Tyverb

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
IAIN/0081/G	This was an application for a group of variations. 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 -	11/12/2024		Annex II and PL	

[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).

	Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0080	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	07/10/2024		Annex II and PL	
IA/0079	A.7 - Administrative change - Deletion of manufacturing sites	14/06/2024	n/a		
IG/1724/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/03/2024	n/a		
IB/0077	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/11/2023	n/a		
IAIN/0076/G	This was an application for a group of variations. 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	10/05/2023	10/05/2024	Annex II and PL	

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
PSUSA/1829/ 202203	Periodic Safety Update EU Single assessment - lapatinib	27/10/2022	n/a		PRAC Recommendation - maintenance
IAIN/0074	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/06/2022	n/a		
IA/0073/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.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	02/05/2022	n/a		

II/0072/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to add skin fissures to the list of adverse drug reactions (ADRs) with frequency common, following recently analyzed safety data regarding skin fissures. The Package Leaflet is updated accordingly. The ATC code is also updated. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	30/01/2023	SmPC and PL	
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2021	28/10/2021	PL	
IB/0071/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	18/08/2021	n/a		
IB/0069/G	This was an application for a group of variations.	17/12/2020	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IA/0068	A.7 - Administrative change - Deletion of manufacturing sites	04/12/2020	n/a		
IB/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/10/2020	28/10/2021	SmPC, Annex II, Labelling and PL	
IA/0066	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	12/02/2020	n/a		
PSUSA/1829/ 201903	Periodic Safety Update EU Single assessment - lapatinib	03/10/2019	n/a		PRAC Recommendation - maintenance

R/0060	Renewal of the marketing authorisation.	25/07/2019	19/09/2019	SmPC, Annex II, Labelling and PL	
IA/0065/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.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	16/09/2019	17/09/2020	Annex II and PL	
II/0062	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	11/07/2019	19/09/2019	Annex II	
IA/0064/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a	01/07/2019	n/a		

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/04/2019	22/05/2019	SmPC	
IB/0058/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.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of	14/02/2019	n/a		

	the finished or intermediate product - Other variation B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products				
II/0057	Update of section 4.6 of the SmPC in order to update the safety information on pregnancy and breast-feeding following review of the company Core Data Sheet (CDS). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Estonia and Lithuania in the Package Leaflet. Moreover, the MAH took the opportunity to make minor editorial changes in the Labelling of the bottle presentations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/12/2018	22/05/2019	SmPC, Labelling and PL	Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with Tyverb and for at least 5 days after the last dose. Breast-feeding must be discontinued in women who are receiving therapy with Tyverb and for at least 5 days after the last dose.

PSUSA/1829/ 201803	Periodic Safety Update EU Single assessment - lapatinib	04/10/2018	n/a		PRAC Recommendation - maintenance
II/0051	Update of sections 4.1, 4.4 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 listed as a condition (ANX027.4) in the Annex II; a Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II has been updated accordingly. A revised RMP version 35.1 has also been approved. The variation leads to amendments to the Summary of Product Characteristics and Annex II and to the Risk Management Plan (RMP). The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II: "To present data in patients with hormone receptor-positive metastatic breast cancer, not currently intended for chemotherapy, and previously treated with trastuzumab from: A randomised and controlled clinical trial (EGF114299) in a patient population essentially identical to that of EGF30008 except that subjects must have received prior treatment with trastuzumab, with aromatase inhibitor (AI) +	28/06/2018	30/07/2018	SmPC and Annex II	

	trastuzumab included as the reference arm." C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2018	22/05/2019	SmPC and PL	
IB/0055	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)	20/06/2018	30/07/2018	SmPC	
IG/0950	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)	18/06/2018	n/a		
T/0052	Transfer of Marketing Authorisation	04/04/2018	22/05/2018	SmPC, Labelling and PL	
II/0050/G	This was an application for a group of variations. Submission of the final non-clinical study report 09DMR047 listed as a category 3 study in the RMP. This is a non-clinical mechanistic study related to lapatinib metabolite identification in dog plasma, bile and liver. An updated RMP (version 33.0) is included to reflect the completion of a dog study and integration of the results. Change to the final due date of study EGF117165 to	25/01/2018	22/05/2018	Annex II	

	evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or chemotherapy (category 1, ANX034.2) from June 2018 to June 2019 in Annex II and the RMP. In addition, the MAH took the opportunity to implement the last PRAC PSUR recommendation (EMEA/H/C/PSUSA/00001829/201703) into the RMP (version 33.0), including the removal of two identified risks (rash, diarrhoea) and update of missing information wording (hepatic impairment and renal impairment). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/1829/ 201703	Periodic Safety Update EU Single assessment - lapatinib	28/09/2017	n/a		PRAC Recommendation - maintenance
II/0048/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	22/05/2018	SmPC, Annex II, Labelling and PL	The MAH updated the SmPC in order to: - add in section 4.4 a warning on concentration-dependent increase of the QTc interval, concomitant use of CYP3A4 inhibitors, and a strengthened recommendation of ECG monitoring (), - to add to the tabulated list of adverse reactions in section 4.8 Ventricular arrhythmias/Torsades de Pointes, electrocardiogram QT prolonged (frequency Not known)

					and to reflect that amongst serious cutaneous reactions, Stevens - Johnson syndrome and Toxic Epidermal Necrolysis has been observed (frequency Not known). - add in section 5.1 information on the effect of lapatinib on the QT-interval evaluated in study EGF114271, a single blind, placebo-controlled, single sequence crossover study in patients with advanced cancer. The Package Leaflet is updated accordingly.
PSUSA/1829/ 201603	Periodic Safety Update EU Single assessment - lapatinib	29/09/2016	n/a		PRAC Recommendation - maintenance
IAIN/0046/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	11/05/2016	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging				

	site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/1829/201503	Periodic Safety Update EU Single assessment - lapatinib	08/10/2015	n/a		PRAC Recommendation - maintenance
IAIN/0045/G	This was an application for a group of variations. 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.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	13/07/2015	29/06/2016	Annex II and PL	
II/0041/G	This was an application for a group of variations. Submission of a revised RMP in order to include general updates in the RMP regarding posology update, addition of some new studies to Pharmacovigilance Activities and addition of details of three newly available study reports; timelines have been also changed for study EGF114299 and study EGF117165 and RMP (final version adopted is v29.0) and annex II have been updated accordingly.	25/06/2015	29/06/2016	Annex II	

	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/1829/ 201409	Periodic Safety Update EU Single assessment - lapatinib	23/04/2015	19/06/2015	SmPC and PL	Please refer to Tyverb PSUSA-1829-201409 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
T/0043	Transfer of Marketing Authorisation from Glaxo Group Ltd. to Novartis Europharm Limited. Transfer of Marketing Authorisation	30/03/2015	05/05/2015	SmPC, Labelling and PL	
II/0042	Submission of data analysis of the available pharmacokinetic sampling of patients enrolled in LANTERN trial (LAP113130) in comparison to historical data in order to fulfil the MEA 023.3 which is meant to examine lapatinib dose adjustments with specific CYP3A4 inducers. An updated RMP was submitted which included a summarised outcome of study LAP113130 (LANTERN). C.I.13 - Other variations not specifically covered	23/04/2015	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0037	Update of section 5.1 of the SmPC with information on lapatinib effect on CNS metastasis further to comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO) (SOB 002.4). Annex II is also updated further to the fulfilment of the specific obligation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	17/02/2015	SmPC, Annex II and PL	
R/0039	Renewal of the marketing authorisation.	22/01/2015	22/01/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated. Furthermore, the CHMP confirmed the recommendation adopted in variation II/37 to grant for Tyverb Marketing Authorisation no longer subject to Specific Obligations.
II/0038	Update of section 5.1 of the SmPC further to disease-free survival (DFS) results from hormone receptor-positive patients in the adjuvant EGF106708 (ALTTO) study (REC 037). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	18/12/2014	11/02/2015	SmPC	

