RoActemra

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
IB/0083	B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	11/04/2019	n/a		
II/0082	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	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).

PSUSA/2980/201804	Periodic Safety Update EU Single assessment - tocilizumab	15/11/2018	15/01/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2980/201804.
II/0076	Extension of Indication for RoActemra 162 mg solution for injection in pre-filled syringe formulation to include the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, weighting at least 10kg, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to methotrexate or where treatment with methotrexate is inappropriate) or in combination with methotrexate. This new indication is supported by the data from study WA28118, a Phase Ib, Open-Label, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, and Safety of Tocilizumab Following Subcutaneous Administration to Patients sJIA. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are being updated accordingly. In addition, sections 4.2, 4.8 and 5.2 of the SmPC of the RoActemra 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal IV study WA18221 in sJIA. The MAH has also made the following amendments in the RoActemra 20 mg/mL concentrate for solution for infusion formulation: • Update of sections 4.8 and 5.2 to align the information on pJIA for RoActemra SC and IV (variation EMEA/H/C/955/II/72).	20/09/2018	29/10/2018	SmPC, Labelling and PL	Please refer to the scientific discussion RoActemra EMEA/H/C/000955/II/76.

	• Update of the PL to implement the changes related to the new indication for the treatment of CAR T cell-induced severe or life-threatening CRS (variation EMEA/H/C/955/II/78). Changes made to the SmPC, Labelling and Package Leaflet for RoActemra 20 mg/mL concentrate for solution for infusion formulation, RoActemra 162 mg solution for injection in pre-filled syringe formulation, RoActemra 162 mg solution for injection in pre-filled pen to bring them in line with the current QRD template and SmPC guideline were reviewed and accepted by the CHMP. Finally, the MAH has updated the RMP to implement changes related to the new indication for the treatment of CAR T cell-induced severe or life-threatening CRS (variation EMEA/H/C/955/II/78). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0078	Extension of indication to include 'treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older' for the RoActemra 20mg/ml concentrate for solution for infusion. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/06/2018	23/08/2018	SmPC and PL	See Scientific Discussion.

N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	29/10/2018	PL	
IB/0080/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.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	08/08/2018	n/a		
IA/0077/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.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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/05/2018	n/a		
II/0072	Extension of Indication to include “the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis)	22/02/2018	12/04/2018	SmPC, Labelling and	

	in patients 2 years of age and older, who have responded inadequately to previous therapy with methotrexate" for RoActemra; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			PL	
T/0075	Transfer of Marketing Authorisation	20/02/2018	06/04/2018	SmPC, Labelling and PL	
II/0074/G	This was an application for a group of variations. Please refer to the Recommendations section above B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	22/02/2018	12/04/2018	SmPC, Labelling and PL	The product information was updated to include information on the newly introduced single-use auto-injector pen for RoActemra, intended for the treatment of adult rheumatoid arthritis and giant cell arthritis, using the already approved 162 mg/0.9 mL solution for injection pre-filled syringe with a new hypodermic needle.
PSUSA/2980/ 201704	Periodic Safety Update EU Single assessment - tocilizumab	26/10/2017	n/a		PRAC Recommendation - maintenance
IB/0073	B.II.d.2.d - Change in test procedure for the finished	28/09/2017	n/a		

	product - Other changes to a test procedure (including replacement or addition)				
II/0066	Extension of indication to include treatment of giant cell arteritis in adult patients for the subcutaneous formulation of RoActemra based on the Phase III study WA28119 (GiACTA). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect information relevant to this indication. The Package Leaflet is updated in accordance. The Marketing Authorisation Holder took the opportunity to make administrative changes to Sections 4.6 and 5.3 of the SmPC. The Package Leaflet is updated in accordance. Furthermore, the updated RMP version 21.0 has been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/07/2017	18/09/2017	SmPC, Annex II and PL	Please refer to the scientific discussion RoActemra EMEA/H/C/000955/II/0066.
IB/0070	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/05/2017	18/09/2017	SmPC	
PSUSA/2980/ 201610	Periodic Safety Update EU Single assessment - tocilizumab	05/05/2017	n/a		PRAC Recommendation - maintenance
IB/0069	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	01/03/2017	18/09/2017	SmPC	
II/0067/G	This was an application for a group of variations.	23/02/2017	n/a		

