Xolair

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IA/0087	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/05/2018		Labelling and PL	
T/0085	Transfer of Marketing Authorisation	20/03/2018	26/04/2018	SmPC, Labelling and PL	
IA/0086	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the	24/04/2018	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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	Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
IAIN/0083	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	01/08/2017	n/a		
PSUSA/2214/201612	Periodic Safety Update EU Single assessment - omalizumab	06/07/2017	n/a		PRAC Recommendation - maintenance
IB/0082/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	17/05/2017	n/a		
IA/0081	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	02/05/2017	n/a		
IB/0079	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/03/2017	n/a		

IB/0078	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	05/10/2016	n/a		
PSUSA/2214/201512	Periodic Safety Update EU Single assessment - omalizumab	21/07/2016	09/09/2016		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2214/201512.
IB/0077/G	This was an application for a group of variations. 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	29/04/2016	n/a		
II/0075	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on anaphylaxis. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1 and to include some editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	09/09/2016	SmPC, Annex II and PL	The product information has been updated to include safety information on anaphylaxis. Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%. In addition, a warning has been included on the product information on that a history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.
IB/0072	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/09/2015	n/a		

IB/0071/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.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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	07/09/2015	n/a		
PSUSA/2214/ 201412	Periodic Safety Update EU Single assessment - omalizumab	09/07/2015	n/a		PRAC Recommendation - maintenance
R/0068	Renewal of the marketing authorisation.	23/04/2015	22/06/2015	SmPC, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Xolair continues to be favourable.

IAIN/0070	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/05/2015	n/a		
PSUV/0061	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IA/0067	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/12/2014	n/a		
IB/0066/G	This was an application for a group of variations. B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product A.1 - Administrative change - Change in the name and/or address of the MAH	02/12/2014	22/06/2015	SmPC, Labelling and PL	
IA/0065/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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an	21/11/2014	n/a		

	approved test procedure 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0064	B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	20/10/2014	n/a		
IB/0063/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	16/10/2014	n/a		
IB/0060/G	This was an application for a group of variations. B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or	02/10/2014	n/a		

	Ph. Eur. 2.9.6 B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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				
IB/0062	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	30/09/2014	n/a		
II/0056	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	25/09/2014	n/a		

	at the site is a biol/immunol method				
IB/0058	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	19/09/2014	n/a		
IB/0059	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/09/2014	n/a		
IB/0057/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.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 B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS 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	17/09/2014	n/a		
II/0054	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	22/06/2015	SmPC and PL	

PSUV/0052	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
IB/0055/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	20/06/2014	n/a		
IAIN/0053	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/05/2014	n/a		
II/0048	Extension of indication to include Xolair as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the	23/01/2014	28/02/2014	SmPC, Annex II and PL	Please refer to the scientific discussion XOLAIR EMEA/H/C/000606/II/0048 for further information.

	SmPC. The Package Leaflet is updated in accordance. Section 4.8 of the SmPC was updated to include the QRD statement promoting the reporting of suspected adverse reactions via the national reporting systems. Additionally, editorial changes were made to sections 4.4 of the SmPC, Annex II and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUV/0050	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0046	Update of sections 4.4 and 4.8 to reflect recent data from the EXCELS study and two new meta-analyses on malignancies and arterial thromboembolic events (ATE). Moreover, the information on thrombocytopenia has been updated in section 4.8 of the SmPC as requested by the CHMP following the assessment of PSUR 15. Editorial changes have also been made to the SmPC, Annex II, Labelling and the PL in accordance with the latest QRD template. In addition, the list of local representatives in the PL has been revised to amend the contact details of several representatives. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	28/02/2014	SmPC, Annex II, Labelling and PL	In controlled clinical trials and during interim analyses of an observational study (EXCELS), a numerical imbalance of ATE (including stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death) was observed. In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91 1.91). In a new analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24 5.71). With regards to malignancies, based on the final data from the EXCELS study and the pooled analysis of the controlled

					clinical trials, there is no indication that Xolair treatment is associated with an overall increased risk of malignancies. There are a few imbalances with respect to individual cancer types and the data are too limited to draw any firm conclusions. However, an increased risk of malignancies associated with Xolair cannot be completely excluded taking into account that the study period is of five years. Also, the data in adolescents are still very limited. Therefore, 'malignancies in adults and adolescents ≥12 years of age' is being downgraded from an important identified risk to an important potential risk in the RMP although this will be closely monitored in future PSURs.
IA/0051/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.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	10/10/2013	n/a		
IB/0049	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	30/08/2013	n/a		
IB/0047/G	This was an application for a group of variations.	08/05/2013	n/a		

