Erbitux

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
II/0103	Submission of an updated RMP version 19.2 in order to re-classify important identified risks and important potential risks and to remove them from the summary of safety concerns, following the PRAC assessment for PSUSA/00000635/202309.	16/01/2025	n/a		

[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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	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				
II/0099	Update of sections 4.2, 4.4 and 4.9 of the SmPC in order to introduce every two-weeks (Q2W) dosing regimen as an alternative to the already approved every week (Q1W) dosing regimen for the indications of metastatic colorectal cancer (CRC) and the recurrent/metastatic squamous cell cancer of the head and neck (SCCHN) in combination with platinum-based chemotherapy, based on pharmacokinetic (PK)-TGI-OS modelling and simulations. The Package Leaflet is updated accordingly. The RMP version 19.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2024	19/12/2024	SmPC, Annex II and PL	SmPC new text Colorectal cancer In patients with metastatic colorectal cancer, cetuximab is used in combination with chemotherapy or as a single agent (see section 5.1). Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with Erbitux. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3, and 4) mutations. Erbitux may be administered in a weekly or every other week dose regimen. Weekly dose regimen Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m2 body surface area (BSA). All subsequent weekly doses are 250 mg/m2 each. Biweekly dose regimen Erbitux is administered once every other week. Each dose is 500 mg cetuximab per m2 body surface area. For the dosage or recommended dose modifications of concomitantly used chemotherapeutic agents, refer to the product information for these medicinal products. They

					must not be administered earlier than 1 hour after the end of the cetuximab infusion. It is recommended that cetuximab treatment be continued until progression of the underlying disease. Squamous cell cancer of the head and neck In combination with radiation therapy In patients with locally advanced squamous cell cancer of the head and neck, cetuximab is used concomitantly with radiation therapy. It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab therapy until the end of the radiation therapy period. Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m2 body surface area (BSA). All subsequent weekly doses are 250 mg/m2 each. In combination with platinum-based chemotherapy In patients with recurrent and/or metastatic squamous cell cancer of the head and neck, cetuximab is used in combination with platinum-based chemotherapy followed by cetuximab as maintenance therapy until disease progression (see section 5.1). Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion. Erbitux may be administered in a weekly or every other week dose regimen. Weekly dose regimen

					Erbitux is administered once a week. The initial dose is 400 mg cetuximab per m2 body surface area (BSA). All subsequent weekly doses are 250 mg/m2 each. Biweekly dose regimen Erbitux is administered once every other week. Each dose is 500 mg cetuximab per m2 body surface area. The initial dose should be given slowly to minimize risk of infusion related reactions. The recommended infusion period is 120 minutes. For subsequent cetuximab administration the infusion rate must not exceed 10 mg/min. If initial infusion is well tolerated the recommended infusion period for weekly dose regimen of 250 mg/m2 is 60 minutes and recommended infusion period for biweekly dose regimen of 500 mg/m2 is 120 minutes. With the second and third occurrences of severe skin reactions, cetuximab therapy must again be interrupted. If the reaction has resolved to grade 2 treatment may only be resumed with a dose reduction of 20% (200 mg/m² BSA in the weekly dosing regimen, 400 mg/m² BSA in the biweekly dosing regimen) after the second occurrence and with a dose reduction of 40% (150 mg/m² BSA in the weekly dosing regimen, 300 mg/m² BSA in the biweekly dosing regimen) after the third occurrence. When cetuximab was administered in a biweekly dose regimen (500 mg/m² every other week), serum concentrations reached stable levels after five weeks of cetuximab monotherapy. Mean peak cetuximab concentration was 297 microgram per mL in week 5, the corresponding mean trough concentration was 31.0

					microgram per mL. For more information, please refer to the Summary of Product Characteristics.
II/0102	Update of section 5.1 of the SmPC based on results from study CALGB/SWOG 80405; this is a phase 3 trial of irinotecan/5-fu/leucovorin or oxaliplatin/5-fu/leucovorin with bevacizumab, or cetuximab (C225), or with the combination of bevacizumab and cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum, with efficacy as primary objective. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2024		SmPC	For more information, please refer to the Summary of Product Characteristics.
IB/0100	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/08/2024	n/a		
IA/0101/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/08/2024	19/12/2024	Annex II	
II/0098/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a	23/05/2024	19/12/2024	Annex II	

	starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile) B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
PSUSA/635/202309	Periodic Safety Update EU Single assessment - cetuximab	16/05/2024	n/a		PRAC Recommendation - maintenance
IB/0096/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or	31/07/2023	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IB/0095/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.1.z - Change in the specification parameters and/or limits 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)	27/09/2022	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				
II/0094/G	This was an application for a group of variations. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product B.I.e.2 - Introduction of a post approval change management protocol related to the AS	01/09/2022	n/a		
IA/0093	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	25/05/2022	24/04/2023	SmPC	
II/0092	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	03/03/2022	n/a		

IB/0091/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	21/09/2021	n/a		
PSUSA/635/202009	Periodic Safety Update EU Single assessment - cetuximab	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0089/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	16/12/2020	n/a		
IB/0088/G	This was an application for a group of variations.	06/01/2020	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/01/2020	25/06/2020	PL	
IB/0086	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/08/2019	n/a		
IAIN/0085/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	12/07/2019	25/06/2020	Annex II and PL	
T/0084	Transfer of Marketing Authorisation	03/05/2019	22/05/2019	SmPC, Labelling and PL	
IA/0083	B.I.b.1.b - Change in the specification parameters	18/12/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0082	To update sections 4.4 and 4.8 of the SmPC to amend existing warning and safety information on Interstitial lung disease (ILD). The RMP (version 19.0) is updated accordingly and also to include changes recommended as part of procedure EMEA/H/C/PSUSA/00000635/201709. The MAH also took the opportunity to make a minor correction to the Annex II of the Product Information C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/10/2018	22/05/2019	SmPC and Annex II	Cases of interstitial lung disease (ILD), including fatal cases, have been reported, with the majority of patients from the Japanese population. Confounding or contributing factors, such as concomitant chemotherapy known to be associated with ILD, and pre-existing pulmonary diseases were frequent in fatal cases. Such patients should be closely monitored. In the event of symptoms (such as dyspnoea, cough, fever) or radiographic findings suggestive of ILD, prompt diagnostic investigation should occur. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient be treated appropriately.
PSUSA/635/201709	Periodic Safety Update EU Single assessment - cetuximab	17/05/2018	n/a		PRAC Recommendation - maintenance
IB/0081	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/03/2018	n/a		
IA/0080	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	15/12/2017	n/a		
II/0078/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a	09/11/2017	n/a		

	starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)				
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/06/2017	22/05/2019	Labelling	
IB/0076	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	20/06/2016	n/a		
IB/0075	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	14/01/2016	n/a		
IA/0074	A.7 - Administrative change - Deletion of manufacturing sites	21/12/2015	n/a		
PSUSA/635/201409	Periodic Safety Update EU Single assessment - cetuximab	10/04/2015	n/a		PRAC Recommendation - maintenance
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2014	05/12/2014	PL	
IG/0500	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	17/11/2014	n/a		

	PSMF location				
IB/0068/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	15/09/2014	n/a		
IB/0070/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	02/09/2014	n/a		
IG/0461	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	22/07/2014	n/a		
II/0066	Update of section 5.1 of the SmPC with efficacy data by RAS (KRAS and NRAS) tumour status from the CRYSTAL (EMR 62 202-013) and FIRE3 studies C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	26/06/2014	05/12/2014	SmPC and Annex II	The submission of results of studies CRYSTAL and FIRE-3 by RAS status has been requested in order to the address issues related to the efficacy of Erbitux further to the restriction of the colorectal cancer indication, for which the evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with Erbitux. Upon

	data				submission of the application for the restriction of indication in October 2013, analyses of the interaction between RAS mutation status and treatment outcome in the pivotal first-line phase III cetuximab trials EMR 62 202-013 (CRYSTAL – cetuximab in combination with irinotecan-based chemotherapy) and FIRE-3 (randomised first-line phase III comparing head-to-head FOLFIRI combined with either cetuximab or bevacizumab in KRAS wild-type mCRC) were still ongoing. The Erbitux Product Information has been updated in order to include these new efficacy data by RAS tumour status. The data lend further support to the restriction of the Erbitux metastatic colorectal cancer indication to patients with wild-type RAS (KRAS and NRAS) tumours.
IA/0067/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	10/06/2014	n/a		
PSUV/0064	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IB/0065/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.II.f.1.b.5 - Stability of FP - Extension of the shelf	28/03/2014	05/12/2014	SmPC	