	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
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.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	08/12/2016	n/a		
PSUSA/2980/ 201604	Periodic Safety Update EU Single assessment - tocilizumab	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0057	Extension of Indication to include the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) for the RoActemra subcutaneous formulation; as a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation	23/06/2016	29/07/2016	SmPC and PL	Refer to the Scientific Discussion Zontivity- H-C-2814-II-05

	holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the MAH took the opportunity to update the contact details of the local representative in Germany in the Package Leaflet. Further, the updated RMP version 18.1 has been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0061	Submission of the final clinical study report for study WA29049, as requested in MEA 030.6 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/07/2016	n/a		
IB/0063	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	27/06/2016	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2016	29/07/2016	Annex II	
PSUSA/2980/ 201510	Periodic Safety Update EU Single assessment - tocilizumab	13/05/2016	n/a		PRAC Recommendation - maintenance
IG/0668/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a	22/03/2016	n/a		

	manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/2980/ 201504	Periodic Safety Update EU Single assessment - tocilizumab	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0056	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	16/10/2015	n/a		
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/07/2015	29/07/2016	PL	
IG/0573	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	01/07/2015	n/a		
IB/0051	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	22/05/2015	n/a		
II/0050	Submission of the final Clinical Study Report for Study WA18221 'Tender' in order to address the post-authorisation measure MEA 036. An update RMP version 16.4 was provided as part of the application. The application proposes no changes to the product information	21/05/2015	n/a		N/A

	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/0049	Submission of the final CSR of study WA 22762 (SUMMACTA) to fulfil MEA 044; as a consequence of the analyses of the final study results a revised RMP (version 16.6) has been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/05/2015	n/a		
IA/0052	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	19/05/2015	n/a		
PSUSA/2980/ 201410	Periodic Safety Update EU Single assessment - tocilizumab	07/05/2015	n/a		PRAC Recommendation - maintenance
IB/0048/G	This was an application for a group of variations. 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 -	30/03/2015	n/a		

	Replacement/addition of a site where batch control/testing takes place				
II/0038	Update of section 5.2 of the SmPC to further characterize the PK profile of tocilizumab following IV and SC administration, based on newly available IV data generated as part of the development of the SC formulation of tocilizumab. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	17/07/2015	SmPC	
II/0046	Submission of the revised RMP version 16.5 with information from the final CSR of study WA19926 (FUNCTION) 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	26/02/2015	n/a		
II/0044	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier	18/12/2014	n/a		
II/0043	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	20/11/2014	n/a		

	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				
IG/0497	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	18/11/2014	n/a		
PSUV/0041	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IB/0042	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/09/2014	n/a		
II/0032	Extension of Indication to include treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and the Package Leaflet are updated. In addition, minor editorial changes are implemented in the SmPC, Annex II and PL. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/07/2014	01/09/2014	SmPC, Annex II and PL	Please refer to the assessment report RoActemra-H-C-955-II-32.
IB/0040	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	30/07/2014	17/07/2015	SmPC, Labelling and PL	

II/0039	Update of section 4.8 of the SmPC to add Stevens-Johnson Syndrome (SJS). Section 4 of the PL is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	01/09/2014	SmPC and PL	Two cases of non-fatal reports of Stevens-Johnson Syndrome (SJS) were identified during routine RoActemra pharmacovigilance, one of which was medically confirmed. The event rate in tocilizumab-treated patients did not exceed the event rate those in patients exposed to other biological therapies for autoimmune conditions. SJS is a rare but severe hypersensitivity reaction. Based on the strength of the evidence in the medically confirmed SJS case, rarity, severity and drug association of the condition, and to ensure patient safety, information on SJS cases has been added to section 4.8 of the RoActemra SmPC.
PSUV/0036	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
X/0030	Extension of the Marketing Authorisation to register a new route of administration "subcutaneous use", a new pharmaceutical form "solution for injection", a new strength "162 mg" and a new presentation "pre-filled syringe". Annex I_2.(e) Change or addition of a new route of administration	20/02/2014	23/04/2014	SmPC, Annex II, Labelling and PL	Please refer to the assessment report RoActemra-H-C-955-X-30-AR.
IB/0037	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	09/04/2014	n/a		
II/0035	Update of section 4.4 of the SmPC in order to reflect the outcome of study NA25256, a phase IV study evaluating the humoral immune response after	23/01/2014	01/09/2014	SmPC and PL	Study NA25256 evaluated the immune response and the safety of a pneumococcal and anti-tetanus toxoid vaccine in adult patients with moderate to severe RA treated with MTX