	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0045	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/12/2012	n/a		
IG/0209/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.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	17/08/2012	n/a		
II/0037	Update of the dosing table in section 4.2 "Posology and method of administration" of the SPC to reduce the dosing frequency in certain clinical situations from every two weeks (q2w) to every four weeks (q4w) and doubling the dose. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical,	19/04/2012	25/05/2012	SmPC	Xolair is usually administered subcutaneously every 2 to 4 weeks. The dosing frequency in certain clinical situations (depending on baseline IgE and body weight) is reduced from every two weeks (q2w) to every four weeks (q4w). This revision applies to the portion of the dosing table currently at doses of 225 and 300 mg q2w, switching to every four weeks and doubling the dose. The revision of the dosing table is supported by modelling

	clinical or pharmacovigilance data				and simulation using pharmacokinetic, pharmacodynamic, and clinical trial data from prior clinical trials in allergic asthma. This mechanism-based mathematical model was used in a previous procedure (EMEA/H/C/000606/II/019) to expand the dosing table to include patients with baseline IgE concentrations of up to 1500 IU/mL and is now used to support the assessment of patient safety and efficacy.
IB/0039	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	15/03/2012	25/05/2012	SmPC and PL	
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.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	22/02/2012	n/a		
IAIN/0040	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	21/02/2012	25/05/2012	Annex II and PL	
IB/0038	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/01/2012	25/05/2012	SmPC and PL	The MAH has amended the language in Section 6.6 of the SmPC and in the 'Information for the Health Care Professional" of the PL regarding the procedures applied to

					force the air bubble out of the syringe immediately before injection.
IB/0036/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 batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/01/2012	n/a		
IA/0033	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	18/10/2011	n/a		
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.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	11/07/2011	n/a		
II/0032	Update of section 5.3 'Preclinical safety data' of the Summary of Product Characteristics (SmPC) to include the dose level used in preclinical studies and achieved	19/05/2011	17/06/2011	SmPC	This change of the SmPC is based on a review of previously available non-clinical studies. Chronic administration of omalizumab at dose levels of up to 250 mg/kg (more than

	exposure margins to the maximum clinical dose, based on toxicity studies in monkeys and chimpanzees. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				14-fold the maximum allowable clinical dose of 17.5 mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.
II/0031	Addition of information regarding bioequivalence of the liquid formulation versus the lyophilized vial formulation in section 5.2 of the SmPC. Also, editorial changes were made to section 6.1 of the SmPC, relevant sections of the Labelling and section 6 of Package Leaflet, and the list of local representatives in the PL was updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	17/06/2011	SmPC, Labelling and PL	The results of the above study A2204 demonstrated that the Xolair lyophilized formulation and the Xolair liquid formulation (final market formulation in pre-filled safety syringes) are bioequivalent in subjects with elevated IgE. This was already the conclusion when the respective line extension was assessed in 2008 (procedure X/14) and now clarified in the SmPC.
II/0030	Amendment of the fertility statement in section 4.6 of the Summary of Product Characteristics (SmPC) based on non-clinical fertility studies in primates. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	17/06/2011	SmPC	Based on a review of the already available non-clinical fertility studies, including mating studies, it was clarified in the SmPC that no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg.. Subcutaneous (SC) administration of omalizumab, at doses of 0, 3, 15 and 75 mg/kg once weekly for 6 weeks was well tolerated and did not elicit reproductive toxicity in male