	data				
PSUV/0035	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0036	To postpone the due date for LANTERN Study (MEA 23.4) to February 2015 due to a delay in the provision of the final Clinical Study report (CSR). This data may then assist in considering possible labelling changes to the Tyverb SmPC, in order to provide better guidance to prescribers on a possible combination dosing strategy for patients with CNS metastases, as requested by CHMP during the 01st annual reassessment (EMA//H/C/795/R/01). C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	29/07/2014	n/a		
II/0033	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	11/02/2015	SmPC and Annex II	
PSUV/0032	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
R/0030	Renewal of the marketing authorisation.	23/01/2014	12/03/2014	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Tyverb, subject to the Specific Obligations and Conditions as laid down in Annex II

					to the Opinion.
IB/0031/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	19/02/2014	n/a		
II/0022	Extension of indication to include treatment for adult patients with breast cancer whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with hormone receptor-negative metastatic disease, that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy. As a consequence sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated accordingly. Changes were also made to the PI to bring it in line with the QRD template version 9 and make minor corrections. In addition, the list of local representatives in the PL is revised to add contact details for the representative of Croatia. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2013	25/07/2013	SmPC, Annex II and PL	Please refer to the Scientific Discussion: Tyverb-H-795-II-22.
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	25/07/2013	SmPC, Labelling and PL	

R/0028	Renewal of the marketing authorisation.	21/02/2013	17/04/2013	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, was of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommended the renewal of the conditional MA for Tyverb, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion. In addition, in view of the available information on cardiac toxicity and severe diarrhoea the CHMP considered appropriate to update sections 4.2, 4.4 and 4.8 of product information to strengthen the related warnings. Furthermore, the CHMP considered that section 4.1 of the SmPC should mention for clarity that no data are available on the efficacy of lapatinib in combination with an aromatase inhibitor relative to trastuzumab in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. Based on the data available, the CHMP concluded that the Benefit/Risk balance of lapatinib in the currently approved indications remains favourable.
II/0026	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding hepatotoxicity with the results of a pharmacogenetic analysis from study EGF114471, a sub-study of EGF105485 (TEACH). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	17/04/2013	SmPC	The results of a pharmacogenetic analysis (EGF114471) that was undertaken in the randomised clinical trial EGF105485 (TEACH) confirmed the results of previous retrospective analyses of pharmacogenetic data from multiple clinical trials which suggested an association of a Class II Major Histocompatibility Complex (MHC) locus, centred on the Human Leukocytic Antigen (HLA) alleles - DQA1*02:01 and –DRB1*07:01, with lapatinib-induced elevation in serum alanine aminotransferase (ALT). Results

					from EGF114471 showed convincing evidence of a causal relationship between carriage of the HLA alleles DQA1*02:01 and DRB1*07:01 and lapatinib-induced hepatotoxicity. The cumulative frequency of severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE grade 3) at 1 year of treatment was 2.8% overall. The cumulative frequency in DQA1*02:01 and DRB1*07:01 allele carriers was 10.3% and in non-carriers was 0.5%. Carriage of the HLA risk alleles is common (15 to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1%) in Japanese populations.
II/0027	Update of section 5.1 of the SmPC based on results from interim analyses of two phase III studies which compared lapatinib and trastuzumab in combination with chemotherapy in women with advanced or metastatic breast cancer. 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	17/04/2013	SmPC and PL	Available data from interim analyses of two phase III studies have shown that in some settings Tyverb is less effective than trastuzumab based treatment regimens. A randomised Phase III study (EGF111438) (N=540) compared the effect of the two regimens on the incidence of CNS as site of first relapse in women with HER2 overexpressing metastatic breast cancer. The study was halted as the interim analysis (N=475) showed a low incidence of CNS events and, superior efficacy of the trastuzumab plus capecitabine arm in terms of progression-free survival (PFS) and overall survival (OS). The difference between arms was most pronounced in the post-hoc subgroup (stratified for at randomisation) who had not received prior trastuzumab (prior treatment with trastuzumab is a requirement for the currently approved indication). Thus, the results were statistically significant in the interim analysis of the ITT population and in the subgroup who had not received prior trastuzumab. No statistically significant differences were observed, however, in the subgroup who had received prior trastuzumab

