Avastin

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/0108	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	17/06/2019	n/a		
II/0106/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2019		SmPC and Annex II	

[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).

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IB/0107/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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	14/01/2019	n/a		
PSUSA/403/201802	Periodic Safety Update EU Single assessment - bevacizumab	06/09/2018	n/a		PRAC Recommendation - maintenance
N/0105	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018		PL	
IA/0104	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	13/07/2018	n/a		
IB/0102	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	08/05/2018	n/a		
T/0100	Transfer of Marketing Authorisation	20/02/2018	16/03/2018	SmPC, Labelling and	

				PL	
IA/0101	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	28/02/2018	n/a		
II/0098	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	23/11/2017	n/a		
IB/0099	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	18/10/2017	n/a		
PSUSA/403/201702	Periodic Safety Update EU Single assessment - bevacizumab	28/09/2017	n/a		PRAC Recommendation - maintenance
IB/0097/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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/07/2017	n/a		
II/0095	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	09/06/2017	n/a		
II/0092	C.I.6.a - Change(s) to therapeutic indication(s) -	21/04/2017	02/06/2017	SmPC and PL	Extension of Indication to include the use of Avastin in

	Addition of a new therapeutic indication or modification of an approved one				combination with paclitaxel and carboplatin for the for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated with efficacy and safety information from study GOG-0213. The Package Leaflet and RMP (v. 27.1) are updated in accordance. Summary Please refer to the scientific discussion Avastin EMEA/H/C/00582/II/0092 for further information.
II/0093	4.2 Posology and method of administration Paediatric population The safety and efficacy of bevacizumab in children less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney. 4.8 Undesirable effects Paediatric population The safety and efficacy of Avastin in children less than 18 years old have not been established. In study BO25041 of Avastin added to postoperative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or	26/01/2017	02/06/2017	SmPC and PL	4.2 Posology and method of administration Paediatric population The safety and efficacy of bevacizumab in children less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney. 4.8 Undesirable effects Paediatric population The safety and efficacy of Avastin in children less than 18 years old have not been established. In study BO25041 of Avastin added to postoperative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma, the safety profile was comparable with

	peduncular high-grade glioma, the safety profile was comparable with that observed in other tumour types in adults treated with Avastin. 5.1 Pharmacodynamic properties High-grade glioma In a randomized phase II study (BO25041) a total of 121 patients aged ≥ 3 years to <18 years with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) were treated with post-operative radiation therapy (RT) and adjuvant temozolomide (T) with and without bevacizumab: 10 mg/kg every 2 weeks IV. The study did not meet its primary endpoint of demonstrating a significant improvement of EFS (Central Radiology Review Committee (CRRC)-assessed) when bevacizumab was added to the RT/T arm compared with RT/T alone (HR =1.44; 95% CI: 0.90, 2.30). These results were consistent with those from various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone. Addition of Avastin to RT/T did not demonstrate clinical benefit in study BO25041 in 60 evaluable children patients with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high- grade glioma (HGG) (See section 4.2 for information on paediatric use). 5.2 Pharmacokinetic properties				that observed in other tumour types in adults treated with Avastin. 5.1 Pharmacodynamic properties High-grade glioma In a randomized phase II study (BO25041) a total of 121 patients aged ≥ 3 years to <18 years with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) were treated with post-operative radiation therapy (RT) and adjuvant temozolomide (T) with and without bevacizumab: 10 mg/kg every 2 weeks IV. The study did not meet its primary endpoint of demonstrating a significant improvement of EFS (Central Radiology Review Committee (CRRC)-assessed) when bevacizumab was added to the RT/T arm compared with RT/T alone (HR were consistent with those from various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone. Addition of Avastin to RT/T did not demonstrate clinical benefit in study BO25041 in 60 evaluable children patients with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high- grade glioma (HGG) (See section 4.2 for information on paediatric use). 5.2 Pharmacokinetic properties Paediatric population The pharmacokinetics of bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic

	Paediatric population The pharmacokinetics of bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account. The pharmacokinetics of bevacizumab was well characterized by the paediatric population PK model for 70 patients in Study BO20924 ((1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, bevacizumb exposure trended lower as body weight decreased. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account. The pharmacokinetics of bevacizumab was well characterized by the paediatric population PK model for 70 patients in Study BO20924 ((1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, bevacizumb exposure trended lower as body weight decreased.
IA/0094/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied	06/01/2017	n/a		

	during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.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.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
II/0091	Update of sections 4.2, 4.8, 5.1 of the SmPC in order to update the safety and efficacy, pharmacokinetic information based on the results of paediatric study (BO20924) conducted in children and adolescents presenting with rhabdomyosarcoma (RMS) or non RMS soft tissue sarcoma (NR-STS). As a consequence, section 5.2 has been updated to include pharmacokinetic information resulting from 4 paediatric studies using a population pharmacokinetic model as per the study's objective. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	02/06/2017	SmPC	
PSUSA/403/201602	Periodic Safety Update EU Single assessment - bevacizumab	02/09/2016	n/a		PRAC Recommendation - maintenance