	life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0059	Update of sections 4.2 and 4.4 of the SmPC in order to amend administration recommendations and expand on the existing warning related to infusion-related reactions in the course of Erbitux treatment. Section 4.8 of the SmPC is also amended with deletion of information related to infusion reactions, as this information is being reflected in section 4.4 instead and a cross-reference to section 4.4 is being introduced. In addition, a minor deletion is made in section 4.2 of the SmPC. 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	19/12/2013	05/12/2014	SmPC and PL	Further to a PRAC recommendation, the MAH performed a cumulative review of case reports of cytokine release syndrome. In addition, the MAH conducted a review of the available evidence (from literature) in order to better define the risk of infusion-related reactions and to mitigate this risk with appropriate recommendations in the product information. As a result, information regarding the risk factors, presentation and management of infusion-related reactions, including cytokine release syndrome, was extensively revised in section 4.4 of the SmPC and relevant administration recommendations were updated in section 4.2 of the SmPC.
II/0062	Restriction of the indication for the treatment of colorectal cancer to patients with wild-type RAS tumours in follow-up to CHMP request As a consequence, sections 4.1 and 5.1 of the SmPC are updated. In addition, relevant safety information on the use of Erbitux in patients with mutant RAS tumours is updated in accordance in sections 4.2,	21/11/2013	18/12/2013	SmPC, Annex II and PL	Please refer to the Scientific Discussion: H-558-VAR-II-62-en

	4.3 and 4.4 of the SmPC. Conditions are added in Annex II for submission of results of the CRYSTAL and FIRE III studies by RAS status and of an RMP update in consequence to the amended indication. The Package Leaflet is updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0061	To update the description of the manufacturing process for the working cell banks (WCBs). B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	25/07/2013	n/a		
IA/0060/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	17/05/2013	n/a		
II/0058	Update of sections 4.4 and 4.8 of the SmPC in order to amend the existing warning on skin reactions and	21/02/2013	18/12/2013	SmPC	Four (4) cases of necrotising fasciitis, two of which with fatal outcome, and 1 case of non-necrotising fasciitis have

	the description of these, respectively, with the addition of necrotising fasciitis as a form of skin reaction that has been reported during Erbitux treatment. This updated safety information was identified following a search for relevant cases in the MAH's Global Safety Database. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				been reported in the course of Erbitux treatment. Although a causal relationship between Erbitux and necrotising fasciitis has not been established, skin reactions with Erbitux may become severe, especially in combination with chemotherapy, and the risk of secondary infections (mainly bacterial), including necrotising fasciitis, is increased.
II/0057	Update of section 4.8 of the SmPC in order to amend the severity of mucositis in the course of Erbitux treatment from 'mild to moderate' to 'in some cases severe' following an increased number of relevant cases in the Investigator Sponsored Trial PETACC-8. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make a minor editorial change to the SmPC, 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	13/12/2012	18/12/2013	SmPC, Labelling and PL	Based on the finding of an increased incidence of mucositis in the interim analysis of the PETACC-8 trial, the MAH re-evaluated the severity of mucositis in 13 randomised controlled clinical trials of cetuximab, postmarketing data and literature. Not only mild to moderate, but sometimes also severe mucositis has been reported in the course of treatment with Erbitux.
IG/0224	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2012	n/a		
IB/0055	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change	11/10/2012	n/a		

	for a biological/immunological medicinal product				
II/0054/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs	20/09/2012	n/a		
II/0052/G	This was an application for a group of variations. - To add an alternative stopper. - To delete the 50 mg/10 ml (EU/1/04/281/002) and 250 mg/50 ml (EU/1/04/281/004) presentations of the concentration 5 mg/ml solution for infusion. - To delete the concentration 2 mg/ml solution for infusion (EU/1/04/281/001) B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) C.I.7.b - Deletion of - a strength	19/07/2012	30/08/2012	SmPC, Labelling and PL	

