADME study, with focus on temsirolimus-related material present in faeces, particularly determining the presence of glucuronide or sulphate conjugates (FUM 009), * To determine the IC50 for temsirolimus and sirolimus inhibition of P-gp by in-vitro studies and reporting the data. Depending on the results from the IC50 studies for temsirolimus and sirolimus inhibition of P-gp, additional in vitro studies will be performed to determine the Ki and/or an in vivo interaction study will be considered (FUM 010 & 011). The MAH conducted in vitro inhibition studies with CYP iso-enzymes and P-gp as well as an in vivo study on the elimination of temsirolimus in the faeces. Further to the request of the CHMP, sections 4.5 and 5.2 of the Summary of Product Characteristics (SPC) have been updated to reflect the available data.
II/0010	Update to SPC sections 4.2, 4.4 and 5.2 to provide dosage recommendations for the use of temsirolimus in patients with varying grades of hepatic impairment for the treatment of renal cell carcinoma (RCC). In	19/11/2009	23/12/2009	SmPC and PL	This application is submitted in response to a Follow-Up measure previously committed by the MAH. Temsirolimus pharmacokinetics have been investigated an open-label, dose-escalation study in 112 patients with advanced

	addition, following a review of reports of fatal pulmonary embolism, addition of the term "including fatal outcomes" after the adverse reaction "pulmonary embolus" in SPC section 4.8. The package leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				malignancies and either normal or impaired hepatic function. Based on these study data, no dose adjustment of temsirolimus is recommended for patients with advanced renal cell carcinoma (RCC) and mild to moderate hepatic impairment. For patients with RCC and severe hepatic impairment, the recommended dose for patients who have baseline platelets 100 x 109/l is 10 mg IV once a week infused over a 30-60 minute period. The existing contraindication regarding the use of temsirolimus in patients with mantle cell lymphoma with moderate or severe hepatic impairment remains unchanged.
II/0001	Extension of Indication This type II variation concerns an Extension of Indication to add treatment of adult patients with relapsed and/or refractory mantel cell lymphoma (MCL). Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SPC have been amended and the Package Leaflet has been updated accordingly. Further, the MAH has taken the opportunity to make some minor editorial changes to the annexes and to update the contact details of the UK local representative in the Package Leaflet. In addition, the MAH has updated annex IIB to include the version number of the latest Risk Management Plan (version 2.4) agreed with the CHMP. Furthermore, the CHMP reviewed the data and justifications submitted by the applicant taking into account the provisions of Article 14(11) of Regulation	23/07/2009	14/10/2009	SmPC, Annex II and PL	See Scientific discussion 'Torisel-H-799-II-01'.

	(EC) No. 726/2004, and taking into account the provisions of the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)", and considered that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies based on improved efficacy. Extension of Indication				
IB/0013	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	25/09/2009	n/a		
IB/0012	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	25/09/2009	n/a		
IB/0011	IB_10_Minor change in the manufacturing process of the active substance	25/09/2009	n/a		
IA/0014	IA_13_a_Change in test proc. for active substance - minor change	10/09/2009	n/a		
IB/0007	IB_17_a_Change in re-test period of the active substance	03/06/2009	n/a		
II/0006	Update of DDPS (Pharmacovigilance) Changes to QPPV Update of DDPS (Pharmacovigilance)	23/04/2009	26/05/2009	Annex II	This type II variation concerns an update of the Detailed Description of the Pharmacovigilance System (DDPS) in Module 1.8.1 to reflect a change in the Qualified Person in the EEA for Pharmacovigilance (QPPV). Consequently,

					Annex II has been updated to reflect the latest version of the DDPS agreed with the CHMP (version 2.0).
IA/0009	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	24/04/2009	n/a		
IA/0008	IA_13_a_Change in test proc. for active substance - minor change	24/04/2009	n/a		
II/0003	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/11/2008	07/01/2009	SmPC, Labelling and PL	This type II variation concerns an update of sections 4.4 and 4.8 of the SPC with additional information regarding the risk and timing of hypersensitivity/infusion reactions. In addition, sections 4.4 and 4.5 of the SPC have been updated with further information regarding the risk of delayed angioneurotic oedema with concomitant administration of temsirolimus and ACE inhibitors, and section 4.8 with the ADRs 'pleural effusions' and 'pericardial effusions'. The Package Leaflet has been updated accordingly. Further, the ATC code has been added to section 5.1 of the SPC, and sections 2 and 6.6 of the SPC have been updated as well as the labelling and Package Leaflet for increased clarity with regards to the content of the pack and instructions for dilution and administration of the product. Editorial changes and changes to put the annexes in line with the latest QRD template were also included throughout the product information. Hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, hypersensitivity and anaphylaxis, have been associated with the administration

					of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during the infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered. A benefit-risk assessment should be done prior to the continuation of temsirolimus therapy in patients with severe or life-threatening reactions. If a patient develops a hypersensitivity reaction during the Torisel infusion, despite the premedication, the infusion must be stopped and the patient observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the p
IA/0005	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/12/2008	n/a	Annex II and PL	
IA/0004	IA_13_a_Change in test proc. for active substance - minor change	19/11/2008	n/a		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/04/2008	n/a	PL	