II/0086	Extension of indication to include the combination of bevacizumab with erlotinib for the first line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) activating mutations. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP (v.26.0) are updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/04/2016	02/06/2016	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion Avastin EMEA/H/C/00582/II/0086 for further information.
II/0089	Update of section 4.8 of the SmPC in order to include safety information derived from the phase III study GO25632. In addition, Annex II of the product information is updated as the condition on the investigation of suitable biomarkers to allow identification and selection of a more targeted population (ANX 068) is removed from the list of post authorisation measures. Consequently, the RMP v.26 is updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	02/06/2016	SmPC and Annex II	
WS/0833	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	03/12/2015	n/a		

	B.I.e.2 - Introduction of a post approval change management protocol related to the AS				
II/0087	Update of sections 4.4 and 4.8 of the SmPC in order to amend the existing warning and safety information on increased serum creatinine levels, with or without proteinuria, associated with Avastin use. 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	02/06/2016	SmPC and PL	Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin. Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of Avastin. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with Avastin.
PSUSA/403/201502	Periodic Safety Update EU Single assessment - bevacizumab	10/09/2015	n/a		PRAC Recommendation - maintenance
II/0082	Update of sections 4.2 and 4.8 of the SmPC to include information regarding non-mandibular osteonecrosis in children. In addition, the MAH took the opportunity to update section 4.4 of the SmPC with the inclusion of an instruction to record the batch number to improve drug traceability. 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	23/07/2015	02/06/2016	SmPC and PL	
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		

IB/0084	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	25/06/2015	n/a		
IB/0081	B.I.a.4.b - To add Leptospira PCR with a rejection limit of 'positive for leptospira' as a new in-process test performed at the preharvest cell culture fluid stage of the manufacture of the active substance. In addition, the MAH took the opportunity to update the action limit for Affinity (Protein A Column) Pool from '≤ pH 3.60' to '≥ pH 3.60' in Module 3.2.S.2.4. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	14/04/2015	n/a		
II/0072	Extension of Indication to include treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix for Bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/02/2015	30/03/2015	SmPC and PL	Please refer to the scientific discussion Avastin-H-C-582-II-72.
II/0080	Update of sections 4.6, 4.8 and 5.3 of the SmPC in order to update the safety information regarding the risk of foetal abnormalities based on post-marketing	26/02/2015	30/03/2015	SmPC	In this variation the product information for Avastin has bee updated with further information on risk of foetal malformation, related to clinical cases of foetal abnormalities

	data. In addition, information related to adverse reactions reported in the post-marketing setting in section 4.8 of the SmPC is re-arranged in line with the SmPC guideline. The RMP is updated in order to re-classify embryo-foetal developmental disturbance as an identified risk. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				that have been observed in women treated with Avastin. The following wordings have been included in the product information: In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8). In addition, "congenital, familial, and genetic disorder" has been added as a severe adverse reaction with an unknown frequency
II/0079	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	26/02/2015	n/a		
IB/0078	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/01/2015	n/a		
IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		
R/0068	Renewal of the marketing authorisation.	25/09/2014	17/11/2014	SmPC and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of Avastin in its

					approved indications remains favourable and therefore recommends the renewal of the marketing authorisation with unlimited validity.
IB/0075	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	23/10/2014	n/a		
II/0074	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	17/11/2014	SmPC	
II/0073/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	25/09/2014	n/a		
IB/0076	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/09/2014	n/a		
PSUV/0070	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0063	Extension of indication to include Avastin in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult	26/06/2014	31/07/2014	SmPC and PL	Please refer to the Scientific Discussion Avastin-H-C-582-II-63

	patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0071	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	01/07/2014	n/a		
IB/0069	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/05/2014	n/a		
II/0064	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	30/06/2014	SmPC and PL	
II/0065	Update of section 5.1 of the SmPC with the final results from study BO17707. Annex II has been updated accordingly in order to remove the condition on the final analysis for Overall survival from study BO17707. C.I.11.b - Introduction of, or change(s) to, the	25/04/2014	30/06/2014	SmPC and Annex II	The MAH has submitted the final overall survival data from study BO17707 (ICON-7), a randomised, controlled, open-label Phase III trial in patients with high-risk, early stage (International Federation of Gynecology and Obstetrics [FIGO] Stage I or IIA clear cell or Grade 3 carcinoma) or advanced stage (FIGO Stage IIB or greater, all grades and all