IA/0053/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	13/06/2012	n/a		
IB/0051	- To extend the shelf-life of the active substance from 18 to 24 months. This change applies only to the 5mg/mL presentations. 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	13/02/2012	n/a		
II/0048	Update of section 5.1 of the SmPC with 5-year overall survival data from study EMR 62 202-006 (Erbitux in combination with radiation therapy in locally advanced squamous cell cancer of the head and neck). Furthermore, the MAH took the opportunity to update the PL in line with the SmPC regarding the warnings and recommendations on cardiovascular and eye disorders in the course of Erbitux treatment. Finally, the PI was brought in line with the latest QRD template (version 8.1, October 2011). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	15/12/2011	06/02/2012	SmPC, Annex II, Labelling and PL	Patients in study EMR 62 202-006 (Erbitux in combination with radiation therapy in locally advanced squamous cell cancer of the head and neck) were followed up for survival for 5 years. At the time of submission of this study (extension of indication application EMEA/H/C/000558/II/05), 3-year survival data had been presented. With the updated 5-year survival data, the favourable overall survival difference from the addition of cetuximab to radiation therapy in patients with locally advanced squamous cell cancer of the head and neck appears stable, possibly indicative of an increased cure rate in this patient population.

	clinical, clinical or pharmacovigilance data				
II/0050	B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	19/01/2012	19/01/2012		
II/0047	Modification of the metastatic colorectal cancer indication in combination with FOLFOX4 to an extended combination with FOLFOX but restricted to first line treatment only based on data from the Nordic VII study and additional data on the potential negative dynamic interaction between oxaliplatin (FOLFOX4) and cetuximab in case of KRAS mutation positive tumours and on the potential biological foundation of the apparent relationship between percentage of EGFR positive tumour cells and negative outcome in patients with KRAS mutation positive tumours. Both sets of data are fulfilling an Annex II condition. As a consequence, sections 4.1, 4.2, 4.3, 4.4 and 5.1 of the SmPC were amended with the modified mCRC indication, strengthening of the wording on the requirement for KRAS testing prior to treatment initiation, adoption of a new contraindication against use of cetuximab in combination with oxaliplatin-containing chemotherapy in patients with mutant KRAS metastatic colorectal cancer (mCRC) or for whom KRAS mCRC status is unknown, introduction of prophylaxis treatment recommendations for skin reactions and inclusion of statements regarding paediatric use. The Package Leaflet (PL) was updated accordingly. In	17/11/2011	13/01/2012	SmPC, Annex II and PL	Please refer to the Scientific Discussion Erbitux-H-C-558-II-47

	addition minor editorial amendments were included in the SmPC and PL. Moreover, the Annex II condition (Obligation to conduct post-authorisation measures) was deleted as it was considered fulfilled. 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				
II/0044/G	This was an application for a group of variations. Update of section 4.4 of the SmPC to amend the warning on interstitial lung disease (ILD) and section 4.8 of the SmPC to include ILD and Stevens Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) as adverse drug reactions further to request of the CHMP with assessment of the 9th PSUR. The PL was updated accordingly. In addition, section 4.4 of the SmPC was updated to include a warning on eye disorders further to a CHMP request following PhVWP review of keratitis and ulcerative keratitis cases associated with the use of EGFR inhibitors. Finally, the Pharmacovigilance System version number was removed from Annex II. 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 -	22/09/2011	24/10/2011	SmPC, Annex II and PL	Following additional reports of interstitial lung disease (ILD) reported in Japanese post-marketing surveillance studies, as well as cases of Stevens Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) from the post-marketing setting, the Product Information for Erbitux was updated with the inclusion of ILD and SJS/TEN as Adverse Drug Reactions. Moreover, a warning common to all EGFR inhibitors was added that patients who may develop ocular toxicities while receiving Erbitux should be monitored for evidence of keratitis or ulcerative keratitis and therapy should be interrupted or discontinued if patients present with ulcerative keratitis, while continuation should be carefully considered with keratitis in the absence of corneal ulceration. Erbitux should be used cautiously in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Use of contact lenses has also been associated with keratitis and ulceration of the cornea.

