Zytiga

Proceduralteps 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/0071/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) C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/06/2022		SmPC	C.I.z – To update section 2 of the SmPC to add an equivalency statement between abiraterone and abiraterone acetate.

[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).

IA/0070	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/05/2022	n/a		
PSUSA/15/20 2104	Periodic Safety Update EU Single assessment - abiraterone	02/12/2021	n/a		PRAC Recommendation - maintenance
IB/0069	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	25/11/2021	n/a		
IB/0067/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.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/07/2021	06/01/2022	SmPC, Labelling and PL	
IB/0066/G	This was an application for a group of variations. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	05/05/2021	n/a		

	changes to an approved test procedure 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				
IAIN/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/12/2020	06/01/2022	SmPC and PL	
II/0061	To update the Summary of Product Characteristics section 4.4 and 4.5 and package leaflet as per the PRAC recommendations published on 10th Feb 2020 to add a new warning on Hypoglycemia, the Package Leaflet is updated accordingly. In addition, some minor updates have also been made to Annex II of the product information. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	11/06/2020	06/01/2022	SmPC, Annex II and PL	Cases of hypoglycaemia have been reported when ZYTIGA plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar should be monitored in patients with diabetes. In a CYP2C8 drug drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M III and M IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide.
IB/0062/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	05/06/2020	n/a		

	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold				
II/0058	To update section 5.1 of the SmPC based on final results from study PCR3011 (Lattitude); this is a randomised, double-blind, placebo-controlled study designed to determine the efficacy of abiraterone acetate and low-dose prednisone in men with metastatic hormone-naive prostate cancer. The MAH took the occasion to update the product information as per the latest QRD version and to update local representative for Spain and Hungary in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	23/04/2020	SmPC	The MAH has provided results of the final analysis of OS from study PCR3011. OS results were statistically significant with a HR of 0.661 [95% CI: 0.564, 0.775] and an improvement in median OS of 16.8 months (53.3 months in the AA-P arm and 36.5 months in the Placebo arm).
IA/0060	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	16/10/2019	n/a		
II/0056/G	This was an application for a group of variations. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions B.I.b.1.z - Change in the specification parameters	18/07/2019	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
IA/0057/G	This was an application for a group of variations. 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	25/04/2019	n/a		
IB/0055	C.I.z - Changes (Safety/Efficacy) of Human and	26/02/2019	23/04/2020	SmPC,	

	Veterinary Medicinal Products - Other variation			Labelling and PL	
PSUSA/15/201804	Periodic Safety Update EU Single assessment - abiraterone	13/12/2018	20/02/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/15/201804.
IB/0052/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS B.I.c.1.z - Change in immediate packaging of the AS - Other variation	23/10/2018	n/a		
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	20/02/2019	PL	
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/06/2018	20/02/2019	PL	
PSUSA/15/201704	Periodic Safety Update EU Single assessment - abiraterone	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0047	Extension of Indication to include treatment of newly diagnosed high risk metastatic hormone sensitive	12/10/2017	15/11/2017	SmPC and PL	Please refer to the published Assessment Report Zytiga H-2321-II-47-AR.

	prostate cancer (mHSCP) in adult men in combination with androgen deprivation therapy (ADT) for Zytiga plus prednisone or prednisolone; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The Risk Management Plan was updated in the light of the data submitted (version 14.2). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0048/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 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)	16/06/2017	n/a		

N/0046	Update of Annex IIIA to grey shade the text on the blister foil-immediate packaging of the 500 mg film coated tablets, as agreed with QRD. In addition, the MAH took the opportunity to make linguistic amendments in the CS, DE, EL, ES, HU, IT, MT, PT and RO Labelling and DE package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/01/2017	15/11/2017	Labelling	
PSUSA/15/20 1604	Periodic Safety Update EU Single assessment - abiraterone	01/12/2016	n/a		PRAC Recommendation - maintenance
II/0045	To update the Risk Management Plan. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2016	n/a		
X/0039	Extension application to introduce a new pharmaceutical form associated with new strength (500mg film-coated tablets). Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	15/09/2016	09/11/2016	SmPC, Labelling and PL	
N/0043	Update of the package leaflet with revised contact details of the local representatives for Sweden and Romania.	10/06/2016	09/11/2016	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
R/0038	Renewal of the marketing authorisation.	01/04/2016	26/05/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Zytiga in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0042/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/05/2016	n/a		
IB/0041	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/03/2016	n/a		
IA/0040/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	24/02/2016	n/a		

