Abraxane

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
IA/0118	A.7 - Administrative change - Deletion of manufacturing sites	16/12/2024	n/a		
II/0115	Update section 4.6 of the SmPC based on the Reproductive Toxicity Testing and Labeling recommendations, Food and Drug Administration	12/12/2024		SmPC and PL	SmPC new text Section 4.6 is updated to indicate that female patients of childbearing potential should use effective contraception

[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).

	Guidance (May 2019) and the Non-clinical Working Party/Non-clinical Working Party (S/Nc), European Medicines Agency recommendations (March 2023) on the duration of contraception following the end of treatment with a genotoxic drug. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				during and for at least 6 months after the end of treatment with Abraxane (paclitaxel), when male patients and their female partners of childbearing potential are advised to use effective contraception during and for at least 3 months after the end of treatment with Abraxane (paclitaxel). For more information, please refer to the Summary of Product Characteristics.
IB/0117	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	05/12/2024	n/a		
IAIN/0116	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	08/10/2024	n/a		
IAIN/0114/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	14/09/2023	n/a		

	relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
IA/0113/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	27/06/2023	n/a		
IA/0112/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	12/05/2023	n/a		
IAIN/0111/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	08/03/2023	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
PSUSA/10123 /202201	Periodic Safety Update EU Single assessment - paclitaxel albumin	01/09/2022	n/a		PRAC Recommendation - maintenance
IAIN/0109	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	13/09/2021	02/06/2022	Annex II and PL	
IAIN/0108/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	26/07/2021	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IA/0107	A.7 - Administrative change - Deletion of manufacturing sites	04/06/2021	n/a		
IB/0106	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/04/2021	02/06/2022	SmPC, Labelling and PL	
T/0105	Transfer of Marketing Authorisation	14/01/2021	05/03/2021	SmPC, Labelling and PL	
IB/0104	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/10/2020	04/03/2021	SmPC	
IAIN/0103/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	09/07/2020	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IA/0102	A.7 - Administrative change - Deletion of manufacturing sites	05/05/2020	n/a		
II/0097	Update of sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC based on the results of study ABI-007-PST-001. This was a phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability and efficacy of weekly abraxane in paediatric patients with recurrent or refractory solid tumours, listed in the PIP, submitted in order to fulfil Article 46. The Package Leaflet is updated accordingly. The MAH took the opportunity to make minor editorial changes to the Annex II and to the Labelling. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/01/2020	04/03/2021	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Abraxane-H-C-778-II-97'
IB/0101	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/01/2020	n/a		
PSUSA/10123 /201901	Periodic Safety Update EU Single assessment - paclitaxel albumin	19/09/2019	11/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10123/201901.
IA/0100/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name	27/09/2019	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0099	B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products	07/08/2019	n/a		
IAIN/0098	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	31/07/2019	n/a		
IA/0096	A.7 - Administrative change - Deletion of manufacturing sites	16/05/2019	25/07/2019	Annex II and PL	
II/0092	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	17/01/2019	n/a		

IA/0094	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	05/12/2018	n/a		
IAIN/0093/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 B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/11/2018	25/07/2019	Annex II and PL	
T/0091	Transfer of Marketing Authorisation	28/06/2018	30/07/2018	SmPC, Labelling and PL	
II/0089	Male patients treated with Abraxane are advised to use effective contraception and to avoid fathering not to father a child during and up to six months after	19/07/2018	25/07/2019	SmPC and PL	

	treatment. Paclitaxel at doses below the human therapeutic dose was associated with low fertility when administered prior and during mating in male and female rats and foetal toxicity in rats. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Following intravenous administration of radiolabelled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0090	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	26/06/2018	n/a		
II/0087	Update of section 4.8 of the SmPC in order to include the warning tumour lysis syndrome following a safety cumulative review of this signal. In addition, the marketing authorisation holder took the opportunity to update the wording on section 4.6 to introduce additional recommendation to perform a pregnancy test prior treatment with paclitaxel. The package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	12/04/2018	30/07/2018	SmPC and PL	Following review of 7 cases, 5 of which met the diagnostic criteria of tumour lysis syndrome,the SmPC section 4.8 has been updated to indicate that there have been reports of tumour lysis syndrome during treatment with Abraxane. In addition, section 4.6 of the SmPC has been updated with additional information to conduct pregnancy test for women with childbearing potential prior treatment with Abraxane. With regards to the request to conduct pregnancy test prior treatment, the Package Leaflet has been updated

