EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Docetaxel Zentiva

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
WS/1550	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of Indication to include the treatment of patients with metastatic hormone-sensitive prostate cancer in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for Taxotere and Docetaxel Zentiva; as	19/09/2019	29/10/2019	SmPC and PL	Please refer to Scientific Discussion Taxotere-H-C-0073-WS-1550, Docetaxel Zentiva H-C-0808-WS-1550

[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).

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	a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 1.0 has also been submitted. In addition, the Worksharing applicant took the opportunity to update information on the local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
WS/1648	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning about cases of severe cutaneous reactions and to add acute generalized exanthematous pustulosis as an undesirable effect, respectively. The Package Leaflet is updated in accordance. In addition, the Worksharing applicant (WSA) 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	12/09/2019	29/10/2019	SmPC and PL	Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and closely monitored. If signs and symptoms suggestive of these reactions appear, discontinuation of docetaxel should be considered.
IG/1080	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	15/04/2019	n/a		

	from an already approved manufacturer				
WS/1540	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information following review of a safety signal on secondary malignancies for docetaxel requested in follow-up to EMEA/H/C/PSUSA/00001152/201611; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to correct minor typos throughout the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/02/2019	29/10/2019	SmPC and PL	Second primary malignancies have been reported when docetaxel was given in combination with anticancer treatments known to be associated with second primary malignancies. Second primary malignancies (including acute myeloid leukemia, myelodysplastic syndrome and non-Hodgkin lymphoma) may occur several months or years after docetaxel-containing therapy. Patients should be monitored for second primary malignancies.
T/0056	Transfer of Marketing Authorisation	21/09/2018	26/11/2018	SmPC, Labelling and PL	
IAIN/0055	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	24/08/2018	22/11/2018	SmPC, Labelling and PL	
WS/1267	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order	01/02/2018	22/11/2018	SmPC, Labelling and PL	This systemic review presented cases of enterocolitis, including cases with fatal outcome which were reported in association with docetaxel in approved regimens, including docetaxel monotherapy. Based on review of the MAH's global pharmacovigilance database, worldwide scientific

	to add a warning of enterocolitis in patients with neutropenia and to update the safety information on enterocolitis to reflect fatal outcomes based on the review of the MAH global pharmacovigilance data base, worldwide scientific literature and main pharmacovigilance textbooks. Update of section 4.7.of the SmPC in order to update the information related to the risk of potential effects of alcohol and the side effects of this medicinal product on the ability to drive and use machines, in line with the outcome of EMEA/H/C/PSUSA/00001152/201611. 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				literature, and main pharmacovigilance textbooks, and medical plausibility, the weighted cumulative evidence is sufficient to support a causal association between enterocolitis, including enterocolitis with fatal outcome and Docetaxel. Section 4.8. of the SmPC under gastrointestinal disorder has been accordingly updated to indicate that rare cases of enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, have been reported with a potential fatal outcome (frequency not known) and that rare occurrences of dehydration have been reported as a consequence of gastrointestinal events including enterocolitis and gastrointestinal perforation. Section 4.4. of the SmPC regarding gastrointestinal reactions has likewise been updated on this respect and caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Although majority of cases occurred during the first or second cycle of docetaxel containing regimen, enterocolitis could develop at any time, and could lead to death as early as on the first day of onset. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity. Section 4.7. of the SmPC has been updated to reflect that no studies on the effects on the ability to drive and use machines have been performed. The amount of alcohol in this medicinal product and the side effects of the product may impair the ability to drive or use machines. Therefore, patients should be warned of the potential impact of the amount of alcohol and the side effects of this medicinal product on the ability to drive or use machines, and be advised not to drive or use machines if they experience