	pneumonal and tetanic vaccination in patients treated with tocilizumab. In addition the MAH has taken the opportunity to correct typographical errors throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				only and in combination with TCZ. Adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only.
IB/0033	B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation	08/11/2013	n/a		
R/0031	Renewal of the marketing authorisation.	25/07/2013	25/09/2013	SmPC, Annex II 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 RoActemra continues to be favourable. The CHMP was of the opinion that the renewal could be granted with unlimited validity.
II/0026	Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to extend the indication of tocilizumab to the treatment in combination with methotrexate (MTX) of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Sections 1, 2, 3, 4 and 6 of the Package Leaflet are updated accordingly. In addition, the MAH took the opportunity to include minor editorial changes throughout the PI.	25/04/2013	30/05/2013	SmPC, Annex II and PL	Please refer to the Scientific Discussion RoActemra/H/C/00955/II/26 for further information.

	The requested variation proposed amendments to the Summary of Product Characteristics, 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				
II/0028	Update of section 5.1 of the SmPC in order to include results of a Phase IV, two-arm, randomized, parallel-group, double blind study investigating the reduction of signs and symptoms during monotherapy treatment with tocilizumab 8 mg/kg intravenously versus adalimumab 40 mg subcutaneously in patients with rheumatoid arthritis. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 8 (revision 2) and to update the Package Leaflet based on the results of consulation with target patient groups. 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	30/05/2013	SmPC, Annex II, Labelling and PL	This type II variation is aimed to amend section 5.1 Pharmacodynamic properties of the SmPC to include the results of study WA19924, a Phase IV multicentre, randomised, double-blind, parallel-group study investigating the reduction of signs and symptoms during monotherapy treatment with tocilizumab (TCZ) 8 mg/kg intravenously versus adalimumab (ADA) 40 mg subcutaneously in patients with RA who were intolerant to methotrexate (MTX) or where continued treatment with MTX was inappropriate. Study WA19924 met its primary endpoint and demonstrated a statistically significant superior effect on control of disease activity from baseline to Week 24 with TCZ monotherapy compared with ADA monotherapy. The safety data of study WA19924 were consistent with the label of TCZ. The CHMP concluded that these new data do not change the benefit risk profile of TCZ in the treatment of RA.
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
II/0027	Update of section 4.4 of the SmPC in order to add a warning regarding the risk of false negative screening tests for tuberculosis in line with a request from the CHMP made following the assessment of a PSUR. The	18/10/2012	22/11/2012	SmPC and PL	Review of literature data did not provide evidence of a direct link between the use of tocilizumab and changes in the sensitivity and specificity of tests for tuberculosis (TB) infection. However, false negative screening tests for TB

	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				(including interferon-gamma TB blood test) under tocilizumab exposition have been reported and a causal relationship cannot be excluded. Information about the risk of false negative tests for tuberculosis has been therefore added to the product information.
IB/0025	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	02/08/2012	n/a		
IB/0024	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	29/06/2012	n/a		
IB/0023	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	28/06/2012	22/11/2012	SmPC	Deletion of text in SmPC section 4.8 relating to neutropenia and risk of infections as requested by CHMP following the assessment of FUM.
II/0022	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding the risk of infection related to Interstitial Lung Disease, as requested by the CHMP in the outcome of the most recent PSUR assessment. In addition, the MAH took the opportunity to update the list of local	19/04/2012	25/05/2012	SmPC and PL	Interstitial Lung Disease (ILD) has been recognised as a risk factor for serious infections and poor outcomes, including death. Based on comparison of the data reported for RoActemra and the data available in the literature, the CHMP concluded that at this time there is no clear evidence that the risk of death is specific to therapy with tocilizumab, as

	representatives in the Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				compared with other biologics and immunosuppressive agents. The SmPC has been updated with information on the ILD as an important risk factor for infections, and that postmarketing cases of ILD have been reported for tocilizumab.
IG/0161	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	14/03/2012	n/a		
IG/0125	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	06/12/2011	n/a		
IG/0092/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.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	08/08/2011	n/a		
II/0015	Extension of the indication for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and	19/05/2011	01/08/2011	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion "RoActemra/H/C/000955/II/15" for further information.