	new quality, preclinical, clinical or pharmacovigilance data				accordingly.
IAIN/0088	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	23/03/2018	n/a		
IB/0086/G	This was an application for a group of variations. B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	18/01/2018	30/07/2018	SmPC, Labelling and PL	
IAIN/0085	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	04/09/2017	n/a		
IB/0084/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any	27/07/2017	n/a		

	manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
IAIN/0083	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/05/2017	n/a		
PSUSA/10123 /201601	Periodic Safety Update EU Single assessment - paclitaxel albumin	15/09/2016	11/11/2016	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10123/201601.
IB/0078	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/06/2016	n/a		
IA/0081	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	03/06/2016	n/a		
IAIN/0082	B.V.a.1.d - PMF - Inclusion of a new, updated or	01/06/2016	n/a		

	amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IAIN/0080	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	01/06/2016	n/a		
IA/0079/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	25/04/2016	n/a		
II/0072	Update of section 4.2 of the SmPC in order to update the recommended dose adjustments for NSCLC patients with moderate to severe hepatic impairment. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor mistakes in the Package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	28/07/2015	SmPC and PL	For metastatic breast cancer patients and non-small cell lung cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and AST ≤ 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles.

IG/0590	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	22/07/2015	n/a		
PSUSA/10123 /201501	Periodic Safety Update EU Single assessment - paclitaxel albumin	09/07/2015	n/a		PRAC Recommendation - maintenance
IB/0075	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	03/07/2015	n/a		
IAIN/0074	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	19/05/2015	n/a		
IA/0073/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/05/2015	n/a		
IA/0070/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate	06/03/2015	n/a		

	from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
IAIN/0069/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.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.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer A.7 - Administrative change - Deletion of manufacturing sites	06/03/2015	n/a		
II/0067	Extension of Indication to add a new indication for Abraxane in combination with carboplatin for the	22/01/2015	26/02/2015	SmPC and PL	Please refer to the Scientific Discussion Abraxane-H-C-778-

	first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Consequently sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. Further, sections 4.2 and 6.6 of the SmPC have been updated with a recommendation to flush the intravenous line with sodium chloride to ensure administration of the complete dose. The Package Leaflet has been updated accordingly. Further, an updated RMP version 14.0 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				II-67
II/0065	Update of SmPC sections 4.2 and 5.2 with new recommendations on dose adjustments for patients with hepatic and renal impairment based on the conclusions of new population pharmacokinetics analysis and PPK/PD modelling using data obtained from 8 clinical trials of Abraxane in patients with advanced solid tumours. The existing warning on hepatic impairment in section 4.4 of the SmPC is also amended accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	27/10/2014	SmPC	For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no Abraxane dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function. For metastatic breast cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and AST ≤ 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles (see sections 4.4 and 5.2). For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations. For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage

					recommendations regardless of indication. Adjustment of the starting Abraxane dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to <90 ml/min). There are insufficient data available to recommend dose modifications of Abraxane in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 ml/min). Pharmacokinetic/pharmacodynamic modelling using data from 125 patients with advanced solid tumours indicates that patients ≥65 years of age may be more susceptible to development of neutropenia within the first treatment cycle. Population pharmacokinetic analyses for Abraxane indicate that gender, race (Asian vs. White), and type of solid tumours do not have a clinically important effect on systemic exposure (AUC and Cmax) of paclitaxel. Patients weighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of this finding is uncertain. Following Abraxane administration to patients with solid tumours, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). Based on population pharmacokinetic analysis, the total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.
PSUV/0066	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IAIN/0068	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) -	18/06/2014	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0063	Update of sections 4.2 and 6.6 of the SmpC to include the requirement for use of a 15µm filter in the infusion set used to administer Abraxane following reports of visible strands formation in the Abraxane infusion solution. Instructions to healthcare professionals in the Package Leaflet are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	27/10/2014	SmPC and PL	Following isolated reports of visible proteinaceous strand formation in the Abraxane suspension for infusion, this should be inspected in the vial for particulate matter and it should not be administered, if particulate matter is observed in the vial. The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer Abraxane may result in the formation of such proteinaceous strands. Abraxane should be administered using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of such filter removes strands and does not change the physical or chemical properties of the reconstituted product. Use of filters with a pore size less than 15 µm may result in blockage of the filter.
IAIN/0064	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	17/03/2014	n/a		
II/0062/G	This was an application for a group of variations. This was an application for a group of variations. To increase the batch size of the finished product, add alternative immediate packaging, its supplier, and remove non-significant packaging specification parameters.	20/02/2014	n/a		