					these side effects during treatment.
PSUSA/1152/201611	Periodic Safety Update EU Single assessment - docetaxel	14/09/2017	16/11/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1152/201611.
WS/1203/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	16/11/2017	SmPC and PL	The review of MAH's global pharmacovigilance database and scientific literature have warranted changes in sections 4.4 and 4.8 of the SmPC to reflect that cases of ventricular arrhythmia including ventricular tachycardia (sometimes fatal) have been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide. Baseline cardiac assessment is recommended. Clarifications on persisting events of peripheral sensory neuropathy, congestive heart failure, alopecia, amenorrhoea, peripheral oedema and acute leukaemia in Section 4.8 were also added based on the already submitted 10-year follow-up data for studies TAX316 and GEICAM9805.
II/0051	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/05/2017	16/11/2017	SmPC and PL	A cumulative review of cases of electrolyte balance disorders reported with docetaxel as a suspect product showed a plausible causal association between docetaxel and electrolyte imbalance including in approved docetaxel containing product regimens. Cases of electrolyte imbalance have been reported with docetaxel. Hypokalaemia, hypomagnesaemia, and hypocalcaemia were observed, usually in association with gastrointestinal disorders and in particular with diarrhoea.
IG/0675/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	11/11/2016	24/04/2017	Annex II and PL	

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer				
II/0049	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/05/2016	24/04/2017	SmPC and PL	
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/07/2015	12/05/2016	PL	
II/0047	Update of sections 4.4 and 4.7 of the SmPC to add a warning about the risks with alcohol content in the EU PI. The labelling and 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	21/05/2015	12/05/2016	SmPC, Labelling and PL	
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/01/2015	24/04/2015	PL	

IB/0045/G	This was an application for a group of variations. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	17/12/2014	n/a		
IG/0501/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	05/11/2014	n/a		
IG/0485/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.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	05/11/2014	n/a		

	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				
PSUSA/1152/ 201311	Periodic Safety Update EU Single assessment - docetaxel	25/09/2014	n/a		PRAC Recommendation - maintenance
IG/0454	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	17/07/2014	n/a		
II/0040	Update of sections 4.8 and 5.1 of the SmPC to reflect the results of study GEICAM 9805 after 10-year follow-up. Consequently, Annex II is updated to reflect fulfilment of the related conditions. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and make a few corrections to the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	24/04/2015	SmPC, Annex II and PL	Study GEICAM 9805 was a pivotal, non-blinded, randomized, phase III study, designed to compare disease-free survival after adjuvant chemotherapy following primary surgery for breast cancer in high risk node negative patients receiving one of the following adjuvant combination chemotherapy regimens: TAC (docetaxel, doxorubicin, and cyclophosphamide) or FAC (5-fluorouracil, doxorubicin, and cyclophosphamide). At the median follow up time of 10 years and 5 months, TAC treated patients had a 16,5% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.84, 95% CI (0.65-1.08), p=0.1646). DFS data were not statistically significant but were still associated with a positive trend in favour of TAC. At the median follow up time of 10 years and 5 months, TAC-treated patients had a 9% reduction in the risk of death compared to FAC-treated patients (hazard ratio = 0.91, 95% CI (0.63-1.32)).

					Safety data from GEICAM 9805 on adverse drug reactions persisting into the 10-year follow-up period (including alopecia, amenorrhoea, lymphoedema and asthenia) and cases of cardiac disorders which developed during the follow-up period have been reflected in section 4.8 of the SmPC. The updated safety data do not change the long-term safety profile of docetaxel in a combination regimen with doxorubicin and cyclophosphamide. Overall, the CHMP concluded the benefit risk balance of docetaxel remains positive in its approved indications.
II/0039	Update of sections 4.4 and 4.5 of the SmPC in order to add a warning and update the safety information on interactions with CYP3A4 inhibitors further to the PRAC assessment of a signal. In addition the MAH took the opportunity to correct inconsistencies on the number and grade of alopecia adverse reactions in section 4.8 of the SmPC. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. 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	18/12/2013	31/01/2014	SmPC and PL	Based on available safety information from a literature review performed by the MAH, the CHMP considered that the current wording on the risk of interaction with CYP3A4 inhibitors should be strengthened to reflect that concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided. In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor.
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		