					(relevant for the currently approved second-line indication). A second study (EGF108919) was also terminated at interim analysis due to the superior efficacy with regard to PFS of trastuzumab compared to lapatinib, in combination with a taxane in first line therapy for women with HER2-positive metastatic breast cancer. Tyverb is not approved in this indication. The CHMP concluded that the results confirmed the clinical practice of using trastuzumab-based regimens as a standard of care in this disease setting and considered that the benefit/risk balance of the currently approved indication of Tyverb as second line treatment in combination with capecitabine following therapy with trastuzumab in metastatic breast cancer was not affected by these findings and therefore remained positive. The product information has been updated accordingly.
II/0024	Update of SmPC sections 4.5, 5.1 and 5.2 with information on the variability in exposure depending on when lapatinib is administered in relation to food intake as requested by CHMP following the assessment of FU2 007.1. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/06/2012	31/07/2012	SmPC	At the time of the initial Marketing Authorisation the MAH committed to conduct a food interaction study as Follow-UP Measure (FUM007) to evaluate the food effect on lapatinib exposure, when lapatinib is administered according to the currently proposed recommendation, i.e. 1 hour before/after a meal (EGF111582: Effect of timing and content of meals on lapatinib relative bioavailability in cancer patients). Following assessment of the results of study EGF111582 the SmPC is now updated to reflect that the systemic exposure to lapatinib is affected by the timing of administration in relation to food intake. Relative to dosing 1 hour before a low fat breakfast, mean AUC values were approximately 2- and 3-fold higher when lapatinib was administered 1 hour after a low fat or high fat meal, respectively.

IAIN/0025	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	23/05/2012	31/07/2012	SmPC, Labelling and PL	
R/0021	Renewal of the marketing authorisation.	16/02/2012	13/04/2012		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Tyverb, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IG/0150/G	This was an application for a group of variations. 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.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	05/04/2012	n/a		
IB/0019	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	22/11/2011	n/a		
IA/0018/G	This was an application for a group of variations.	15/07/2011	n/a	Annex II and PL	

	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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				
II/0016	Following CHMP request with assessment of FU2 8.1 the MAH proposed an update of SPC section 4.5 with results from study EGF109275 (effect of long-acting acid-lowering agents on lapatinib absorption). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	23/05/2011	SmPC	Study EGF109275 was an open-label, single sequence study aiming at characterising the effect of elevated gastric pH mediated by the proton-pump inhibitor (PPI), esomeprazole, on the relative bioavailability of lapatinib in subjects with metastatic ErbB2 positive breast cancer. Pre-treatment with a proton pump inhibitor (esomeprazole) decreased lapatinib exposure by an average of 27% (range: 6% to 49%). This effect decreases with increasing age from approximately 40 to 60 years. Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease.
R/0014	Renewal of the marketing authorisation.	20/01/2011	08/04/2011		Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Tyverb, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion and reflected in the MAH's Letter of

					Undertaking (see Attachment 3 of this Assessment Report). The renewal requires no amendments to the terms of the Community Marketing Authorisation.
IB/0015/G	This was an application for a group of variations. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products	04/02/2011	04/02/2011	SmPC, Labelling and PL	
IG/0034/G	This was an application for a group of variations. 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.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	06/01/2011	n/a	Annex II	