	B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0060	Update of section 4.8 of the SmPC in order to update the safety information on the identified risk of alopecia as requested by CHMP and PRAC further to the review of LEG 024 and LEG 024.1. The Package Leaflet is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2013	27/10/2014	SmPC and PL	In the MAH's integrated safety database of all trials with Abraxane as monotherapy for metastatic breast cancer and few other solid tumour indications, 959 patients (73%) out of 1,310 experienced alopecia. Most events were reported as National Cancer Institute-Common Terminology Critera (NCI-CTC) grade 2 severity (83%). At this point there is no conclusive information from clinical trial reports (or from other reports) on the

					reversibility of alopecia caused by Abraxane. Section 4.8 of the SmPC has been updated to include that the majority of alopecia events occurred less than one month after initiation of Abraxane and that pronounced hair loss >=50% is expected for the majority of patients who experience alopecia. The Package Leaflet is updated accordingly.
II/0055	Extension of Indication to include new indication for Abraxane in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated in order to: provide posology recommendations and dose adjustment information, add warnings on sepsis, co-administration with erlotinib, patients with normal CA19-9 at baseline and patients 75 years and older, amend existing warnings on neuropathy and pneumonitis, inform of the absence of expected or shown interactions between Abraxane and gemcitabine, include information on adverse drug reactions expected from the combination of Abraxane and gemcitabine in pancreatic cancer patients and include information from the pivotal trial to the SmPC. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to make minor editorial amendments throughout the Product Information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	21/11/2013	02/12/2013	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion Abraxane-H-C-778-II-55

	modification of an approved one				
IAIN/0061	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/10/2013	n/a		
II/0057/G	This was an application for a group of variations. Addition of a new 250 mg vial presentation. No changes are made to the strength once reconstututed but a larger vial is introduced to contain the larger dose. Minor changes to the manufacturing process, specification, and test procedures are made to support the manufacture of the new presentation and ensure consistency between specifications and testing methods for both presentations. B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.5.c - Change to in-process tests or limits	19/09/2013	03/12/2013	SmPC, Labelling and PL	

	applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion				

	of an obsolete parameter B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IAIN/0059	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/09/2013	n/a		
II/0056	Update of section 4.8 of the SmPC in order to include atrioventicular block as an adverse drug reaction during Abraxane treatment following a relevant case reported in the post-marketing setting. The Package Leaflet is updated accordingly. In addition, the MAH took this opportunity to bring the PI in line with the latest version QRD template (version 9.0). C.I.4 - Variations related to significant modifications	25/07/2013	03/12/2013	SmPC, Annex II and PL	Following a relevant case reported in the post-marketing setting, atrioventricular block was listed as an Adverse Drug Reaction (ADR) of Abraxane therapy with the frequency 'rare'. Atrioventricular block is an already known ADR of conventional paclitaxel cremophor formulations.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0310	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2013	n/a		
IAIN/0052/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of	25/03/2013	03/12/2013	Annex II and PL	

	manufacturing sites				
IG/0278	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	n/a		
IAIN/0054/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	20/03/2013	n/a		
IB/0051	B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP	04/03/2013	n/a		
R/0039	Renewal of the marketing authorisation.	18/10/2012	14/01/2013	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Abraxane continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP therefore recommended that the Abraxane Marketing Authorisation can be renewed with unlimited validity.