II/0037/G	This was an application for a group of variations. Update of section 4.4 to add a warning on cystoid macular oedema based on the results of safety cumulative reviews conducted by the MAH and section 4.8 of the SmPC to include cystoid macular oedema and hyponatraemia in the list of adverse reactions. The package leaflet is updated accordingly. In addition the product information is revised in line with the QRD template version 9. Furthermore, the MAH took the opportunity to add the local representative for Croatia in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	31/01/2014	SmPC and PL	Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. Cases of hyponatraemia have been reported, mostly associated with dehydration, vomiting and pneumonia. Further to the review of the reported cases the CHMP concludes that docetaxel has a possible contributory role in the multifactorial development of hyponatraemia.
II/0036	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning related to respiratory disorders and include interstitial pneumonitis, interstitial lung disease and pulmonary fibrosis as new adverse reactions observed in the post-marketing setting following a relevant cumulative review of the MAH's safety database. The Package Leaflet is updated accordingly. Furthermore, the Annex II is being brought in line with the latest QRD template version 8.3.	21/02/2013	31/01/2014	SmPC, Annex II and PL	Based on a literature review and the MAH's safety database, the CHMP recommended the inclusion of the following additional respiratory disorders in the product information: pneumonitis, interstitial lung disease and respiratory failure. Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported with docetaxel and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy. If

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of docetaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming docetaxel treatment must be carefully evaluated.
N/0033	Update of the local representatives contact details for Ireland, Portugal and the United Kingdom. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/08/2012	31/10/2012	PL	
IB/0034/G	This was an application for a group of variations. 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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	02/08/2012	31/10/2012	SmPC, Annex II and PL	

	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)				
IB/0030/G	This was an application for a group of variations. B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/04/2012	n/a		
R/0021	Renewal of the marketing authorisation.	15/12/2011	08/03/2012	SmPC, Annex II, Labelling 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 Docetaxel Winthrop in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer remains favourable and therefore recommends the renewal of the marketing authorisation with unlimited validity.
IG/0147/G	This was an application for a group of variations.	29/02/2012	n/a		

	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.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/0029	B.III.2.a.1 - 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 - AS	17/02/2012	n/a		
IB/0031	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	14/02/2012	n/a		
II/0022	Update of SmPC section 4.5 regarding interaction between docetaxel and ritonavir as well as update of	15/12/2011	31/01/2012	SmPC and PL	In this variation the MAH has amended the SmPC in order to provide updated recommendations based on clinical

	SmPC section 4.8 regarding the risk of renal dysfunction, respiratory disorders, persisting alopecia and the frequency for leukaemia/MDS in the postmarketing section as requested by CHMP with assessment of PSUR 2. The Package Leaflet was proposed to be 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				cases consistent with an increase in docetaxel toxicity that were reported when it was combined with ritonavir (section 4.5). The mechanism behind this interaction is a CYP3A4 inhibition, the main isoenzyme involved in docetaxel metabolism by ritonavir. In addition, based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, section 4.5 now recommends considering a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor such as azole antifungals, ritonavir and some macrolides (clarithromycin, telithromycin). Moreover, section 4.8 has been updated to include acute respiratory distress syndrome and cases of interstitial pneumonia and pulmonary fibrosis sometimes fatal that have rarely been reported and cases of persisting alopecia. Cases of renal insufficiency and renal failure have also been reported and included in section 4.8 of the SmPC. In about 20% of these cases there were no risk factors for acute renal failure such as concomitant nephrotoxic drugs and gastro-intestinal disorders. Finally, reference to the frequency of acute myeloid leukemia and myelodisplastic syndrome reported in association with doxetaxel when used in combination with other chemotherapy agents and/or radiotherapy has been deleted.
IA/0028	A.7 - Administrative change - Deletion of manufacturing sites	13/01/2012	n/a		
IB/0027/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the	09/01/2012	n/a	Annex II and PL	

