Kineret

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/0092	Update of section 4.8 of the SmPC in order to add 'Injection site amyloid deposits' to the list of adverse drug reactions (ADRs) with frequency not known, based on a review of the clinical study and post-marketing data to evaluate a possible causal association between anakinra (Kineret) and amyloidosis. The Package Leaflet is updated accordingly.	08/02/2024		SmPC and PL	Safety signals for "Injection site amyloid deposits" and "Amyloidosis (systemic)" were identified, and a possible causal association was investigated. Based on the review of a clinical study and post-marketing data the signal for "Injection site amyloid deposits" was verified. However, at present, the signal for "Amyloidosis (systemic)" is unverified and further routine pharmacovigilance is endorsed.

[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.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Consequently, an update of section 4.8 of the SmPC is warranted. 'Injection site amyloid deposits' was added to the list of adverse drug reactions (ADRs) with frequency 'not known'. The Package Leaflet is updated accordingly. For more information, please refer to the Summary of Product Characteristics.
IB/0091	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	15/12/2023	n/a		
II/0090	Submission of an updated RMP version 6.2 in order to add DRESS as an important potential risk as well as the removal of the additional risk minimization measures for serious infections, following the assessment of procedure PSUSA/00000209/202205. Annex II is updated in accordance. 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	06/07/2023		Annex II	Although available evidence is not sufficient to establish a causal association between DRESS and anakinra, DRESS has been reported in patients treated with IL-1 inhibitors, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS is present and an alternative aetiology cannot be established, anakinra should be discontinued and a different treatment considered. In this variation, DRESS is included as an important potential risk in the RMP. The additional risk minimization measures (educational materials for HCPs and reminder card for patients) for the safety concern of serious infections are removed from the RMP as this safety concern is found to be already sufficiently described in the product information.
PSUSA/209/202205	Periodic Safety Update EU Single assessment - anakinra	26/01/2023	24/03/2023	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/209/202205.

IB/0088	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	18/07/2022	24/03/2023	SmPC and PL	
II/0087	C.I.13: Submission of the final report from study SAVE-MORE, as requested as part of procedure EMEA/H/C/000363/II/086. This is a prospective, double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of the early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 patients over 28 days as measured by the ordinal scale of the 11-point WHO-CPS. Following review of the final CSR, the section 5.1 of the SmPC is updated to revise the percentage of patients receiving dexamethasone during treatment. The MAH also took the opportunity to make some editorial changes in the product information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/06/2022	24/03/2023	SmPC	Please refer to Scientific Discussion: Kineret EMEA/H/C/000363/II/0087
II/0086	C.I.6 - Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥ 6 ng/ml	16/12/2021	17/12/2021	SmPC and PL	Please refer to Scientific Discussion 'Kineret-H-C-000363-II-0086'

	for Kineret; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 5.9. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0080/G	This was an application for a group of variations. Update of section 4.4 of the SmPC in order to include new safety information about Macrophage activation syndrome (MAS) in the 'serious infections' subsection and to update the 'pulmonary events' subsections with new safety information. Update of section 4.8 of the SmPC to amend the summary of safety profile, the 'serious infections', the 'neutropenia', 'allergic reactions', 'immunogenicity', 'paediatric population' and the 'injection site reactions' subsections with new safety information. Update of section 5.1 of the SmPC to update the clinical efficacy and safety information in Still's disease. The updates proposed are based on the results from study Sobi.ANAKIN-301 (evaluated in procedure no. EMA/H/C/000363/P46/031) and Sobi.ANAKIN-302	02/09/2021	17/12/2021	SmPC	The safety updates of SmPC sections 4.4, 4.8 and 5.4 are based on the results from study Sobi.ANAKIN-301 (evaluated in procedure no. EMA/H/C/000363/P46/031) and Sobi.ANAKIN-302 (evaluated in procedure no. EMEA/H/C/000363/II/0073) which are published on EMA website.

	(evaluated in procedure no. EMEA/H/C/000363/II/0073). Sobi.ANAKIN-301 was a randomised, double-blind, placebo-controlled, multicenter, phase 3 study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]). Sobi.ANAKIN-302 was a non-interventional, post-authorisation safety study to evaluate long-term safety of anakinra in patients with SJIA. In addition, the MAH took the opportunity to correct in SmPC section 4.8 the MedDRA System Organ Class (SOC) for the adverse reaction 'Injection Site Reaction' and changed the SOC from 'Skin and subcutaneous tissue disorder' to 'General disorders and administration site conditions'; and to align the product information with QRD template 10.2 rev.1. Further, minor editorial corrections were introduced in the SmPC. Those changes are accepted by CHMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0085	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/08/2021	17/12/2021	SmPC and PL	To update section 4.4 of the SmPC with information on drug reaction with eosinophilia and systemic symptoms