	DD 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 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 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/0013	Following CHMP request (FUM30) the MAH proposed an update of SPC section 4.8 with information relating to acute renal failure arising from dehydration due to severe diarrhoea. The package leaflet has been updated accordingly. In addition, information on cardiac function has been revised in PL section 4 to be better aligned with SPC section 4.8 as recommended and a correction has been performed to PL section 6. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	28/07/2010	SmPC and PL	An evaluation of lapatinib and renal failure submitted to the CHMP as part of PSUR 3 (reporting period 13 March 2009 - 12 September 2009). With the assessment of the PSUR it was endorsed by the CHMP that the data do not demonstrate evidence to suggest direct renal toxicity associated with lapatinib. However, in several cases, it seems that lapatinib indirectly is causally related to the renal failure, for example by association with nausea, vomiting, diarrhoea and/or poor oral intake leading to dehydration which may result in renal failure. In addition, nine cases of renal failure secondary to severe dehydration associated with administration of lapatinib have been reported. In these cases the functional renal failure was secondary to a severe dehydration (leading sometimes to hypovolemic shock) due the occurrence of severe gastro-

					intestinal toxicity with diarrhoea. Neither of the patients involved in these cases had pre-existing renal impairment. The CHMP recommended that the possibility of acute renal failure as a result of severe dehydration should be included in the Product Information. Regarding the information on cardiac function in the PL the following description is now listed under common side effects: "an effect on how your heart works" together with further information that in most cases the effect on the heart will not have any symptoms, but if symptoms associated with this side effect are experienced, these are likely to include an irregular heartbeat and shortness of breath.
II/0012	Update of SPC section 4.5 to include information regarding digoxin interaction further to results of a clinical study. In addition, the MAH proposed to add information regarding interaction with docetaxel as well as to strengthen the existing text regarding the interaction information on paclitaxel in SPC section 4.5. The package leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/05/2010	17/06/2010	SmPC and PL	Further to results of several drug-drug interaction studies, the product information is updated in SPC section 4.5 as well as the PL. Lapatinib inhibits the transport protein Pgp in vitro at clinically relevant concentrations. Coadministration of lapatinib with orally administered digoxin resulted in an approximate 80% increase in the AUC of digoxin. Caution should be exercised when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of Pgp, and a reduction in the dose of the Pgp substrate should be considered. Coadministration of lapatinib with intravenous paclitaxel increased the exposure of paclitaxel by 23%, due to lapatinib inhibition of CYP2C8 and/or Pgp. An increase in the incidence and severity of diarrhoea and neutropenia has been observed with this combination in clinical trials. Caution is advised if lapatinib is coadministered with

					paclitaxel. Coadministration of lapatinib with intravenously administered docetaxel did not significantly affect the AUC or Cmax of either active substance. However, the occurrence of docetaxel-induced neutropenia was increased.
II/0004	Extension of indication of Tyverb in combination with an aromatase inhibitor for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer whose tumour overexpress HER-2 not currently intended for chemotherapy. The patients in the pivotal study were not previously treated with trastuzumab or an aromatase inhibitor. SPC sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 have been amended accordingly. Minor editorial changes were also made to the SPC. Consequently, the MAH applied also for an additional pack-size of 84 tablets reflecting the proposed daily dose for this indication. SPC section 6.5, labelling and section 6 of the PL have been updated in this respect. Furthermore, the Package Leaflet has been updated in line with the SPC revisions. Annex II has been revised to reflect the latest approved RMP version. Extension of Indication IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/02/2010	05/05/2010	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: Tyverb-H-795-II-04-SD
R/0010	Renewal of the marketing authorisation.	21/01/2010	29/04/2010	Annex II	