	Change(s) with new additional data submitted by the MAH C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
II/0046	Change in the manufacturer responsible for the quality control testing of the active substance and finished product. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	22/09/2011	22/09/2011		
IG/0076/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.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details 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	01/07/2011	n/a		

IB/0045	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	01/07/2011	n/a		
II/0042	Update of sections 4.1 and 5.1 of the SmPC to restrict the indication in combination with chemotherapy for the treatment of metastatic colorectal cancer to the combination with irinotecan-based chemotherapy or FOLFOX4 only. The warning on cardiovascular disorders in section 4.4 and the information on KRAS testing in sections 4.4 and 5.1 of the SmPC were amended. Section 4.5 of the SmPC was also updated to include an interaction with XELOX. A condition to the marketing authorisation was included requesting the submission of upcoming results from study NORDIC VII in order to re-assess the benefit-risk balance of this restricted indication. 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	23/06/2011	SmPC and Annex II	Please refer to Scientific Discussion Erbitux-H-C-558-II-42.
II/0041	Update of SmPC sections 4.2, 4.4, and 5.2 with information from paediatric PK study. The MAH took the opportunity to update sections 4.6 and 5.1 of the SmPC according to the SmPC guideline (September 2009) and to update the PI according to the latest version of the QRD template (7.3.1, March 2010).	17/03/2011	18/04/2011	SmPC, Annex II and PL	There is no relevant use of Erbitux in the paediatric population in the currently approved indications. However, the MAH has submitted the results of a small paediatric study which suggested that the pharmacokinetics of Erbitux in children and adolescents are similar to those previously observed in adults. No new safety signals were detected in

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				this study.
II/0036/G	This was an application for a group of variations. Addition of alternative concentrated bulk (CB) manufacturers for cetuximab. Changes in the manufacturing process of the active substance. Update of Ph. Eur. TSE Certificates of suitability. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	17/02/2011	09/03/2011		

	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product				
IB/0040	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	06/12/2010	n/a		
II/0039	Update of section 4.8 of the Summary of Product Characteristics (SmPC) with the addition of aseptic meningitis (frequency unknown) following the assessment of PSUR 8 (PSU 028). The Package Leaflet (PL) was updated accordingly. An explanatory statement on the gravity of skin reactions in section 4.8 of the SmPC and subsequently the reference to it in section 4.4 of the SmPC were deleted. Minor editorial changes were also made to the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	05/11/2010	SmPC and PL	Following assessment of PSUR 8 (PSU 028), aseptic meningitis was identified as an adverse drug reaction of cetuximab occurring with an unknown frequency and the Product Information (PI) was amended to include this information. Moreover, the definition of grade 2 and grade 3 skin reactions according to the Common Terminology Criteria of Adverse Events (CTCAE) in section 4.8 of the SmPC was deleted as it does not represent all clinical situations that would require dose adjustment as recommended in section 4.4 of the SmPC. Finally, gastrointestinal (GI) perforation and radiation dermatitis, which may both occur in the course of treatment with cetuximab, will remain under close monitoring in the Risk Management Plan (RMP), but no change in the PI is warranted.
II/0037	Change in the manufacturing process of the finished product. B.II.b.3.c - Change in the manufacturing process of	23/09/2010	04/10/2010		

	the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability				
II/0035	Update of section 5.1 of the Summary of Product Characteristics (SmPC) with final efficacy data from clinical study in metastatic colorectal cancer NCIC (CA225025) and updated efficacy data from pivotal studies CRYSTAL (EMR 62 202-013) and OPUS (EMR 62 202-047). Update of sections 4.2, 4.4, 4.5 and 4.8 of the SmPC based on the above and other studies of Erbitux combination with chemotherapy primarily with the aim to prevent use of Erbitux in patients with mutant KRAS and to include information regarding cardiovascular events. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/06/2010	28/07/2010	SmPC and PL	Updated efficacy data from the colorectal cancer trials in which cetuximab was administered in combination with chemotherapy were reported for patients with wild-type and mutant KRAS tumours (SmPC section 5.1). The updated data confirmed the positive effect in patient with wild-type tumour status and the possibly detrimental effect in patients with mutant KRAS tumours. Warnings against use of cetuximab in patients with mutant KRAS tumours were strengthened (SmPC section 4.2) and awareness was raised towards an increased incidence of cardiovascular adverse events associated with the use of cetuximab coupled with a warning on the use of cetuximab in patients with concomitant cardiovascular risk factors (SmPC section 4.4). Finally, warnings regarding adverse events observed in combination with 5-fluorouracil were generalised to fluoropyrimidines (SmPC sections 4.5 and 4.8).
IB/0038	To delete "do not freeze" from the product information. B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	28/07/2010	n/a	SmPC, Labelling and PL	
II/0033	Update of the Detailed Description of the Pharmacovigilance system (DDPS) to version 9.0. Consequently, Annex II has been updated with the new version number of the agreed DDPS. The MAH	22/04/2010	02/06/2010	SmPC, Annex II, Labelling and PL	With this variation the MAH submitted a new version of the DDPS (core version 9.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted

	also took the opportunity to update Annex II with version number 12.0 of the Risk Management Plan, which was agreed following the recent conclusion of the assessment of PSUR 8, and to introduce changes in the SmPC, Labelling and PL pending since the linguistic review following the recent renewal (EMEA/H/C/000558/R/30). Update of DDPS (Pharmacovigilance)				DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
II/0029	Extension of Indication	19/11/2009	20/01/2010		Please refer to Assessment Report.
II/0032	Change in the batch size of finished product Quality changes	17/12/2009	08/01/2010		
IA/0034	To change a part of the primary packaging material not in contact with the finished product. IA_28_Change in any part of primary packaging material not in contact with finished product	04/12/2009	n/a		
IA/0031	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	04/08/2009	n/a		
R/0030	Renewal of the marketing authorisation.	23/04/2009	17/06/2009	SmPC, Annex II, Labelling and PL	Since the first marketing approval the product labelling for cetuximab has been updated as necessary to reflect identified new risks. Any additional data significant for the assessment of the benefit/risk profile of cetuximab have been submitted and evaluated. The known risks are adequately described and quantified when necessary in the currently approved product labelling. In summary, the

					efficacy data from all data sources reviewed over the last five years confirms that cetuximab, both in its original 2 mg/ml and in its new formulation 5 mg/ml, has an efficacy profile in the approved indications that is in line with the currently approved product labelling. On the basis of cumulative PSUR data since the first approval of cetuximab it is considered that newly identified risks have been adequately addressed and included in the product labelling. The renewal of the MA of cetuximab is therefore supported by a confirmed positive benefit /risk balance. Based on data provided with this application and other known data the conclusion of the assessment is that there are no major changes in the efficacy or safety of Erbitux/Cetuximab affecting the risk benefit balance of the product in any direction. The SPC and the RMP has been regularly updated since the first approval and no further changes are considered urgently needed, i.e. to be included in this application. The CHMP is of the opinion that the renewal can be granted with unlimited validity. The Marketing Authorisation Holder will continue to submit Periodic Safety Update Reports yearly.
II/0028	Addition of an active substance manufacturer. Change(s) to the manufacturing process for the active substance	23/10/2008	24/11/2008	Annex II	
II/0026	Extension of the indication to include treatment of recurrent and/or metastatic squamous cell cancer of the head and neck (SCCHN) in combination with	23/10/2008	24/11/2008	SmPC and PL	Please refer to Scientific Discussion document H-558-II-26-AR.

	platinum-based chemotherapy. Extension of Indication				
II/0027	Manufacture of the existing 100 ml vial size for Erbitux 5 mg/ml at an existing manufacturing site. Change(s) to the manufacturing process for the active substance	23/10/2008	28/10/2008		
II/0024	Change to the manufacuring process of the active substance for Erbitux 5 mg/ml to implement a specific purification step and so to harmonise the process parameters between the existing active substance manufacturing sites. Change(s) to the manufacturing process for the active substance	24/07/2008	29/07/2008		
II/0020	To update the current indication for the use in patients with KRAS wild type metastatic colorectal cancer in combination with chemotherapy and to add a monotherapy indication in KRAS-wild type patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. The Annex II has been amended to include the latest statement on Risk Management Plan. Editorial amendments have been implemented in the annexes. Furthermore, the package leaflet has been revised following the results of User Testing. Extension of Indication	30/05/2008	17/07/2008	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion document H-558-II-20-AR.