					cynomolgus monkeys. The same doses and dosing schedule were administered to female monkeys for 13 weeks (three menstrual cycles) before mating, during the mating period (maximum of two menstrual cycles) and during early pregnancy (up to Day 25 of gestation) to evaluate omalizumab effects on female fertility. Omalizumab, at weekly doses up to 75 mg/kg, had no influence on the normal occurrence of menstrual cycles, or on follicular development, ovulation and luteal function as demonstrated by the normal secretion of progesterone and 17?-estradiol throughout each menstrual cycle. Furthermore, continuing treatment did not influence subsequent successful fertilization or implantation.
II/0029	Addition of anti-therapeutic antibodies in section 4.8 of the Summary of Product Characteristics (SmPC), with a cross-reference in section 4.4, based on a systematic review of information on anti-Xolair antibodies, as requested by the CHMP. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	17/06/2011	SmPC	A total of 6,096 patients, representing 18,373 samples have been analyzed for the development of anti-omalizumab antibodies (ATA) in the clinical program or for post-marketing cases. Out of these patients, five ATA (+) cases (One Fab (+), four Fc (+) cases) have been identified, all representing clinical trial patients. The Fab positive case indicates that there might be a possible association between the development of this antibody and a loss of treatment effect. Other than that, there is so far no indication that patients with detectable levels of anti-drug antibodies against omalizumab share a common profile or experience specific adverse events. However, it is not possible to draw any firm conclusions from the very limited data available.
II/0028/G	This was an application for a group of variations. To change the current manufacturing site for Xolair 75 mg powder for solution for injection. To introduce a new quality control site for Xolair 75 mg	17/03/2011	29/03/2011		

	powder for solution for injection. To change the batch size of the manufacture of Xolair 75 mg powder for solution for injection. To change the in-process controls applied during the manufacture of Xolair 75 mg powder for solution for injection. To change the testing monograph for Xolair 75 mg powder for solution for injection. To introduce a minor change in the manufacturing process for Xolair 75 mg and 150 mg powder for solution for injection. To change the immediate packaging for Xolair 75 mg and 150 mg powder for solution for injection. The glass vial is changed from "clear glass vial, type I borosilicate" to "colourless glass vial, hydrolytic glass type I". The rubber stopper is changed from "bromobutyl rubber, latex free" to "chlorobutyl rubber coated with a fluoro resin laminate, latex free". B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				

	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test				
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	21/12/2010	n/a	Annex II	

	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.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/0021	Update of section 4.8 of the SmPC with information on Arterial Thromboembolic Events (ATE). Editorial changes have been made to section 4.4 of the SmPC. Update of Summary of Product Characteristics Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/09/2010	12/11/2010	SmPC and PL	In controlled clinical trials and an ongoing observational study, a numerical imbalance of Arterial Thromboembolic Events was observed in Xolair-treated patients. ATE included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). Although no causal association between Xolair treatment and ATEs can be concluded, the recorded ATEs are interpreted as a safety signal which justifies an inclusion in the SmPC of this information.
R/0027	Renewal of the marketing authorisation.	24/06/2010	06/09/2010	SmPC, Annex II and PL	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 Xolair continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Xolair continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Xolair but requires an additional five-year renewal on the basis of pharmacovigilance grounds. An increased adverse reaction rate for cardiac/cerebrovascular events was observed among

					patients treated with omalizumab compared with placebo treated patients in the unstratified analyses. The possible mechanisms for the higher number of cardiac adverse events in patients treated with omalizumab is still unknown, and the impact on known mechanisms for ischemic/thromboembolic risk, such as effects on blood pressure, atherosclerosis, or blood clotting function as well.
II/0026	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	30/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (8.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed core DDPS.
II/0024	Changes to the manufacturing facility of the drug substance. Change(s) to the manufacturing process for the active substance	18/02/2010	11/03/2010		
II/0025	Changes to analytical procedures for the drug substance and drug product Change(s) to the test method(s) and/or specifications for the active substance	21/01/2010	09/02/2010		
II/0023	Changes in an IPC method of the drug substance manufacturing process. Change to the test procedure and/or specification of a raw material	21/01/2010	09/02/2010		