II/0047	Update of section 4.8 of the SmPC in order to add sepsis and neutropenic sepsis as uncommon Adverse Drug Reactions in the course of Abraxane treatment in conclusion to the assessment of the 7th PSUR. The Package Leaflet is updated accordingly. 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	13/12/2012	03/12/2013	SmPC and PL	In follow-up to the assessment of the 7th PSUR (1st yearly PSUR corresponding to MAH's PSUR 7 and 8), covering the period from 07 January 2011 to 06 January 2012, sepsis and neutropenic sepsis were included in the list of Adverse Drug Reactions (ADRs) observed in the course of Abraxane treatment.
IAIN/0049	B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	10/12/2012	n/a		
II/0044	Update of section 4.8 of the SmPC to include cystoid macular oedema as a rare adverse drug reaction, based on post-marketing experience. The Package Leaflet is 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	15/11/2012	03/12/2013	SmPC and PL	A review of the Abraxane safety database was conducted and the results indicated that patients treated with Abraxane may develop cystoid macular oedema. Upon diagnosis of cystoid macular oedema, treatment with Abraxane should be discontinued.
IAIN/0046	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/09/2012	n/a		

IA/0045	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/08/2012	n/a		
IB/0042	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	02/08/2012	n/a		
IAIN/0043/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	26/07/2012	14/01/2013	Annex II and PL	
II/0037	Update of section 4.4 of the SmPC in order to amend the existing warning on hypersensitivity reactions to inform of the occurrence of very rare cases of anaphylactic reactions with fatal outcome in the course of Abraxane treatment. 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	Severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have recently been reported in patients treated with Abraxane in post-marketing surveillance studies. If a hypersensitivity reaction occurs, Abraxane should be discontinued immediately, symptomatic treatment should be initiated and the patient should not be rechallenged with paclitaxel.

II/0033/G	This was an application for a group of variations. To add an alternative manufacturing site for the finished product and minor changes to the manufacturing process. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	21/06/2012	21/06/2012		
IAIN/0041	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	30/05/2012	n/a		
IG/0168/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	24/05/2012	n/a		

	C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0034	Update of sections 4.4 and 4.8 of the SmPC in order to introduce a warning regarding close monitoring of patients for signs and symptoms of pneumonitis and to amend the frequency of interstitial pneumonitis in patients receiving Abraxane, based on a MAH safety database review following an increased incidence of relevant cases in study CA046 (Abraxane in combination with gemcitabine vs gemcitabine alone in patients with metastatic pancreatic cancer). The Package Leaflet 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	15/03/2012	20/04/2012	SmPC and PL	Following cases of interstitial pneumonitis reported in a clinical study in patients with pancreatic cancer in which Abraxane was given in combination with gemcitabine, a review of the Abraxane safety database was conducted and a warning was added in the Product Information to caution of the potential development of this complication in the course of Abraxane treatment. Moreover, the frequency of this side-effect was updated from 'rare' to 'uncommon' (occurring in >1 in 1000 to <1 in 100 patients) based on overall clinical trial experience.
IA/0036	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/03/2012	n/a		

IAIN/0035	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	21/02/2012	n/a		
IAIN/0031	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/11/2011	n/a		
IG/0100/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site	23/08/2011	n/a		

	undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0030	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	05/07/2011	n/a		
II/0023	Update of section 4.8 of the Summary of Product Characteristics (SmPC) to include Stevens-Johnson syndrome and toxic epidermal necrolysis as very rare events further to the CHMP request following evaluation of the 4th PSUR. In addition, sections 4.8 and 6.6 of the SmPC have been updated to include extravasation. The PL has been updated accordingly. Finally, the MAH took the opportunity to correct some minor inconsistencies and typographical errors in the Product Information. 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	19/05/2011	29/06/2011	SmPC, Labelling and PL	Further to the assessment of the 4th PSUR, the CHMP concluded that based on the two cases of Stevens Johnson-syndrome and one case of toxic epidermal necrolysis reported in patients treated with Abraxane, section 4.8 of the SmPC should be updated to include this information. In addition, since one case of extravasation has been reported following administration of Abraxane in a clinical trial, sections 4.8 and 6.6 of the SmPC have been updated to include this adverse reaction. Both changes have been made in order to bring Abraxane (albumine-bound paclitaxel) SmPC in line with the SmPCs of solvent-based paclitaxels. Finally, some minor inconsistencies and typographical errors have been corrected in the SmPC, Labelling and PL.
IA/0029/G	This was an application for a group of variations.	08/06/2011	n/a		

	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0024	C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	12/05/2011	n/a	Annex II	To notify of the adoption of the Celgene pharmacovigilance system, as described in the Detailed Description of the Pharmacovigilance System. This variation also includes an update to the annexes to remove the version number of the DDPS from Annex IIB, as required in the latest QRD

					product information template.
IA/0028	A.1 - Administrative change - Change in the name and/or address of the MAH	11/05/2011	n/a	SmPC, Annex II, Labelling and PL	
IA/0027	B.III.1.a.1 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	04/05/2011	n/a		
IA/0026	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	26/04/2011	n/a		
IA/0025	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	19/04/2011	n/a		
T/0022	Transfer of Marketing Authorisation	01/02/2011	10/03/2011	SmPC, Labelling and PL	
IA/0021	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	15/09/2010	n/a		