	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				histological subtypes) epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma, to evaluate the addition of bevacizumab (B) to standard chemotherapy with carboplatin (C) and paclitaxel (P). The results of the protocol-specified, final analysis of OS showed that a total of 714 patients had died (352 [46.1%] in the CP arm and 362 [47.4%] in the CPB7.5+ arm), with an unstratified HR = 0.99, 95% CI [0.85; 1.15] and a stratified HR = 0.96, 95% CI [0.83; 1.11]. The median survival times were estimated to be 58.0 months in the CP arm (95% CI [53.2; 67.1]) and 57.4 months in the CPB7.5+ arm (95% CI [51.9; 65.0]). No detrimental effect of adding bevacizumab to chemotherapy is seen.
II/0066	Update of section 5.1 of the SmPC with the results from the final analysis from study AVF4095g. Annex II has been updated accordingly in order to remove the condition on the final analysis for Overall Survival from study AVF4095g. The requested variation proposed amendments to the Summary of Product Characteristics and Annex II. 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	20/02/2014	30/06/2014	SmPC and Annex II	The final analysis of Overall Survival (OS) from study AVF4095g was submitted, with a cut-off date of 19 July 2013 and included an additional 34 months of follow-up since the first interim analysis of OS. At the time of the final OS cut-off, 353 deaths (72.9% of the ITT population) had occurred and no difference in OS was seen with bevacizumab treatment added to chemotherapy. Kaplan-Meier estimated median OS was comparable in both treatment arms, with a HR of 0.952 (95% CI: 0.771, 1.176, log rank p □ 0.6479). Section 5.1 of the SmPC has been updated to include these data and Annex II been updated accordingly in order to remove the condition on the final analysis for Overall Survival from study AVF4095g.
II/0061	Update of section 4.4 of the SmPC on diabetes as a risk factor for developing arterial thromboembolic events following review of the MAH's safety database.	19/09/2013	30/06/2014	SmPC and PL	Based on two internal independent analyses of the MAH's integrated clinical safety database for bevacizumab which identified a potential new safety signal for increased risk of

	The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet with the addition of the Croatian representative. Furthermore, the PI is being brought in line with the latest QRD template (version 9.0) and minor editorial changes were made. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				arterial thromboembolic events (ATEs) among bevacizumab-treated patients with diabetes compared to chemotherapy-treated patients, section 4.4 of the SmPC has been updated on diabetes as a risk factor for developing ATEs. The Package Leaflet has been updated accordingly.
IA/0062	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	05/08/2013	n/a		
IB/0060	Revision of a warning in SmPC section 4.4 regarding the potential risk of systemic adverse events following intravireal injection of anti-VEGF treatments. C.I.3.a - 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 - Changes with NO new additional data are submitted by the MAH	02/07/2013	30/06/2014	SmPC	
II/0058/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC with the	25/04/2013	27/05/2013	SmPC and PL	Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with Avastin. This condition is usually secondary to wound healing complications,

	addition of information on necrotising fasciitis. The Package Leaflet has been updated accordingly. In addition section 4.8 of the SmPC has been updated to add the incidence of gastrointestinal perforations in metastatic renal cell cancer patients. 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.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated. Sections 4.4 and 4.8 of the SmPC have been updated with this information. In addition, section 4.8 of the SmPC has been updated to include the incidence (up to 2.0%) of gastrointestinal perforations in metastatic renal cell cancer patients.
II/0057	Update of Annex II of the PI in order to remove the condition on the biomarkers for VEGF-A from studies BO177007 and GOG-218. In addition the MAH took the opportunity to make some editorial changes to the SmPC. 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	21/02/2013	27/05/2013	SmPC and Annex II	The MAH fulfilled the second part of the commitment to submit PFS analysis from the plasma biomarker VEGF-A study BO17707. The results on the correlation of plasma markers for VEGF-A with PFS and OS in study GOG-218 were previously submitted on 7 June 2012 and assessed as part of ANX 073 (CHMP Opinion in December 2012). The biomarker data from study BO17707 showed that biomarker levels of baseline plasma VEGF-A did not have any prognostic value or predictive value of treatment benefit with bevacizumab on PFS. The CHMP agreed that the following Annex II condition can be removed from the PI: "The MAH shall submit results from the plasma biomarker for VEGF-A from study BO17707 with PFS analysis as well as the results from the GOG-218 study on the correlation of plasma markers for VEGF-A with PFS and OS analyses".
II/0056/G	This was an application for a group of variations. Update of section 4.8 of the SmPC with regards to	21/02/2013	27/05/2013	SmPC, Annex II and PL	The product information of Avastin has been updated to reflect that serious wound healing complications, including anastomotic complications, have been reported, some of

	wound healing complications further to the request of the CHMP in the assessment of the 9th PSUR. In addition, a warning in section 4.4 of the SmPC has been included in relation to traceability of the medicinal product. The MAH has taken the opportunity to correct an error in the package leaflet in the description of pulmonary embolisms and to introduce minor editorial corrections in the SmPC and PL. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. 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 C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				which had a fatal outcome. In addition, a warning in section 4.4 of the SmPC has been included in relation to traceability of the medicinal product.
II/0054	Change to the manufacture of the active substance B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	21/02/2013	n/a		
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		

II/0053	Update of sections 4.8 and 5.1 of the SmPC to add efficacy and safety data further to the completion of study ML18147 (a phase III study of Avastin plus crossover fluoropyrimidine-based chemotherapy in patients with mCRC). This variation application addresses post-authorisation measure 041. In addition the MAH took the opportunity to make some editorial changes to the SmPC and PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	27/05/2013	SmPC and PL	The SmPC has been updated to include efficacy and safety results from study ML1847.Study ML18147 was a Phase III randomised, controlled, open-label trial investigating Avastin 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen. The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen (ITT = 819). Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and the difference was not significant. The MAH submitted this variation further to the completion of study ML18147 in order to fullfill FUM 041. In addition the MAH took the opportunity to make some editorial changes to the SmPC and PL.
II/0046	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	24/10/2012	SmPC, Annex II, Labelling and PL	Please refer to Assessment Report EMEA/H/C/00582/II/0046.
IB/0052/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements	31/08/2012	n/a		