					(DRESS).
II/0083	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	08/07/2021	n/a		
II/0084	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/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	17/06/2021	n/a		
II/0078	Submission of the final report from study (Sobi-ANAKIN-201) listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study to evaluate the safety of Kineret in the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including reuse of syringe. The RMP version 5.4 has been updated to reflect completion of this study. In addition, the RMP is updated to include information about a completed paediatric study (Sobi.ANAKIN-301) assessed as per Article 46 of Reg No 1901/2006 (EMEA/H/C/000363/P46/031). This was a randomised, double-blind, placebo-controlled,	10/06/2021	n/a		Please refer to Scientific Discussion Kineret EMEA/H/C/000363/II/0078.

	multicenter, phase 3 study which evaluated the efficacy, the safety, pharmacokinetics and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0082	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/05/2021	n/a		
IB/0081	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	16/03/2021	n/a		
IB/0079/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	28/01/2021	n/a		

IB/0077	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	02/12/2020	n/a		
IB/0076/G	This was an application for a group of variations. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised 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	24/11/2020	n/a		

IB/0075	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/07/2020	n/a		
IB/0074	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	29/05/2020	n/a		
II/0073	Submission of the final report from study (Sobi.ANAKIN-302) listed as a category 3 study in the RMP and in accordance with Article 46 of Regulation (EC) No 1901/2006. This is a non-interventional, post-authorisation safety study to evaluate long-term safety of anakinra (Kineret) in patients with systemic juvenile idiopathic arthritis. The RMP version 5.3 has also been updated to reflect the completion of the study. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/05/2020	n/a		Please refer to Scientific Discussion Kineret-H-C-000363-II-73.
II/0070	Extension of indication to include the treatment of Familial Mediterranean Fever (FMF) for Kineret, to be given in combination with colchicine, if appropriate; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 5.2 has also been updated. Furthermore, the PI is brought in line with the latest	26/03/2020	28/04/2020	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Kineret EMEA/H/C/000363/II/0070

	QRD template version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0072	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/04/2020	n/a		
PSUSA/209/201905	Periodic Safety Update EU Single assessment - anakinra	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0071	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	19/11/2019	n/a		
IA/0069	A.7 - Administrative change - Deletion of manufacturing sites	11/11/2019	n/a		
IB/0067/G	This was an application for a group of variations. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised 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.2.b - Change in test procedure for the finished	06/05/2019	n/a		

	product - Deletion of a test procedure if an alternative method is already authorised 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.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0064/G	This was an application for a group of variations. Update of section 4.4 of the SmPC in order to add a warning on pulmonary events based on post-marketing data. The package leaflet is updated accordingly. Consequently, the important potential risks and the list of target medical events in the RMP (version 4.7) are updated to include pulmonary events and a specific follow-up questionnaire is created. The RMP is also revised in line with the GVP Module V RMP template (revision 2). In addition, the due date for submission of the final study report for the category 3 post-authorisation study (Sobi ANAKIN-302) in patients with Still's disease is extended until 31 December 2019. Furthermore, the MAH took the opportunity to move the text about macrophage activation syndrome (MAS) and malignancies from section 4.8 to 4.4 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	14/03/2019	09/03/2020	SmPC and PL	During post-marketing use events of interstitial lung disease, pulmonary alveolar proteinosis and pulmonary hypertension have been reported mainly in paediatric patients with Still's disease treated with IL-6 and IL-1 inhibitors, including Kineret. Patients with trisomy 21 seem to be overrepresented. A causal relationship with Kineret has not been established. Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis) are added as an important potential risk in the risk management plan (version 4.7). Annex 4 of the RMP has been supplemented with a detailed questionnaire for pulmonary events including requests on event onset, patient history, Kineret treatment, Kineret batch number, concomitnat disease(s), concomitant medications, event description, investigations, laboratory data, and blood test history. Since a causal relationship between macrophage activation syndrome (MAS) and Kineret has not been established, the already approved information on MAS has been moved from section 4.8 to section 4.4 of the SmPC.

	data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IB/0066	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	04/03/2019	n/a		
IB/0065	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	27/02/2019	n/a		
IB/0062	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	19/12/2018	n/a		
IB/0063	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	12/12/2018	n/a		
IA/0061	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	11/10/2018	n/a		
II/0060	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	20/09/2018	n/a		
II/0056	Extension of indication to include a new indication for	22/02/2018	06/04/2018	SmPC, Annex	Please refer to the scientific discussion Kineret

	Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.4) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template version 10. In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the SmPC and Package leaflet. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			II, Labelling and PL	EMEA/H/C/000363/II/0056.
II/0058	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	07/12/2017	06/04/2018	Annex II	
IA/0059	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	19/10/2017	06/04/2018	SmPC, Labelling and PL	
IA/0057	A.7 - Administrative change - Deletion of manufacturing sites	21/09/2017	n/a		

IB/0055	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	29/03/2017	n/a		
IB/0053/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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	18/01/2017	n/a		
IB/0054/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.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	14/12/2016	n/a		

	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				
PSUSA/209/201605	Periodic Safety Update EU Single assessment - anakinra	01/12/2016	n/a		PRAC Recommendation - maintenance
II/0051/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to add increased blood cholesterol, with a very common frequency as new ADR as a result of review of post-marketing data and re-evaluation of clinical study 03 AR-0298. Section 4.8 of the SmPC is also updated to add thrombocytopenia as new ADR, with a common frequency, as result of recommendation received from PRAC on signal SDA026. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2016	02/06/2016	SmPC and PL	
II/0050/G	This was an application for a group of variations. 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/control, and secondary packaging, for	04/06/2015	02/06/2016	SmPC and PL	

	biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products				
IB/0049	To align the annexes following the approval of the line extension and extension of indication previously approved. In addition, minor corrections are made to the labelling of the graduated syringe. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/05/2014	27/06/2014	SmPC, Labelling and PL	

IAIN/0048	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	08/04/2014	n/a		
IB/0047/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.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	10/01/2014	n/a		
X/0042	Extension of the Marketing Authorisation to add a new strength (100 mg/0.67 ml) presented in a graduated single-use pre-filled syringe to allow a new dose regimen required for a new indication CAPS (Cryopyrin-Associated Periodic Syndromes) patients. Annex I_2.(c) Change or addition of a new strength/potency	19/09/2013	15/11/2013	SmPC, Annex II, Labelling and PL	Please refer to the assessment report Kineret-H-000363-X-0042-AR.
IB/0045	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	13/09/2013	n/a		

IA/0046	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	04/07/2013	n/a		
II/0044/G	This was an application for a group of variations. This was an application for a group of variations: change in test procedures and change the acceptance criteria for an approved method. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	21/02/2013	n/a		
II/0043/G	This was an application for a group of variations. This was an application for a group of variations to change the manufacturer of a starting material and change in test procedure for a starting material. 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.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				
IB/0041/G	This was an application for a group of variations. 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 for a biological/immunological medicinal product A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	11/01/2013	15/11/2013	Annex II	
IB/0040	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/11/2012	n/a		
IB/0039	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	08/11/2012	n/a		

	or addition) for the AS or a starting material/intermediate				
II/0037	Introduction of a post approval change management protocol related to the active substance. B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	20/09/2012	n/a		
II/0036/G	This was an application for a group of variations. 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.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.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	20/09/2012	n/a		
IB/0035/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	18/07/2012	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0038	C.I.7.z - Deletion of formulation	22/06/2012	25/10/2012	SmPC, Labelling and PL	Deletion of the presentation vials: Kineret 100 mg solution for injection in a vial, EU/1/02/203/004. Further updates concern the implementation of the latest QRD template.
II/0033/G	This was an application for a group of variations. 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.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability 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	24/05/2012	n/a		

	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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 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				
IG/0162	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	30/03/2012	n/a		
N/0032	Inclusion of Braille on all presentations of Kineret. The MAH also took the opportunity to make minor linguistic changes in annex IIIA of the Greek, Estonian, Lithuanian, Maltese, Slovak and Swedish Product Information annexes. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/11/2011	25/10/2012	Labelling	