	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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing 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 applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0020	Update of the Summary of Product Characteristics (SmPC) and the Package Leaflet (PIL), to indicate the acceptable gauge of the needle (21G) which should be used for withdrawal of the concentrate	22/09/2011	24/10/2011	SmPC and PL	

	from the vial when preparing the solution for infusion. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0019	Update of SmPC sections 4.4, 4.8 and 5.1 following the final results of study TAX316. In addition, the MAH took the opportunity to introduce corrections in SmPC section 4.1 and Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	24/10/2011	SmPC and Annex II	The TAX 316 study has been conducted to support the extension of indication of Taxotere in the adjuvant treatment of patients with operable breast cancer with positive axillary lymph nodes (EMEA/H/C/073/II/54, Commission Decision 5 January 2005). The primary objective of this parallel, nonblinded, randomized phase 3 study was to compare disease-free survival (DFS) after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to 5 fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) in operable breast cancer patients with positive axillary lymph nodes. The secondary objective was to compare overall survival (OS), toxicity, and quality of life between the 2 above-mentioned arms, and to evaluate pathologic and molecular markers for predicting efficacy. The 10-year follow-up visit was the last follow-up visit, occurring 120 months after the last administration of study drugs (a range of 4 months was allowed, meaning that it should have occurred at least 116 months after the last administration of study drugs). The final analysis was performed with an actual median follow up of 96 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. Incidence of relapses at 10 years was

					reduced in patients receiving TAC compared to those who received FAC (39% versus 45%, respectively) i.e. an absolute risk reduction by 6% (p = 0.0043). Overall survival at 10 years was also significantly increased with TAC compared to FAC (76% versus 69%, respectively) i.e. an absolute reduction of the risk of death by 7% (p = 0.002). As the benefit observed in patients with 4+ nodes was not statistically significant on DFS and OS, the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis. Overall, the study results demonstrate a positive benefit risk ratio for TAC compared to FAC. With regard to safety in patients treated with the TAC regimen fo
IG/0091	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	05/07/2011	n/a	Annex II	
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/04/2011	n/a	Labelling	
IG/0061	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/04/2011	n/a		
IG/0024/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	21/10/2010	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter) 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				
II/0012	Update of SPC section 4.1 to add a new indication for docetaxel in combination with doxorubicin and cyclophosphamide for adjuvant treatment of patients with operable node-negative breast cancer. Adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer. This extension of indication is based on results of the Geicam 9805 study. Consequently, SPC sections 4.2, 4.4, 4.8 and 5.1 as well as the Package Leaflet have been updated. In addition, the MAH took the opportunity to perform a correction in SPC section 6.6 and PL concerning the preparation guide for the 20mg/1ml, 80mg/4ml and 160mg/8ml concentrate for solution for infusion presentations. Extension of Indication	20/05/2010	06/07/2010	SmPC and PL	Please refer to the Scientific Discussion "Docetaxel Winthrop-H-C-808-II-12".
IB/0017	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	01/07/2010	n/a		
IG/0004/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance	06/05/2010	n/a	Annex II	

	system as described in the DDPS - Change in the QPPV 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.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/0014	To add a new presentation of 160 mg/8 ml of Docetaxel Winthrop concentrate for solution for infusion (one vial formulation) to the currently approved 20 mg/1 ml and 80 mg/ 4ml presentations. Quality changes	18/03/2010	05/05/2010	SmPC, Labelling and PL	
II/0013	Changes to the starting material used in the manufacturing process of the active substance (docetaxel) and to the manufacturing process of an intermediate. Addition and deletion of alternative manufacturing sites of the active substance. Quality changes	22/04/2010	28/04/2010		