II/0036/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/01/2016	26/05/2016	SmPC and PL	
II/0037	Update of section 4.5 of the SmPC to include a statement highlighting the potential interaction between spironolactone and abiraterone and section 5.1 of the SmPC in order to highlight the fact that spironolactone was not allowed to be used in the pivotal studies for ZYTIGA as spironolactone binds to the androgen receptor and may increase PSA levels. In addition, the Marketing authorisation holder (MAH) took the opportunity to a make minor editorial change in section 4.8 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/12/2015	26/05/2016	SmPC	
PSUSA/15/20	Periodic Safety Update EU Single assessment -	06/11/2015	n/a		PRAC Recommendation - maintenance

1504	abiraterone				
II/0035/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
II/0027	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/06/2015	26/05/2016	SmPC and PL	
PSUSA/15/20 1410	Periodic Safety Update EU Single assessment - abiraterone	07/05/2015	n/a		PRAC Recommendation - maintenance
IB/0033	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	15/04/2015	n/a		
IA/0032	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	12/03/2015	n/a		

IG/0526/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/03/2015	28/07/2015	Annex II and PL	
IB/0029/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	03/03/2015	n/a		

	authorisation, including the RMP - Other variation				
IB/0030/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	25/02/2015	n/a		
IA/0026	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/12/2014	n/a		
II/0025	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	28/07/2015	SmPC	
PSUV/0024	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IB/0023/G	This was an application for a group of variations. 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	10/09/2014	n/a		

	increase compared to the originally approved batch size				
II/0022	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/07/2014	28/07/2015	SmPC	
PSUV/0019	Periodic Safety Update	22/05/2014	18/07/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0019.
II/0018/G	This was an application for a group of variations. Update of section 4.5 of the SmPC with information regarding OATP1B1 and CYP2C8 inhibition by abiraterone based on the results of the drug-drug interaction studies FK10383 and 212082PCR1011, respectively, included in the RMP. The MAH took the opportunity to update due dates of studies included in the RMP and address minor updates requested in conclusion to the assessment of previous RMP versions. Changes were also made to the PI to bring it in line with the SmPC guideline. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	22/05/2014	18/07/2014	SmPC and PL	In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Although these results indicate that no clinically meaningful increases in exposure are expected when ZYTIGA is combined with drugs that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of drugs eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IAIN/0021/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary 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	08/05/2014	n/a		
IB/0020/G	This was an application for a group of variations. 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 B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	26/03/2014	n/a		
PSUV/0017	Periodic Safety Update	21/11/2013	16/01/2014	SmPC and PL	"Update of section 4.8 of the SmPC to add the adverse reaction sepsis with a frequency common following an

					increased incidence of sepsis for abiraterone vs. placebo in a combined analysis of studies COU AA-301 and COU-AA-302. The Package leaflet is updated accordingly. Please refer to Zytiga-H-C-2321-PSUV-0017 - Scientific conclusion and grounds recommending the variation to the terms of the marketing authorisation."
IB/0016	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/11/2013	n/a		
II/0014/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to add allergic alveolitis as a rare Adverse Drug Reaction (ADR) following one relevant case from the post-marketing setting. The Package Leaflet was proposed to be updated accordingly. Submission of the report of a food-interaction study included in the RMP, which did not require changes to the Product Information were proposed in consequence. Update of the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/11/2013	16/01/2014	SmPC and PL	Based on a single spontaneous report a causal relationship between abiraterone and allergic alveolitis could not be excluded. Section 4.8 of the SmPC has been updated in order to add allergic alveolitis as a rare Adverse Drug Reaction (ADR). The Package Leaflet was proposed to be updated accordingly. The MAH also submitted a food-interaction study included in the RMP (Study 212082PCR2008), but no changes to the Product Information were proposed in consequence since the information currently included in the SmPC is considered appropriate. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