II/0020	Update of section 5.2 of the SmPC with pharmacokinetic data from study CA201 related to body weight further to a CHMP request in conclusion to FU2 006.2. The Marketing Authorisation Holder (MAH) took the opportunity to update the Product Information according to the latest version of the QRD template (version 7.3.1, March 2010). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	06/09/2010	SmPC, Annex II and PL	Study CA201 was a phase I/II efficacy, safety and pharmacokinetic study conducted in Chinese patients. The results showed significant differences in pharmacokinetic parameters in Chinese patients compared to Caucasians. However, these differences were attributed to differences in body weight and not to ethnic factors. An analysis of patient exposure (AUCinf) against body weight indicated a trend toward reduced AUC at 260 mg/m2 Abraxane, with decreased body weight. Patients weighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of this finding is uncertain.
II/0018	Inclusion of left ventricular dysfunction, congestive heart failure and pancytopenia as rare adverse reactions in section 4.8 of the SmPC and update to section 4 of the Package Leaflet (PL) to reflect these changes. Modification of section 4.4 of the SmPC to strengthen the relationship between administration of Abraxane and rare incidences of cardiotoxicity based on experience to date. The MAH took the opportunity to update the product information in line with the QRD template (version 7.3 dated 10/2009), improve readability of the Labelling and correct some minor grammatical and typographical errors in the Labelling 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	22/04/2010	02/06/2010	SmPC, Labelling and PL	Following a cumulative review of cardiotoxicity reports with the use of Abraxane prompted by three cases of left ventricular dysfunction reported within PSURs, the terms 'left ventricular dysfunction' and 'congestive heart failure' were added to the table of ADRs of section 4.8 of the SmPC and the existing warning on cardiotoxicity in section 4.4 of the SmPC was reworded to strengthen the relationship between administration of Abraxane and cardiotoxicity. The term 'pancytopenia' was added to the ADRs table of SmPC section 4.8 to reflect confirmed or purported cases of concurrent anaemia, leukopenia and thrombocytopenia, all of which are already listed ADRs of Abraxane. Section 4 of the PL was amended according to the SmPC changes.
IA/0019	B.V.a.1.d - PMF - Inclusion of a new, updated or	16/03/2010	n/a		

	amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IA/0017	IA_01_Change in the name and/or address of the marketing authorisation holder	07/08/2009	n/a	SmPC, Labelling and PL	
IB/0016	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	03/08/2009	n/a	SmPC	
II/0013	This type II variation concerns an update of the SPC, upon request by the CHMP following the assessment of FUM 004, FU2 006.1 and PSU 007 (PSUR 1), to update the information on pharmacokinetics in sections 5.2 with the results of studies CA019 and CA201, to update section 4.4 with a statement highlighting that Abraxane should not be substituted for or with other paclitaxel formulations, and to update section 4.8 with further safety information and section 4.5 with further information about potential interactions in line with the Core Data Sheet. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the SPC, labelling and Package Leaflet in line with the latest QRD templates (version 7.2) and to update Annex II to reflect the latest version of the Risk Management Plan agreed with the CHMP (version 5.0). Update of Summary of Product Characteristics,	25/06/2009	29/07/2009	SmPC, Annex II, Labelling and PL	This type II variation concerns an update of the SPC, upon request by the CHMP following the assessment of FUM 004, FU2 006.1 and PSU 007 (PSUR 1), to update the information on pharmacokinetics in sections 5.2 with the results of studies CA019 and CA201, to update section 4.4 with a statement highlighting that Abraxane should not be substituted for or with other paclitaxel formulations, and to update section 4.8 with further safety information and section 4.5 with further information about potential interactions in line with the Core Data Sheet. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the SPC, labelling and Package Leaflet in line with the latest QRD templates (version 7.2) and to update Annex II to reflect the latest version of the Risk Management Plan agreed with the CHMP (version 5.0). SPC Section 5.2: In a repeat dose study with 12 patients receiving Abraxane administered intravenously at the approved dose,