II/0029	Update of section 4.4 of the SmPC to amend the warning on allergic reactions to specify that anaphylactic reactions and angioedema have been reported as allergic reactions associated with administration of anakinra. Section 4.8 is updated to add the events of rash and allergic reactions including anaphylactic reactions, angioedema, urticaria and pruritus. The MAH also took the opportunity to make a correction in the user intructions section of the of the package leaflet and to amend the product information to bring it in line with the QRD template (v.7.3.1). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC and PL	Safety analyses for allergic reactions concomitant with the use of anakinra were performed covering from 14 November 2001 to 25 February 2008 and from 26 February 2008 to 13 May 2010. The analyses included all spontaneous, literature, registry, health-authority reports, and reports from clinical trials that were received by the MAH. The first analysis presents a total of 252 events (41 from clinical trial, 18 from registries studies and 193 from spontaneous reporting) of allergic reactions associated with anakinra exposure from 186 cases (37 from clinical trials [21 serious], 13 from registries studies [11 serious] and 136 [37 serious] from spontaneous reporting). The second analysis presents 31 events of allergic reactions associated with anakinra exposure from 20 medically confirmed case reports. Ten of these reports contained in total 15 serious adverse events. No case reports had a fatal outcome. Based on the data presented from the post-marketing registry study and spontaneous reports the following events are considered possible adverse drug reactions following anakinra administration: rash, urticaria, pruritus, angioedema and anaphylactic reaction. From the clinical trials data, there is supportive evidence of association with hypersensitivity reactions including urticaria, rash and pruritus. Therefore the existing warning on allergic reactions in Section 4.4 is amended to specify that these reactions can include anaphylactic reactions and angioedema. In section 4.8 allergic reactions (including anaphylactic reactions, angioedema, urticaria and pruritus) are reported with a frequency of uncommon (?/1,000 to <1/100). Rash is reported with the same frequency.

IA/0031/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.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	02/02/2011	n/a	Annex II	
IA/0030/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the	04/11/2010	n/a	SmPC, Annex II, Labelling and PL	

	back-up procedure of the QPPV				
IB/0028	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	26/01/2010	n/a	SmPC	
IA/0027	Change in the adress of a manufacturer of the finished product. IA_05_Change in the name and/or address of a manufacturer of the finished product	09/11/2009	n/a		
IA/0026	IA_09_Deletion of manufacturing site	07/10/2009	n/a		
IA/0025	IA_09_Deletion of manufacturing site	07/10/2009	n/a		
IA/0024	IA_09_Deletion of manufacturing site	07/10/2009	n/a		
IA/0023	IA_09_Deletion of manufacturing site	07/10/2009	n/a		
II/0020	Changes to QPPV Update of DDPS (Pharmacovigilance)	29/05/2009	30/06/2009	Annex II	The MAH has provided its Detailed Description of the Pharmacovigilance System describing the pharmacovigilance system to be utilized by Biovitrum AB (publ). Consequently Annex II has been updated with standard text to reflect the latest versions of the DDPS (version 1.0) agreed with the CHMP.
IA/0022	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	10/06/2009	n/a	Annex II and Labelling	
IA/0021	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	14/04/2009	n/a		

T/0019	Transfer of Marketing Authorisation	04/11/2008	20/11/2008	SmPC, Labelling and PL	Transfer of the Marketing Authorisation from Amgen Europe B.V. to Biovitrum AB (publ).
II/0018	Change(s) to the manufacturing process for the active substance	24/04/2008	29/04/2008		
II/0017	Change(s) to the test method(s) and/or specifications for the finished product	21/02/2008	26/02/2008	SmPC and PL	Amendment to specifications and product information in order to reflect the presence of protein particles.
II/0016	To update section 4.8 of the SPC to include the incidence of neutralising antibodies observed in clinical studies in paediatric patients, further to the CHMP request dated 16 November 2006. Additionally, the MAH proposed to amend the contact details for some local representatives (Belgium, Luxemburg and Latvia) in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	24/04/2007	SmPC and PL	Following the assessment of two clinical studies with Kineret in paediatric subjects with polyarticular-course juvenile rheumatoid arthritis, it emerged that the forming of neutralising antibodies was more common in children (6%) than in adults (3%). Therefore, the CHMP concluded that section 4.8 "Undesirable effects" of the SPC should be updated to include the incidence of neutralising antibodies observed in clinical studies in paediatric patients.
II/0015	Change(s) to the manufacturing process for the finished product	22/03/2007	27/03/2007		
R/0014	Renewal of the marketing authorisation.	24/01/2007	20/03/2007		The CHMP was of the opinion that the quality, safety and efficacy of Kineret continued to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of this medicinal product remained favourable. Therefore, the renewal of its marketing authorisation was granted with unlimited validity.
II/0013	To update section 4.8, and 5.1 of the SPC by	28/06/2006	28/07/2006	SmPC, Annex	During the assessment of PSUR n. 6 (covering the period