IB/0015	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	18/10/2013	n/a		
II/0012	Update of section 5.3 of the SmPC based on the results of a 6-month mouse and a 2-year rat carcinogenicity study requested by the CHMP (MEA 011). C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/09/2013	16/01/2014	SmPC	Abiraterone acetate was not carcinogenic in a 6 month study in the transgenic (Tg.rasH2) mouse. In a 24 month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone and rat specific. Abiraterone acetate was not carcinogenic in female rats.
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0010	Update of sections 4.4 and 4.5 of the SmPC in order to include a warning against use of strong CYP3A4 inducers during treatment with abiraterone and to amend the information on interactions of abiraterone with inducers and inhibitors of CYP3A4, based on the results of two relevant studies (PCR 1002 and PCR 1003). The MAH also took the opportunity to make a minor amendment of information related to overdose in section 4.9 of the SmPC and to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0.	25/07/2013	16/01/2014	SmPC, Annex II and PL	In a clinical pharmacokinetic interaction study (PCR 1003) of healthy subjects pretreated with the strong CYP3A4 inducer rifampicin, 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55%. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St. John's wort [Hypericum perforatum]) during treatment with Zytiga are to be avoided, unless there is no therapeutic alternative. In a separate clinical pharmacokinetic interaction study (PCR1002) of healthy subjects, coadministration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				meaningful effect on the pharmacokinetics of abiraterone.
IA/0011	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 currently approved batch size	21/05/2013	n/a		
IA/0009	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 currently approved batch size	17/12/2012	n/a		
II/0008	Change in the specification of the finished product. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	15/11/2012	15/11/2012		
II/0004/G	This was an application for a group of variations. Extension of Indication to include new population for Zytiga in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to:	15/11/2012	18/12/2012	SmPC, Labelling and PL	Please refer to the Scientific Discussion Zytiga-H-C-2321-II-04-G.

	add a new contraindication in patients with severe hepatic impairment, a new posology recommendation on concomitant LHRH administration in patients not surgically castrated and new warnings related to hyperglycaemia, use with chemotherapy and potential risks of anaemia and sexual dysfunction; update posology recommendations and warnings related to heart failure, mineralocorticoid toxicities, hepatotoxicity and hepatic impairment; update the existing warning in patients with a history of cardiovascular disease, the table of adverse drug reactions and cross references from the pharmacokinetic information to the safety sections of the SmPC; include information from the pivotal study in the SmPC. In the second variation, recommendations were updated in section 4.6 of the SmPC and the results from reproductive and developmental toxicity studies were included in section 5.3 of the SmPC. The Package Leaflet is updated in accordance. Finally, minor changes were made to the SmPC, Labelling and Package Leaflet. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				

II/0003	Update of section 4.5 of the SmPC in order to introduce a warning on CYP2C8 inhibition by abiraterone. In addition, the MAH took the opportunity to introduce changes to the PL requested in conclusion to the assessment of FUM 010 and consequential changes to the Labelling. Furthermore, the MAH took the opportunity 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	19/07/2012	30/08/2012	SmPC, Labelling and PL	Based on in vitro data, ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2C8. Examples of medicinal products metabolised by CYP2C8 include paclitaxel and repaglinide. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8.
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
IA/0006	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	26/07/2012	n/a		
IA/0005	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 currently approved batch size	26/07/2012	n/a		
II/0002	Update of section 4.8 of the SmPC in order to include bone fractures as an adverse drug reaction of Zytiga. The Package Leaflet is updated in accordance. The PL is amended in order to reflect existing warnings in the SmPC and minor changes are made to sections	19/04/2012	25/05/2012	SmPC, Labelling and PL	Following a targeted reanalysis of data on adverse events related to fractures (excluding pathological fractures) submitted during the initial Marketing authorisation Application for Zytiga, the marketing Authorisation Holder (MAH) added fractures to the list of Adverse Drug Reactions

	4.4, 4.8 and 6.5 of the SmPC and to the PL. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.1 and minor editorial changes are made to it. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				(ADRs) of the medicine.
IA/0001/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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	23/01/2012	n/a		