II/0022	To change the specifications of a raw material. Change to the test procedure and/or specification of a raw material	21/01/2010	09/02/2010		
II/0019	Update of section 4.2 `Posology and method of administration´ of the SPC and section 3 of the PL to amend the current dosing table to include patients with baseline IgE concentrations of up to 1500 IU/mL. Additional information was added under the heading 'Characteristics in patient populations' in section 5.2 of the SPC. Moreover, Annex II was updated to reflect the updated RMP. Finally, the contact number of the Estonian, Slovenian, Latvian and Finnish local representatives was updated and some minor editorial changes were applied to several sections of the SPC and PL. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	25/01/2010	SmPC, Annex II and PL	PKPD information was provided to support clinical efficacy. A graphical analysis of the relationship between free IgE levels and clinical outcome measures (change in symptom score, peak expiratory flow and rescue medication) indicated that free IgE levels need to be markedly suppressed to obtain a sufficient clinical response. The MAH showed that the model, irrespective of body weight, can predict the suppression of free IgE levels reasonably on average for the available data and that there are no strong indications that body weight would have impact on the relationship between free IgE levels and clinical outcome. Data concerning free IgE levels and clinical outcome measures following the administration of omalizumab according to the newly proposed dosing schedule recommendations was provided for all patients with baseline IgE concentrations of up to 1500 IU/mL. Despite the fact that in study 2210 there was a tendency toward somewhat higher free IgE levels in patients with high baseline IgE levels compared with the "typical" patient, suggesting that the relationship between free IgE levels and clinical outcome depends on the baseline IgE levels, there were no concerns from an efficacy point of view as the dose was high enough for efficacy. Therefore, this dosing recommendation was included in the SPC.

					The MAH initially proposed a dose recommendation for a weight span of 150-200 kg in the new dosing table. However, the PKPD model developed was not based on patients with such high body weight. Thus, the request to include patients with body weight > 150 kg in the SPC was not accepted. The MAH committed to specific safety reporting to gather long-term safety data given
II/0020	Extension of shelf-life for the active substance Change(s) to shelf-life or storage conditions	19/11/2009	02/12/2009		
II/0018	To extentthe indication to children (6 to <12 years of age) as add-on therapy to improve allergic asthma control. Minor editorial corrections to Greek and Hungarian versions of the annexes were included. Extension of Indication	25/06/2009	27/07/2009	SmPC, Annex II and PL	Please refer to Scientific Discussion: Xolair-H-C-606-II-18
X/0014	Extension of the product line by addition of a new pharmaceutical form: solution for injection (75 mg and 150 mg strengths). Annex I_2.(d) Change or addition of a new pharmaceutical form	20/11/2008	10/02/2009	SmPC, Labelling and PL	This application is a line extension of the currently approved product Xolair, 75 mg and 150 mg, powder and solvent for solution for injection. The current application concerns the introduction of a new pharmaceutical form, solution for injection, presented in pre-filled syringes and as two strengths, 75 mg and 150 mg. The quality of Xolair solution for injection (75mg and 150mg) is considered to be acceptable. Quality properties of the new formulation are described sufficiently. Physicochemical and biological aspects relevant to the uniform clinical

					performance of the product have been investigated and are controlled in a satisfactory way. As confirmed by comparative stability studies, stability profiles of lyophilised powder and solution for injection are similar. No new degradation products are observed in the solution for injection compared to lyophilised powder. The clinical documentation comprises a pharmacokinetic and pharmacodynamic (PK and PD) study comparing the lyophilisate and the liquid formulations. Bioequivalence was demonstrated between the liquid formulation of Xolair and the lyophilisate formulation of Xolair. In the bioequivalence studies there were no indications of new or unexpected adverse events following single doses of the new Xolair formulation, i.e. solution for injection. The safety profile of the product is not altered by introduction of the new dosage form. On the basis of demonstrated bioequivalence between the new liquid formulation and the marketed lyophilisate formulation, it is expected and therefore considered that the solution for injection and the authorised lyophilisate formulation have the same efficacy and safety.
II/0017	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet To amend the Summary of Product Characteristics (SPC) in order to include "serum sickness" in sections 4.4 and 4.8 of the SPC . The Package Leaflet was also updated to reflect the changes in the SPC. To update the Product Information using the latest QRD	20/11/2008	07/01/2009	SmPC, Annex II, Labelling and PL	Following the assessment of the 10th PSUR of the product the CHMP recommended that "serum sickness" is added to section 4.8 of the SPC with other symptoms like fever and lymphadenopathy. The MAH identified 18 cases in their safety database. They have also reviewed the scientific literature, as a consequence the section 4.4 of the SPC has been amended to provide information on the onset and the treatment of the serum sickness reactions.