	systemic corticosteroids. Consequentially, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. Annex II, IIIA and the package leaflet have been updated accordingly. Annex II has also been updated to delete the DDPS version number and reflect the last version of the RMP. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0013	Update of sections 4.2, 4.4 and 4.8 of the SmPC with information regarding serious infections, monitoring of liver function tests including bilirubin, the frequency of "Total bilirubin increased" and "Hypercholesterolaemia" as well as neutropenia and the use in patients with lower absolute neutrophil count. The PL has been amended accordingly. The Alert card has also been amended to include text on reactivation of infections, including hepatitis B. This variation application is submitted further to the request of the CHMP following assessment of PSUR 2. Annex II is also updated to reflect the version number of the revised RMP. 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	17/02/2011	18/03/2011	SmPC, Annex II, Labelling and PL	The MAH agreed to implement the changes requested by the CHMP further to the assessment of the RoActemra PSUR#2 regarding monitoring of liver function tests, changes to the frequency of "Total bilirubin increased" and "Hypercholesterolaemia". Based on the fact that baseline pre-treatment neutrophil counts are the strongest predictor of subsequent neutropenia with tocilizumab treatment, the MAH agreed to update the SmPC to state that initiation of treatment is not recommended in patients with absolute neutrophil count below 2 x 109/l. The MAH also updated the SmPC to mention that serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra.

II/0016/G	This was an application for a group of variations. Changes in the manufacture of the finished product 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.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product	20/01/2011	31/01/2011		
II/0014	Update of sections 4.4 and 4.8 of the SPC following a post-marketing report of a patient who experienced a fatal anaphylactic reaction with her 5th infusion of RoActemra. The PL is updated accordingly. Annex II is also updated to reflect the version number of the revised RMP submitted with this application. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC, Annex II and PL	The MAH proposes to amend section 4.4 of the SmPC to warn prescribers that if an anaphylactic or other serious hypersensitivity/serious infusion related reaction occurs, administration of tocilizumab should be stopped immediately and RoActemra should be permanently discontinued. Section 4.8 has been amended to reflect that the fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab. The recommended changes to the SmPC are intended to clarify patient management in cases of anaphylaxis and serious hypersensitivity reactions. The frequency of hypersensitivity reactions has been amended in the PL, to reflect the adverse drug reaction table in the SmPC.
II/0007	Extension of the indication to include a statement that RoActemra reduces the progression of joint damage and improves physical function when given in combination with methotrexate. Changes have been included to sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 of	22/04/2010	04/06/2010	SmPC, Annex II and PL	Please refer to the Scientific Discussion "RoActemra/H/C/000955/II/007" for further information.

	the SmPC. The package leaflet has been updated accordingly. Moreover, Annex II has been updated to reflect the latest agreed RMP version number. Minor corrections have also been made to section 10 of the SmPC. Extension of Indication				
II/0010	Roche - Update of the detailed description of the pharmacovigilance system (version 4.1). Annex II has been updated accordingly. In addition, Annex II has been updated in line with the latest QRD templates. Update of DDPS (Pharmacovigilance)	18/03/2010	27/04/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 4.1) 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/0009	Update of section 4.6 of the summary of product characteristics to modify the duration of contraception required for female patients from 6 months to 3 months after the last dose of tocilizumab treatment. The package leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	30/03/2010	SmPC and PL	The t½ life of tocilizumab is approximately 13 days. Therefore, follow up for 65 days should be sufficient, and 90 days adequate, and allows for inter- patient variability. The MAH has shown that markers for tocilizumab mechanism of action (soluble interleukin 6 receptor and C-Reactive Protein [CRP]) returned to baseline after a period of 5 t½ lives. Therefore the modification of the duration of contraception required for patients from 6 to 3 months after the last dose of tocilizumab is endorsed by the CHMP.
II/0008	Update of section 4.4 of the summary of product characteristics to include information regarding the association between severe neutropenia and serious infections further to the request of the CHMP in conjunction with the assessment of PSUR 1 covering the period 11 October 2008 to 10 April 2009.	18/02/2010	30/03/2010	SmPC	Further to the assessment of the RoActemra PSUR No. 1 - Period covered: 11 October 2008 - 10 April 2009, the CHMP requested the MAH to update the SmPC to mention that treatment related neutropenia can increase the risk of serious infections. Although no clear association between severe neutropenia and serious infections has been seen to date in clinical trials with RoActemra, the MAH agreed to