IB/0025	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	27/05/2008	n/a	SmPC	
II/0022	Change(s) to the manufacturing process for the active substance Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	28/02/2008	SmPC and PL	Addition of infusion set materials, namely ethyl vinyl acetate bags and polypropylene perfusor syringes, to be used for administration of Erbitux 5 mg/ml.
II/0021	Change(s) to the manufacturing process for the active substance	21/02/2008	26/02/2008		
IB/0023	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening IB_37_a_Change in the specification of the finished product - tightening of specification limits	15/01/2008	n/a		
II/0019	Change(s) to the manufacturing process for the finished product	18/10/2007	23/10/2007		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/08/2007	n/a	PL	
IA/0016	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	25/06/2007	n/a		
IA/0018	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	14/06/2007	n/a		
IA/0017	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	14/06/2007	n/a		

IA/0015	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	14/06/2007	n/a		
IA/0014	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	14/06/2007	n/a		
IB/0012	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening IB_37_a_Change in the specification of the finished product - tightening of specification limits	26/04/2007	n/a		
II/0010	The MAH has applied to update the information on hypomagnesaemia in the SPC sections 4.4 and 4.8, inclusion of "myocardial infarction, cardiac arrest" in association with infusion related reactions and replacement of the term "stenocardia" with the term "angina pectoris" under SPC section 4.8. Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	27/02/2007	SmPC and PL	
X/0009	The Marketing Authorisation Holder applied for the addition of a new formulation at strength of 5 mg/ml cetuximab. Annex I_2.(c) Change or addition of a new strength/potency	14/12/2006	20/02/2007	SmPC, Labelling and PL	This Line Extension concerns a new formulation containing glycine, citric acid, Tween 80 and sodium chloride presented at a strength of 5mg/ml cetuximab and available in 4 presentations (10, 20, 50 and 100 ml vials). The previously approved formulation contains 2mg/ml of cetuximab in phosphate-buffered saline (PBS), presented in a 50 ml vial. This Line extension application also introduced an additional manufacturer of the finished product as well as changes to the manufacturing process of the active substance.

					Following initial evaluation of this medicinal product it was established that precipitation of cetuximab occurs during storage, yielding visible particles. Also, sub-visible particles were present at levels exceeding the Ph.Eur. limits for parenteralia. However, the product was exempted from this test since it is used with a filter for administration. The new formulation resolves this issue and as a consequence the administration of Erbitux 5 mg/ml does not require use of an in-line filter and this has been adequately reflected in the Summary of Product Characteristics and Package Leaflet. The quality of the product has been demonstrated to be satisfactory. Outstanding issues identified during the evaluation will be addressed and evaluated as part of on-going post-marketing follow-up measures. Comparative pharmacokinetic and toxicology studies did not raise concerns and were satisfactory. Clinical data were not provided which was considered acceptable. All requirements with respect to quality, efficacy and safety for this product have been satisfactorily fulfilled and as a consequence the CHMP issued a positive opinion for Erbitux 5 mg/ml.
II/0005	Treatment in combination with radiation therapy of patients with locally advanced squamous cell cancer of the head and neck. Extension of Indication	23/02/2006	29/03/2006	SmPC and PL	The MAH applies for an extension of the indication in combination with radiation therapy for the treatment of patients with locally advanced squamous cell cancer of the head and neck (SCCHN). Please refer to the Scientific Discussion "Erbitux-H-558-II-05".
II/0008	Change(s) to the manufacturing process for the active substance	26/01/2006	07/02/2006		

II/0007	Change(s) to the manufacturing process for the active substance	14/12/2005	21/12/2005		
II/0006	Change(s) to the manufacturing process for the active substance	14/12/2005	21/12/2005		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	13/09/2005	SmPC and PL	The product information was updated to include that hypomagnesaemia (loss of a mineral called magnesium in the blood) has been reported with Erbitux.
II/0001	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	27/07/2005	03/08/2005		
II/0002	Change(s) to the manufacturing process for the active substance	23/06/2005	06/07/2005		