IB/0016	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	17/03/2010	n/a		
IB/0015	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)	05/03/2010	n/a	SmPC and PL	
II/0009	This type II variation concerns an update of SPC section 4.3 to remove the existing contraindication for pregnant and breast-feeding women as well as an update to sections 4.4 and 4.6 regarding the contraceptive measures for women and men for all strengths. The Package Leaflet has been updated accordingly. Furthermore, the expression of the strength for the two initially approved 20mg (20mg/0.5ml) and 80mg (80mg/2ml) strengths was amended in the SPC, labelling and package leaflet. In addition, the MAH took the opportunity to make editorial changes throughout the SPC and package leaflet for the 20mg/0.5ml and 80mg/2ml strengths to further align with the 20mg/1ml and 80mg/4ml strengths. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/11/2009	18/12/2009	SmPC, Labelling and PL	The current approved information on lactation states that docetaxel is a lipophilic substance but it is not known whether it is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued for the duration of docetaxel therapy. Therefore, when a woman has to be treated after delivery of the baby, docetaxel should be prescribed due to the severity of the disease and a lactating woman should stop breastfeeding instead of not being treated with docetaxel and continuing breastfeeding. This is justified by the benefit for the treated woman compared to the benefit of breastfeeding. Therefore, CHMP agreed that breast-feeding is removed as a contraindication from SPC section 4.3. In accordance with the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005) as well as taking into account that an alternative safer treatment is not an option and as the treatment cannot be delayed, the MAH considered that an absolute contraindication for pregnant women is not justified. The CHMP agreed to the

					removal of the contraindication for pregnant women justified by the therapeutic indication of docetaxel and in accordance with the above mentioned guideline. Contraceptive measures are indeed justified by the pharmacodynamic properties of docetaxel. Docetaxel acts on mitotic cells by promoting the assembly of tubulin into stable microtubules and inhibits theirs disassembly which leads to a marked decrease of free tubulin. As spermatogenesis occurs during adulthood, male gamete could bear DNA aberrations that justify several spermatogenetic cycles after treatment in order to eliminate such gametes. Furthermore, docetaxel may pass into seminal fluid and may have effect on the foetus. This risk occurs only during 7 days after treatment, which is the duration of full elimination of docetaxel in faeces and urine. Taking into account
X/0008	Annex I_2.(d) Change or addition of a new pharmaceutical form	24/09/2009	30/11/2009	SmPC, Labelling and PL	
II/0011	Changes to the test methods and specifications for the finished product Change(s) to the test method(s) and/or specifications for the finished product	24/09/2009	06/10/2009		
IB/0010	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	27/05/2009	n/a		
II/0007	Update of Summary of Product Characteristics	23/10/2008	25/11/2008	SmPC	This variation concerns an update of the SPC, upon request by CHMP following the assessment of PSUR 1, to add

					information regarding potential interaction with potent CYP3A4 inhibitors to section 4.5 and to add the ADR 'scleroderma-like changes' to section 4.8. Docetaxel should be administered with caution in patients concomitantly receiving potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, azole antifungals like ketoconazole or itraconazole). A drug interaction study performed in patients receiving ketoconazole and docetaxel showed that the clearance of docetaxel was reduced by half by ketoconazole, probably because the metabolism of docetaxel involves CYP3A4 as a major (single) metabolic pathway. Reduced tolerance of docetaxel may occur, even at lower doses. Sclerodermal-like changes usually preceded by peripheral lymphedema have been reported with docetaxel.
II/0005		24/07/2008	n/a		
IA/0006	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	16/04/2008	n/a		
II/0001	Extension of Indication	18/10/2007	23/11/2007	SmPC, Annex II, Labelling and PL	This type II variation concerns an extension of the current Head and Neck indication with removal of the word "inoperable" from the indication below: "Docetaxel Winthrop (docetaxel) in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck". Sections 4.1, 4.2, 4.8 and 5.1 of the SPC have been amended and the Package Leaflet has been updated accordingly. In

					addition, the MAH took the opportunity to make minor editorial changes to the SPC and to update the annexes in line with the latest QRD template. Please refer to the Scientific Discussion "Docetaxel Winthrop-H-C-808-II-01".
II/0003	Quality changes	18/10/2007	24/10/2007		
II/0002	Quality changes	18/10/2007	24/10/2007		
IA/0004	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	16/08/2007	n/a		