	and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
II/0044	Update of section 4.4 of the SmPC in order to revise the wording on the adverse reactions that have been reported from unauthorised intravitreal use of Avastin based on recently published clinical trials. 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 and PL	Based on recently published data individual cases and clusters of serious ocular adverse events have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness. In addition, a reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse events including non ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. The PI has been updated to reflect the above results.
II/0051	Update of section 5.1 of the SmPC with the final overall survival data from study GOG-0218 (Post authorisation measure). The Annex II is updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC and Annex II	The approval of Avastin for Epithelial Ovarian Cancer (EOC), Fallopian Tube Cancer (FTC) and Primary Peritoneal Cancer (PPC), was based on data from the final progression-free survival (PFS) analysis of study GOG-0218. In this variation, final overall survival (OS) data from study GOG-0218 were submitted, with 878 deaths (46.9% of the ITT population) having occured. Although the OS difference between treatment arms was not statistically significant, the median overall survival time was 43.8 months in the CPB15+ (long-duration bevacizumab) arm compared with 40.6 months in the CPP (control) arm with a hazard ratio of 0.879 (95% CI: 0.745, 1.038; p = 0.0641). The post authorisation measure to provide final OS date from study GOG-0218 was considered fulfilled and deleted form the annex II.

					Additionally, based on updated safety analyses and patient narratives, no new safety concerns were noted. Overall, the updated safety and efficacy data do not affect the positive benefit/risk balance.
II/0047/G	This was an application for a group of variations. Update of section 5.1 of the SmPC with the results from two studies in children aged > 3 years old with relapsed or progressive high-grade glioma. In addition, section 4.2 of the SmPC has been updated to include a statement that Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma. 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	16/02/2012	19/03/2012	SmPC	Please refer to Scientific Discussion `Avastin-H-C-582-II-0047/G-Assessment Report-Variation'
II/0049	Additional site for the manufacture of the finished product B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	15/03/2012	15/03/2012		
II/0048	Update of section 4.5 of the SmPC to include safety	15/12/2011	06/02/2012	SmPC	Results from the randomized phase III studies, PACCE and

	information on the interaction between bevacizumab and anti-EGFR treatments in the mCRC indication and section 4.8 of the SmPC to clarify that part of the cases of Microangiopathic Haemolytic Anaemia (MAHA)/Thrombotic Microangiopathy (TMA) occur in patients who are not treated with sunitinib further to the assessment of the PSURs 7 and 8. The requested variation proposed amendments to the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. In addition, renal thrombotic microangiopathy which already included in the table of adverse reactions reported in post-marketing setting may be clinically manifested as proteinuria (not known) with or without concomitant sunitinib use.
IB/0050	B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	30/01/2012	n/a		
II/0042	Additional site for the manufacture of the active substance B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	17/11/2011	19/12/2011	Annex II	
II/0041	Extension of indication to include the use of Avastin, in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B,	17/11/2011	19/12/2011	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion "Avastin-H-C-582-II-0041-Assessment Report-Variation"

	III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication. The Risk Management Plan and the Package Leaflet have been updated accordingly. In addition, a minor change was made to the Labelling. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0045	Update of sections 4.4 and 4.8 of the SmPC in order to include gall bladder perforation as requested by the CHMP further to the assessment of FUM 066. The PL has been updated accordingly. Finally the MAH took the opportunity to make minor changes in section 4.4 of the SmPC to clarify the wording on thromboembolic events and in section 4.8 of the SmPC to update the wording on Central Nervous System (CNS) haemorrhage.	20/10/2011	24/11/2011	SmPC and PL	Further to a CHMP's request a cumulative review of gall bladder perforations in order to investigate a possible causal association with bevacizumab, and if possible to establish a plausible mechanism of action has been performed by the MAH. Data from the integrated clinical safety database, an epidemiological database and the company's safety database were analysed by the MAH. In addition, a relevant epidemiological study was reviewed. Based on the results of these analyses sections 4.4 and 4.8 of the SmPC have been updated in order to include that cases of gall bladder perforation were observed in the post marketing setting. Finally the MAH took the opportunity to make minor changes in section 4.4 of the SmPC to clarify the wording on thromboembolic events and in section 4.8 of the SmPC to update the wording on CNS haemorrhage. The wording in section 4.8 has been updated to reflect the fact that the two studies (AVF3752g and AVF3671g) including patients with untreated brain metastases mention have been completed and it was confirmed that there were no additional patients with treated brain metastases experiencing CNS