II/0011	Update of SPC sections 4.4 and 4.5 regarding information on interaction with midazolam as well as update of SPC section 4.5 regarding the interaction between lapatinib and irinotecan upon CHMP request. The PL is updated accordingly. Furthermore, SPC section 4.9 has been revised to provide up to date information regarding overdose following CHMP assessment of the last PSUR. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	27/04/2010	SmPC and PL	Coadministration of lapatinib with orally administered midazolam resulted in an approximate 45% increase in the AUC of midazolam. There was no clinically meaningful increase in AUC when midazolam was dosed intravenously. Therefore it is suggested that lapatinib is unlikely to significantly alter the pharmacokinetics of intravenously administered drugs that are substrates of CYP3A4. However, coadministration of lapatinib with orally administered medicines with narrow therapeutic windows that are substrates of CYP3A4 (e.g. cisapride, pimozide and quinidine) or CYP2C8 (e.g. repaglinide) should be avoided. Coadministration of lapatinib with irinotecan (when administered as part of the FOLFIRI regimen) resulted in an approximate 40% increase in the AUC of SN 38, the active metabolite of irinotecan. The precise mechanism of this interaction is unknown, but it is assumed to be due to inhibition of one or more transport proteins by lapatinib. Adverse reactions should be carefully monitored if lapatinib is co-administered with irinotecan, and a reduction in the dose of irinotecan should be considered. Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with lapatinib. In patients who took up to 5000 mg of lapatinib, symptoms observed include known lapatinib associated events and in some cases sore scalp and/or mucosal inflammation. In a single case of a patient who took 9000 mg of lapatinib, sinus tachycardia (with otherwise normal ECG) was also observed. In the majority of cases, symptoms resolved upon interruption of lapatinib treatment.

II/0009	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0008	Register of alternative manufacturer for stage 2 in the synthesis of the active pharmaceutical ingredient and upscaling of batch size Quality changes	22/10/2009	05/11/2009		
II/0005	Update of SPC section 4.8 with the Adverse Drug Reactionss "hypersensitivity reactions including anaphylaxis" with the frequency rare and "nail disorders including paronychia" with the frequency common. The PL has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	05/11/2009	SmPC and PL	From a search of the company's clinical worldwide safety database a total of 21 cases of hypersensitivity reactions were retrieved in the overall dataset, of which 16 cases were found unassessable or too confounded. Although a disproportionality analysis performed by the MAH did not indicate that there was a signal, the CHMP considered that there is a possible causal relationship between administration of lapatinib and hypersensitivity reactions, including anaphylactoid reactions. Due to the potential severity of the reaction the SPC and PIL has been amended. A total of 55 reports of nail disorders were retrieved from the company's worldwide safety database, of which six fulfilled the criteria for being non-evaluable. The remaining 49 cases have been further reviewed. Furthermore, a literature review revealed evidence of a class effect for skin and nail disorders associated with tyrosine kinase

					inhibitors. The CHMP considered that there is a causal relationship between administration of lapatinib and nail disorders. The estimated incidence "common" is supported by clinical trial data.
IA/0007	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/07/2009	n/a		
IA/0006	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/07/2009	n/a		
R/0002	Renewal of the marketing authorisation.	22/01/2009	25/03/2009		Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated to support a Conditional Marketing Authorisation and considered that the benefit risk profile of Tyverb has not changed since time of Conditional marketing Authorisation.
II/0003	Update of Detailed Description of the Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	26/02/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 6.1) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
II/0001	Update of section 5.3 to include 2-year carcinogenicity study results. In addition, the MAH took the opportunity to include the Marketing Authorisation numbers and the date of authorization in the respective sections of the SPC and labelling as well as to update the list of local representatives in	22/01/2009	26/02/2009	SmPC, Labelling and PL	The carcinogenicity studies with lapatinib were conducted in mice and rats. Although increased mortality led to the early termination of the high dose groups in male mice and female rats, the carcinogenicity studies were of acceptable quality to reach conclusions about the carcinogenic potential of lapatinib. The exposure to lapatinib at the

	the package leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet				highest evaluable doses were >2 times higher than the clinical exposure at te maimum daily dose of 1250 mg. The mouse study showed no evidence of a carcinogenic potential. There was an increased incidence of benign haemangioma of the mesenteric lymph nodes in both male and female rats. The incidences were within the background range from historical data, and although a relation to treatment cannot be fully excluded the findings do not raise concerns for the current indication. In the rat study there were findings of renal infarcts and papillary necrosis, not previously described in non clinical toxicology studies. The MAH argued that the renal infarcts are related to a long-standing chronic dermal inflammation/infection of the skin resulting from skin lesions caused by lapatinib. There was no evidence from clinical trials that the renal findings are of clinical relevance.