	Labelling and Package Leaflet				intrapatient variability in systemic paclitaxel exposure (AUCinf) was 19% (range = 3.21%-27.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses. The protein binding of paclitaxel following Abraxane was evaluated by ultrafiltration. The fraction of free paclitaxel was significantly higher with Abraxane (6.2%) than with solvent-based paclitaxel (2.3%). This resulted in significantly higher exposure to unbound paclitaxel with Abraxane compared with solvent-based paclitaxel, even though the total exposure is comparable. This is possibly due to paclitaxel not being trapped in Cremophor EL micelles as with solvent-based paclitaxel. SPC section 4.5: The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4. SPC section 4.8: The following ADRs were added to be consistent with the Core Data Sheet: Severe hypersensitivity; bone marrow suppression; keratitis; arrhythmia; supraventricular tachycardia; bradycardia; cardiac arrest; pulmonary emboli; pulmonary thromboembolism; nail changes and nail

					pigmentation/coloration; increased bilirubin; radiation pneumonitis.
II/0012	Update of DDPS (Pharmacovigilance)	25/06/2009	29/07/2009	Annex II	This type II variation concerns an update of the Detailed Description of the Pharmacovigilance system (DDPS) in Module 1.8.1. Consequently, Annex II has been updated to reflect the latest version of the DDPS agreed with the CHMP (version 4.0).
2PMF/0014	Inclusion of the updated or amended Plasma Master File (Grifols EMEA/H/PMF/000002/04) in the marketing authorisation dossier	15/07/2009	n/a		
IA/0015	IA_09_Deletion of manufacturing site	25/06/2009	n/a		
II/0008	This type II variation concerns an update of sections 4.2, 4.4, and 5.2 of the SPC in line with the results of Study CA037 performed to evaluate the safety and pharmacokinetics in patients with hepatic impairment. The MAH also proposed to move the existing statement on the use of contraception from section 4.4 to 4.6 of the SPC and to make a minor change to section 5.1 for increased clarity. Update of Summary of Product Characteristics	19/02/2009	02/04/2009	SmPC	This type II variation concerned an update of sections 4.2, 4.4, and 5.2 of the SPC in line with the results of Study CA037 performed to evaluate the safety and pharmacokinetics in patients with hepatic impairment. The pharmacokinetic profile of Abraxane administered as a 30 minute infusion was evaluated in 15 out of 30 patients with three levels of hepatic impairment based on serum bilirubin and liver enzyme levels. Since the toxicity of paclitaxel can be increased with hepatic impairment, administration of Abraxane in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. Patients with severe hepatic impairment (bilirubin > 5 x ULN or ASL/ALT > 10 x ULN) have not been studied and

					should not be treated with Abraxane. The appropriate dose regimen in patients with less severe hepatic impairment is unknown. A dose reduction in patients with bilirubin >2 ULN must be considered since paclitaxel clearance is decreased in patients with high bilirubin levels. In addition, the CHMP agreed with the MAH's proposal to move the existing statement on the use of contraception from section 4.4 of the SPC to section 4.6: "Sexually active men and women should use effective methods of contraception during treatment and up to six months after treatment for men, and one month after treatment for women." Finally, the CHMP agreed with the MAH's proposal to add the following information to section 5.1 of the SPC for increased clarity: "Abraxane contains human serum albumin paclitaxel nanoparticles, where the paclitaxel is present in a non-crystalline, amorphous state."
IB/0010	IB_10_Minor change in the manufacturing process of the active substance	10/02/2009	n/a		
IA/0011	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	16/01/2009	n/a		
II/0003	The MAH applied for refinements in the manufacturing process of the finished product. Update of or change(s) to the pharmaceutical documentation	25/09/2008	03/10/2008		

IA/0009	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	02/09/2008	n/a		
MF/0007	2PMF (2nd step of PMF certification procedure)	19/08/2008	n/a		
IA/0006	IA_05_Change in the name and/or address of a manufacturer of the finished product	11/07/2008	n/a		
MF/0005	2PMF (2nd step of PMF certification procedure)	09/07/2008	n/a		
IA/0004	IA_01_Change in the name and/or address of the marketing authorisation holder	17/06/2008	n/a	SmPC, Labelling and PL	
IA/0002	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/02/2008	n/a		
IA/0001	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/02/2008	n/a		