					haemorrhage.
II/0043/G	This was an application for a group of variations. Update of sections 4.4, 4.6 and 4.8 of the Summary of Product Characteristics (SmPC) to include ovarian failure observed in NSABP C-08 study. The PL has been updated accordingly. In addition to this, the wording on congestive heart failure (CHF) in section 4.8 of the SmPC has been revised to include an increased incidence of CHF with a cumulative doxorubicin dose greater than 300 mg/m2 observed in BO20603 study. Finally, the MAH made a minor change in section 4.8 of the SmPC in order to reflect better the System Organ Class (SOC) of osteonecrosis of the jaw. 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	23/06/2011	27/07/2011	SmPC and PL	In NSABP C-08, a phase III trial of Avastin in the adjuvant treatment of patients with colon cancer, a substudy with premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Sections 4.4, 4.6 and 4.8 of the SmPC and the PL have been updated to include this information. In addition, in an analysis of the study BO20603 an increased incidence of CHF was observed when patients with DLBCL received bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m2. The MAH proposed to update the wording on CHF in section 4.8 of the SmPC accordingly and to add that close clinical observation with appropriate cardiac assessments should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m2 when combined with bevacizumab.
II/0033	To extend the indication to the use of Avastin in combination with capecitabine for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant	19/05/2011	29/06/2011	SmPC and Annex II	Please refer to the Scientific Discussion document H-582-II-33-AR.

	setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. For further information about HER2 status, refer to section 5.1. Consequently, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication accordingly. Finally Annex II has been updated in order to take into account the latest version of the RMP. Extension of Indication				
II/0040	Update of sections 4.4 and 4.8 of the SmPC to revise the wording on proteinuria and arterial thromboembolic events further to the assessment of the 7th PSUR. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/01/2011	24/03/2011	SmPC	This proposed update results from the evaluation of the 7th PSUR. Following the review of the Wu S. et Al (2010 Aug; J Am Soc Nephrol 21(8):1381-9) meta-analysis and the evaluation of the Roche Clinical Trial data, it has been concluded that the dose dependent relationship does not exist only for Grade 1 proteinuria. Therefore the section 4.4 of the SmPC wording has been updated accordingly. Furthermore, the higher incidence of high grade proteinuria observed in mRCC patients and reported in the meta-analysis is primarily driven by the results of the CALGB 90206 study which allowed patients with a higher level of baseline proteinuria to entry the study. This can be explained by difference in protocol design compared to AVOREN (BO17705) study, which allowed patients with a baseline proteinuria up to <2 grams/24 hours to be enrolled. Therefore, the wording of the section 4.8 of the SmPC has been updated to better reflect the data from the AVOREN study, which was the pivotal study which led to the approval of the mRCC indication. In addition to this, since the imbalance in ATEs was not only

					observed in five randomized clinical trials but also in additional trials, including E4599, the MAH proposed to update section 4.4 of the SmPC accordingly. Finally section 4.8 of the SmPC was slightly modified to add information on the chemotherapy combination used in study AVF2192g.
A20/0038	Review of all available data on the combination of Avastin with either paclitaxel or docetaxel for the treatment of first-line metastatic breast cancer, particularly the results of the AVF3694g study and its impact on the benefit-risk balance.	15/12/2010	28/02/2011	SmPC, Annex II and PL	Please refer to the assessment report published after deletion of commercially confidential information: EMEA/H/C/582/A20/0038
II/0039	Update of sections 4.4 and 4.8 of the SmPC to include information on cases of osteonecrosis of jaw (ONJ) associated with co-administration with bevacizumab and bisphosphonates further to the assessment of the FUM 65. The PL has been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/11/2010	20/12/2010	SmPC and PL	Based on the cases of ONJ retrieved from the Eudravigilance database and the MAH's safety database, a number of cases have been reported in patients treated with Avastin. The majority of cases occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk factor. Caution should therefore be exercised when Avastin and bisphosphonates are used either simultaneously or sequentially.
II/0037	Update of section 4.5 of the Summary of Product Characteristics to include wording on increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) which have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC as requested by the CHMP further to the assessment of FUM 63. In addition, the Labelling has been updated to	21/10/2010	26/11/2010	SmPC and Labelling	The PK and safety of bevacizumab (Bv) in combination with different anti-neoplastic agents were evaluated in two studies 1) Bv in combination with cisplatin/paclitaxel and 2) Bv in combination with irinotecan/5-FU/leucovorin (IFL). In addition to this, the PK of Bv in adult patients was characterised in 10 clinical trials. Finally, a thorough analysis of the incidences of neutropenia/febrile neutropenia in Bv clinical trials was performed together with an analysis of events adjusted by observation time in all trials and in trials

	replace ''batch'' by ''lot''. Finally the MAH took the opportunity to correct some typographical errors in the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				pooled by tumour indication. Based on the results of the above studies, the CHMP concluded that a PD interaction may be suspected in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC and that the MAH should include the following wording in section 4.5 of the SmPC: ''Combination with platinum- or taxane-based therapies (see sections 4.4 and 4.8) Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC''.
II/0036	Update of section 4.4 of the SmPC to include a warning on adverse reactions reported following unapproved intravitreal use with Avastin. This proposed update results from a safety review conducted by the Marketing Authorisation Holder (MAH). The Package Leaflet has been updated accordingly. Based on a safety review of ocular events after off-label intravitreal/intraocular Avastin use, performed by the MAH it has been concluded by the CHMP that information on eye disorders from unapproved intravitreal use should be included as a safety warning in section 4.4 of the SmPC. Therefore the SmPC has been updated to include a warning that infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis	22/07/2010	31/08/2010	SmPC and PL	Based on a safety review of ocular events after off-label intravitreal/intraocular Avastin use, performed by the MAH it has been concluded by the CHMP that information on eye disorders from unapproved intravitreal use should be included as a safety warning in section 4.4 of the SmPC. Therefore the SmPC has been updated to include a warning that infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage have been reported following unapproved intravitreal use of Avastin. The PL has been updated accordingly.