	Update of Summary of Product Characteristics				update section 4.4 of the SmPC as recommended by the CHMP.
II/0012	Change to the manufacture of the drug product Change(s) to the manufacturing process for the finished product	18/03/2010	29/03/2010		
II/0011	Changes to the storage of the drug substance and drug product Change(s) to the manufacturing process for the active substance	18/03/2010	23/03/2010		
II/0005	Update of section 4.8 of the summary of product characteristics regarding gastrointestinal perforations based on a review of safety data. Annex II has been updated with the new version number (version 5.0) of the adopted RMP. Update of Summary of Product Characteristics and Labelling	22/10/2009	20/11/2009	SmPC and Annex II	As of 31st December 2008, 40 cases of gastrointestinal perforation have been reported with tocilizumab (33 confirmed cases, 4 suspected cases, plus 3 iatrogenic/trauma cases). Thirty-two perforations were located in the lower GI tract and at least 56% of these were associated with diverticular disease. Most cases had confounding factors such as NSAID/corticosteroid use, past medical history of diverticulitis, inflammatory bowel disease and/or peptic ulcer disease. However, there have been a few reports of gastrointestinal perforation that were not associated with diverticular disease. Epidemiological data indicate that the incidence of GI perforations with tocilizumab does not appear to be significantly higher than expected in the RA population. The SPC has been updated to include additional information on gastrointestinal perforation.
II/0006	Change to the control of the drug substance	22/10/2009	12/11/2009		

	Change(s) to the test method(s) and/or specifications for the active substance				
II/0004	Update of section 4.5 of the Summary of Product Characteristics (SPC) regarding pharmacokinetics of simvastatin and methotrexate in combination with tocilizumab. Additionally, a correction has been made to remove the requirement for monitoring of medicinal products metabolized via CYP2C19. Update of Summary of Product Characteristics	24/09/2009	28/10/2009	SmPC	This variation application was submitted in order to update the SPC to reflect the results of a drug interaction study designed to investigate the pharmacokinetics of simvastatin (a substrate for CYP3A4) and methotrexate (MTX) in combination with tocilizumab (TCZ) in rheumatoid arthritis (RA) patients. This study demonstrated that administration of TCZ in RA patients significantly reduced the exposure of simvastatin to levels close to those found in non-RA patients and this effect persisted for 5 weeks after TCZ administration. In addition, TCZ administration had no effect on MTX exposures. Additionally, a correction has been made to remove the requirement for monitoring of medicinal products metabolized via CYP2C19 based on a drug interaction study with omeprazole (a CYP2C19 substrate) which demonstrated that the effect of tocilizumab on omeprazole is not clinically meaningful.
II/0003	Update of sections 4.2 and 4.4 of the Summary of Product Characteristics (SPC) regarding dose recommendations if liver function test abnormalities are observed. Following the linguistic review process during January 2009, corrections have been made to the Bulgarian, Czech Republic, Danish and Dutch Annexes and to the contact details of the Latvian representative. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	28/10/2009	SmPC and PL	Following an internal review of the current SPC, the MAH identified the need for improvement regarding the recommendations on dose modification for liver function test. The SPC has been revised in order to ensure that consistent advice is given on how to handle alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations of > 1 to 3 x upper limit of normal (ULN), regardless of whether levels had decreased from > 3 to 5 x ULN or not. The CHMP concluded that the recommendations for the clinical management of liver enzyme elevations remain essentially unchanged and are accepted. However it

					should be emphasised that the patients should be carefully monitored while being treated with the reduced dose of RoActemra or after restarting the full dose treatment or the treatment after interruption. There is no information available at the time being that the proposed dose amendment is safe for the patients with impaired liver function especially during long term treatment.
II/0002	Changes to the manufacturing process and control of the drug substance Change(s) to the manufacturing process for the active substance	24/09/2009	29/09/2009		
IB/0001	IB_17_b_Change in the storage conditions for the active substance	01/04/2009	n/a		