	template. To update the Detailed Description of the PhV System (DDPS). Update of DDPS (Pharmacovigilance) Update of Summary of Product Characteristics, Labelling and Package Leaflet				The Package Leaflet has been amended to reflect the changes of the SPC and other changes, as detailed in the scope, have also been introduced in the Product Information.
II/0016	Change in the manufacturing facility of the active substance. Change(s) to the manufacturing process for the active substance	24/07/2008	29/07/2008		
II/0015	Change in the manufacturing facilities of the finished product. Change(s) to the manufacturing process for the finished product	24/07/2008	29/07/2008		
II/0013	Change(s) to the manufacturing process for the active substance	24/04/2008	30/04/2008		
II/0011	Change(s) to the test method(s) and/or specifications for the active substance	24/04/2008	30/04/2008		
II/0012	Change(s) to the manufacturing process for the active substance	21/02/2008	25/02/2008		
II/0010	Change(s) to the test method(s) and/or specifications for the finished product	21/02/2008	25/02/2008		

II/0009	Change(s) to the manufacturing process for the finished product	21/02/2008	25/02/2008		
II/0008	Change(s) to the manufacturing process for the active substance	21/02/2008	25/02/2008		
II/0007	To update section 4.4 and 4.8 of the SPC to include the possibility of local and systemic allergic reactions including anaphylaxis and anaphylactic shock beyond 2 hours and even beyond 24 hours after the injection, systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), worsening pulmonary symptoms, cardiac complications, and/or neuropathy, idiopathic severe thrombocytopenia, arthralgia, myalgia, joint swelling and alopecia further to the CHMP assessment of PSUR 7. The frequency of the adverse reactions remains unknown. The PL has been updated accordingly. Additionally, a paragraph on parasite infections has been added to bring it in line to the SPC. Update of Summary of Product Characteristics	26/04/2007	30/05/2007	SmPC and PL	Following the assessment of PSUR 7, the CHMP requested to update the SPC to include further information on anaphylactic/anaphylactoid and hypersensitivity reactions, joint and muscle disorders, eosinophilia, hypereosinophilic syndromes, Churg-Strauss and related disorders. Section 4.4 and 4.8 have been amended to include the possibility of local and systemic allergic reactions including anaphylaxis and anaphylactic shock beyond 2 hours and even beyond 24 hours after the injection, systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), worsening pulmonary symptoms, cardiac complications, and/or neuropathy, idiopathic severe thrombocytopenia, arthralgia, myalgia, joint swelling and alopecia. The frequency of the adverse reactions remains unknown. Section 4.7 has also been amended to improve clarity. The PL has been updated accordingly. In addition a paragraph on parasite infections has been added to bring it in line to the SPC. Bulgaria and Romania have also been included in section 6 of the PL.
II/0003	Change(s) to the manufacturing process for the finished product Change(s) to the test method(s) and/or specifications for the finished product	27/04/2006	04/05/2006		

II/0002	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	23/03/2006	24/04/2006	Annex II, Labelling and PL	
II/0005	Change(s) to the test method(s) and/or specifications for the finished product	23/03/2006	31/03/2006		
II/0004	Change(s) to the manufacturing process for the active substance	23/03/2006	31/03/2006		
II/0001	Change(s) to the manufacturing process for the active substance	23/03/2006	31/03/2006		
IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	20/02/2006	20/02/2006	SmPC, Labelling and PL	