	and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage have been reported following unapproved intravitreal use of Avastin. The PL has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0035/G	This was an application for a group of variations. Update of section 4.4 of the Summary of Product Characteristics (SmPC) to amend the wording regarding neutropenia and infections as requested by the CHMP further to the assessment of the renewal procedure. In addition, section 4.8 of the SmPC has been updated to include wording on gastrointensinal ulcer based on a safety review conducted by the MAH. The Package Leaflet has been updated accordingly. Furthermore, sections 4.2 and 4.6 of the SmPC have been updated in accordance with the latest QRD template (version 7.3.1, March 2010) and sections 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated in accordance with the SmPC guideline (revision 2, September 2009). The MAH took the opportunity to make some editorials chnages to the Product Information. Finally, Annex II has been updated to include the latest version number of the RMP.	20/05/2010	06/07/2010	SmPC, Annex II and PL	This group of type II variations concerns an update of section 4.4 of the SmPC to revise the wording of neutropenia and infectionsas requested by the CHMP during the evaluation of the renewal procedure. In addition to this, section 4.8 of the SmPC has been updated to include wording on gastrointestinal ulcer based on a safety review conducted by the MAH. The Package Leaflet has been updated accordingly. Section 4.6 of the SmPC has been updated in accordance with the latest QRD template (version 7.3.1, March 2010) in order to include data on women of childbearing potential and fertility. In addition to this, section 4.2 of the SmPC has been updated in accordance with the latest QRD template (version 7.3.1, March 2010) to revise the method of administration. Finally, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated in accordance with the SmPC guideline (revision 2, September 2009) to include information on the paediatric population. Finally Annex II has been updated to include the latest

	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				version number of the RMP.
II/0034	Update of sections 4.4 and 4.8 of the SmPC to include information on risks of hypersensitivity reactions and infusions reactions related to the administration of bevacizumab. This update results from a safety review on the issue conducted by the MAH. The PL has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/04/2010	02/06/2010	SmPC and PL	Based on a safety review of hypersensitivity cases performed by the MAH it has been concluded by the CHMP that there is enough evidence to confirm the causal role of bevacizumab in the occurrence of the hypersensitivity reactions and infusion reactions. Therefore the SmPC has been updated to include a warning in section 4.4 for patients that they may be at risk of developing infusion/hypersensitivity reaction and that close observation is recommended. Furthermore, section 4.8 has been updated to include the incidence of these reactions in some clinical trials of Avastin and to add the immune system disorders under Post-marketing experience.
R/0031	Renewal of the marketing authorisation.	22/10/2009	21/12/2009	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Avastin remains positive, but considers that its safety profile will continue to be closely monitored especially for known risks as documented in the current product labeling congestive heart failure, bleeding / haemorrhage (pulmonary haemorrhage, cerebral / intracranial haemorrhage), gastrointestinal perforation, neutropenia and also for off-label intravitreal use in ocular diseases. Considering the large number of patients currently enrolled

					in clinical trials and post-marketing studies for the product as well as the continued report of adverse events received by the MAH, the safety profile of Avastin will continue to be monitored closely. For the above reasons, the CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Avastin, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IA/0032	IA_09_Deletion of manufacturing site	31/07/2009	n/a	Annex II	
II/0030	Update of SPC section 4.5 to include information on Avastin in combination with interferon alpha 2a or in combination with chemotherapies, update of section 5.1 to remove text no longer relevant concerning study BO17704 and to include the results of the final overall survival analysis from study BO17705 and update of section 5.2 with information of distribution and elimination based on availability of completed studies. Update of Summary of Product Characteristics	25/06/2009	23/07/2009	SmPC	The basis of updating section 4.5 is the same as that behind the update to section 5.2, the data being presented Report No. 1031796. The overall conclusions remain the same. New population pharmacokinetic data from study BO17706 did not show clinically relevant pharmacokinetic differences between patient populations. Results from pharmacokinetic study NO20254 do not change the established pharmacokinetics profile of bevacizumab. The description of the pharmacokinetics of bevacizumab in this larger oncology population is presented in Report No. 1031796, and supports the revised wording. The data from study forms the basis for proposing the amended text above. The result from the study is an outcome of a modelling exercise based on ten clinical studies including 732 patients with different kinds of cancer (metastatic colorectal carcinoma, metastatic breast carcinoma, non small cell lung carcinoma, prostate cancer, renal cell and small cell lung carcinoma. The revised wording of section 5.2 is considered adequate and provides updated information in relation to the pharmacokinetics of