	including the incidence of anti-anakinra antibodies in clinical studies and that the incidence of these antibodies has no implications on safety and efficacy of the product following the CHMP assessment of PSUR No. 6. To include in sections 4.4 and 6.5 of the SPC a warning that the vial stopper and/or the needle cover of the prefilled syringe contains a derivative of latex that may cause allergic reactions. Section 2 of the PL has been updated accordingly. To update section 6 "Further information" of the PL in order to clarify information on how to inject the product following feedback from patients. To update the Annexes in line with the EMEA QRD template version 7.0. Update of Summary of Product Characteristics, Labelling and Package Leaflet			II, Labelling and PL	from 14 May 2004 to 13 November 2004), the MAH was requested to highlight and justify any differences between the European SPC and the Core Data Sheet (CDS). One substantive divergence was pointed out that concerned the occurrence of antibodies which are "common" in clinical trials and for which a statement was given in section 4.8 of the CDS but was not to be introduced into the SPC. The MAH informed that whilst antibodies to Kineret had been detected in clinical study subjects, the presence of antibodies had not been associated either with the occurrence of adverse effects or with reduced efficacy. The MAH explained that pharmacovigilance surveillance had not detected either any unexpected reductions in efficacy over long-term treatment, or any anaphylactoid or other adverse reactions for which a causal link to the development of antibodies had been suspected. The CHMP concluded that, even tough not an intentional finding, the formation of antibodies has been observed as "common" in clinical trials (across the studies whereby anti-anakinra antibodies were assessed, neutralising antibodies were observed in approximately 2% of all subjects receiving anakinra for up to 3 years of duration), and therefore, in accordance with the SPC guideline, all adverse reactions should be included in the SPC if they are at least possibly causally related, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual reports. Thus the CHMP concluded that the physician should be made aware of the findings and that sections 4.8 "Undesirable effects" and 5.1 "Pharmacodynamic

					properties" of the SPC should be updated to include the incidence of anti-anakinra antibodies in clinical studies and that the incidence of these antibodies has no implications on safety and efficacy of the product.
IA/0012	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	16/11/2005	n/a	Annex II	
II/0011	Change(s) to shelf-life or storage conditions	13/10/2005	19/10/2005		
II/0010	This variation relates to an update of section 4.4 of the SPC concerning the incidence of serious infections in patients with asthma treated with Kineret, the use of Kineret in patients with pre-existing malignancy and the vaccination of patients being treated with Kineret. This variation relates to an update of section 4.5 of the SPC with regard to the concurrent use of Kineret and TNF antagonists. This variation relates to an update of section 4.8 of the SPC on serious infections and malignancies as requested by the CHMP following the assessment of PSUR No. 5 for Kineret. Update of Summary of Product Characteristics	23/06/2005	27/07/2005	SmPC	The SPC was updated to include that for a small number of patients with asthma, the incidence of serious infection was higher in Kineret-treated patients (4.5%) vs. placebo-treated patients (0%). In a placebo-controlled clinical trial, no difference was detected in anti-tetanus antibody response between Kineret and placebo treatment groups when a tetanus/diphtheria toxoid vaccine was administered concurrently with Kineret. No data are available on the effects of vaccination with other inactivated antigens in patients receiving Kineret. No data are available on either the effects of live vaccination or on the secondary transmission of infection by live vaccines in patients receiving Kineret. Therefore, live vaccines should not be given concurrently with Kineret. This new information is added in the SPC. The MAH proposed to include in the SPC that the concurrent use of Kineret with etanercept or any other TNF antagonist is not recommended. Following the assessment of PSUR No. 5 for Kineret, covering the period from 14 November 2003 to 13 May

					2004, the CHMP requested the Marketing Authorisation Holder (MAH) to update section 4.8 "Undesirable effects" of the SPC on serious infections and on malignancies. In observations up to 3 years, the serious infection rate remained stable over time and in clinical studies and post-marketing experience, rare cases of opportunistic infections have been observed and included fungal, mycobacterial, bacterial, and viral pathogens. Infections have been noted in all organ systems and have been reported in patients receiving Kineret alone or in combination with immunosuppressive agents. Also rheumatoid arthritis (RA) patients may be at a higher risk (on average 2-3 fold) for the development of lymphoma. In clinical trials, whilst patients treated with Kineret had a higher incidence of lymphoma than the expected rate in the general population, this rate is consistent with rates reported in general for RA patients. Furtherm
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/12/2004	n/a	PL	
II/0008	Change(s) to the test method(s) and/or specifications for the finished product Change(s) to shelf-life or storage conditions	20/11/2003	24/11/2003		
II/0007	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or	22/05/2003	26/05/2003		

	specifications for the finished product Quality changes				
II/0006	Update of Summary of Product Characteristics	23/01/2003	23/04/2003	SmPC	
II/0003	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 Change(s) to container	23/01/2003	24/01/2003		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/10/2002	23/10/2002	PL	
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	07/06/2002	11/07/2002	SmPC	
I/0002	20a_Extension of shelf-life or retest period of the active substance	08/07/2002	10/07/2002		