					bevacizumab. The Summary of Product Characteristics was also updated with a the results of the final Overall Survival data for study BO17704.
II/0024	Extension of the indication for the treatment of metastatic breast cancer in combination with paclitaxel or docetaxel. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	23/07/2009	SmPC, Annex II and PL	Please refer to the Scientific Discussion document H-582-II-24-AR.
II/0026	Additional site for the manufacture of the drug substance. Tightening of drug substance and drug product specifications. Change(s) to the manufacturing process for the active substance	23/04/2009	29/05/2009	Annex II	
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/04/2009	n/a	Labelling	
II/0025	Update to section 4.3 "Contraindications", and section 4.4 "Special Warnings and Precautions for Use", section 4.8 "Undesirable Effects" to remove the contraindication in patients with untreated CNS metastases and section 5.1 "Pharmacodynamic Properties" to include the results of the final overall survival analysis from BO17704 study and the results of the retrospective independent radiological review of tumour assessments from BO17705 study in order to fulfil relevant post-approval commitments. The	19/02/2009	25/03/2009	SmPC and PL	Avastin (bevacizumab) was contraindicated in patients with untreated central nervous system (CNS) metastases on the basis of a single case of fatal intracranial bleeding in a patient with metastatic hepatocellular carcinoma, however the causal relationship of this event with bevacizumab was not confirmed. The use of bevacizumab in patients with CNS metastases has not been contraindicated in the USA. Since then, with greater experience of bevacizumab use, gathered through the extensive clinical development program, as well as the use of the product in clinical practice, the need to

	Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				continue maintaining the contraindication for bevacizumab use in patients with CNS metastases was reevaluated. To this end, a retrospective review of safety data in patients with CNS metastases, with specific focus on the risk of intracranial bleeding in patients with CNS metastases, was carried out. Genentech had conducted a review of data from two post-marketing studies conducted in patients with treated CNS metastases, as part of post-approval commitment made to the FDA at the time of the original approval for Avastin in the USA, as mentioned above. Based on the results of this safety review, a contraindication for bevacizumab use in patients with brain metastases is no longer justified. There is no biological or pharmacological rationale to suspect that the incremental benefit derived from bevacizumab would be any different in patients with brain metastases, than those without. In addition the MAH applied to include the results of the final overall survival analysis from BO17704 (randomised, double-blind phase III study of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy) and the results of the retrospective independent radiological review of tumour assessments from BO17705 study (Avastin in combination with interferon alfa-2
IA/0027	IA_28_Change in any part of primary packaging material not in contact with finished product	16/12/2008	n/a		
II/0023	Update of section 4.5 "Interactions with other medicinal products and other forms of interaction" to	24/07/2008	29/08/2008	SmPC and PL	In April 2008 information on cases of microangiopathic hemolytic anemia (MAHA) occurred in a Phase I clinical study

	include information on Microangiopathic hemolytic anaemia cases with unapproved combination of Avastin with sunitinib and section 4.8 "Undesirable effects" of the SPC to include the terms "dysphonia" and "renal thrombotic microangiopathy". Editorial changes and corrections have been implemented. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				on the combination of Avastin with escalating doses of sunitinib malate (Sutent) was provided and discussed in CHMP. Consequently, the SPC is updated section 4.5 "Interactions with other medicinal products and other forms of interaction" and a Dear HealthCare Professional Letter is circulated by the MAH. Amendments have been introduced to the SPC as a consequence to new safety information which are considered appropriate. The Package Leaflet has been updated accordingly. Under 4.8 "Undesirable effects" of the SPC a table inserted to give an easy-read overview of the safety concerns seen after marketing of this product. Minor changes to the section on CHF and the PIL are also implemented.
II/0022	Change(s) to the manufacturing process for the finished product	24/07/2008	29/07/2008		
II/0021	Change(s) to shelf-life or storage conditions	30/05/2008	26/06/2008		
II/0020	The MAH applied to update the summary of product characteristics following the fulfilment of follow-up measures: Section 4.2. and Section 5.2 were revised following the results of a PK study in a limited number of paediatric patients; Section 5.1 was revised with the updated results from study E2100 in metastatic breast cancer. The text under 5.1 referring to the mechanism of action of bevacizumab is revised to provide more detailed information. Furthermore, in Section 4.8 "pulmonary hypertension" was added and the incidence of venous thromboembolic events was revised.	24/01/2008	26/02/2008	SmPC	Pharmacokinetics data have been obtained in a limited number of paediatric patients but there are still insufficient data on efficacy and safety of bevacizumab in children and adolescents to recommend its use in this patient population. This fact is reflected in the Summary of Product Characteristics. Results from the report for study E2100 in metastatic breast cancer were reflected in the SPC to provide updated information to the treating physician. Although the treatment effect of adding bevacizumab to weekly paclitaxel, measured by hazard ratios, remains unchanged and is confirmed by an independent review, the absolute numbers of the median

	Update of Summary of Product Characteristics				PFS and response rates have changed. The text referring to the mechanism of action of bevacizumab is now more detailed. Changes were also introduced to update section 4.8 with new information in relation to incidence of venous thromboembolism and pulmonary hypertension, which is considered sufficient and provides the treating physician with appropriate information.
II/0014	Extension of indication to use Avastin in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum. The MAH took the opportunity to implement editorial changes to the Package Leaflet as a result of the user testing procedure. Extension of Indication	13/12/2007	25/01/2008	SmPC and PL	Please refer to the Scientific Discussion.
II/0015	Extension of indication to include Avastin in combination with interferon alfa-2a for first line treatment of patients with advanced and/or metastatic renal cell cancer. Extension of Indication	15/11/2007	14/12/2007	SmPC and PL	Please refer to the Scientific Discussion.
II/0019	Update of the SPC Sections 4.4 and 4.8 to include information relating to fistulae cases and section 6.6 to clarify instructions on the dilution of bevacizumab solution for infusion. The Package Insert is also updated accordingly.	20/09/2007	24/10/2007	SmPC and PL	A detailed analysis of all events of fistula reported in the bevacizumab safety database, confirm that fistula formation has been reported in patients treated with Avastin in both approved and unapproved settings (e.g., ovarian cancer) and in some cases with fatal outcome. The observed incidence of gastrointestinal (GI) fistula in clinical trials was

	Update of Summary of Product Characteristics and Package Leaflet				2%. Fistula with bevacizumab treatment was already labeled in the Avastin SPC under gastrointestinal (GI) perforations in section 4.8. In May 2007, this new safety information was communicated globally to all healthcare professionals expected to use Avastin, including clinical trial investigators, in the form of a Direct Healthcare Provider Communication. The Product Information is now amended to include warnings on the risk of developing fistulae and instructions to discontinue Avastin in such cases. Additionally, clarifications to ensure correct dilution of Avastin are given.
II/0016	Change(s) to the manufacturing process for the active substance	20/09/2007	24/10/2007	Annex II	
II/0009	"Avastin, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology." Extension of Indication	19/07/2007	21/08/2007	SmPC and PL	Please refer to the Scientific Discussion.
II/0012	Change(s) to the manufacturing process for the active substance	21/06/2007	26/06/2007		
IB/0018	IB_36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals	13/06/2007	n/a		
IA/0017	IA_28_Change in any part of primary packaging material not in contact with finished product	30/05/2007	n/a		
II/0013	Update of SPC sections 4.4 and 4.8 with information	22/03/2007	23/04/2007	SmPC and PL	A recent review of bevacizumab (Avastin) safety data was

	on neutropenia, congestive heart failure, pulmonary haemorhage/ haemoptysis; section 4.8 to include a statement on venous thromboembolic events and to consolidate safety information. The Package Leaflet was revised accordingly. Minor editorial changes were also introduced in the SPC and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				performed with a focus on neutropenia and venous thromboembolic events, to further explore and specify the incidence and characteristics of these events during treatment with bevacizumab, as part of regular pharmacovigilance activities. The MAH also reviewed Avastin safety data to address a request made by the CHMP, following the review of the 1st Periodic Safety Update Report (PSUR), to update (SPC) with regards to information relating to congestive heart failure events. Based on the results of these reviews, it is proposed to update Sections 4.4 (Special warnings and precautions for use) and the corresponding texts in the Section 4.8 (Undesirable effects) of the SPC with information on neutropenia, congestive heart failure, pulmonary haemorhage/haemoptysis and section 4.8 to include a statement on venous thromboembolic events and to revised accordingly the Package Leaflet. In addition, the MAH proposed a revision to the presentation format of the safety information in Section 4.8 of the SPC, with the aim of consolidating safety data and providing more comprehensive information.
II/0008	"Avastin in combination with paclitaxel for first-line treatment of patients with metastatic breast cancer". The MAH has also updated the Package Leaflet to include the Romanian and Bulgarian contact details in the list of local representatives. Extension of Indication	22/02/2007	27/03/2007	SmPC and PL	Please refer to the Scientific Discussion.
II/0010	Change(s) to the test method(s) and/or specifications for the active substance	24/01/2007	29/01/2007		

IA/0011	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/01/2007	n/a	Annex II and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	01/06/2006	04/07/2006	SmPC and PL	Update of sections 4.4 and 4.8 of the SmPC with addition of information on Reversible Posterior Leukoencephalopathy Syndrome (RPLS) and hypertensive encephalopathy, update of information on gastrointestinal perforations. In addition, Section 4.8 has been revised to clarify the wording regarding tumour-associated haemorrhage, to address a request from the CHMP, following the review of the 1st PSUR and to include information on rare cases of nasal septum perforation. The Package Leaflet is also revised accordingly, where relevant. In addition, contact details of the local representatives in the Patient Leaflet have been updated.
II/0006	Change(s) to the manufacturing process for the finished product	01/06/2006	01/06/2006		
II/0005	Change(s) to the manufacturing process for the active substance	23/03/2006	27/03/2006		
II/0002	Change(s) to the manufacturing process for the active substance	26/01/2006	02/02/2006		
II/0003	Update of Summary of Product Characteristics, Labelling and Package Leaflet	17/11/2005	23/12/2005	SmPC, Annex II, Labelling and PL	Update of the SPC in section 4.8 and section 4 of the PL to include adverse events reported in study AVF2192g regarding congestive heart failure and elderly patients and for the implementation of the latest QRD template.
IA/0004	IA_01_Change in the name and/or address of the marketing authorisation holder	08/11/2005	n/a	SmPC, Labelling and PL	

IA/0001	IA_09_Deletion of manufacturing site	01/06/2005	n/a		