Lucentis

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IAIN/0104/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release -	05/10/2023		Annex II and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/2609/ 202210	Periodic Safety Update EU Single assessment - ranibizumab	12/05/2023	n/a		PRAC Recommendation - maintenance
IB/0103	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/03/2023	n/a		
II/0101	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update information on preterm infants based on final results from study CRFB002H2301E (RAINBOW extension), listed as a PAES in the Annex II; this is an extension study to evaluate the long term efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity. The Annex II and Package Leaflet are updated accordingly. The RMP version 22.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to	09/02/2023		SmPC, Annex II and PL	Please refer to Scientific Discussion Lucentis EMEA/H/C/000715/II/0101.

	new quality, preclinical, clinical or pharmacovigilance data				
IA/0100/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol 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.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	22/11/2022	n/a		

	material/intermediate/reagent - Tightening of specification 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0098	Update of section 4.6 of the SmPC in order to update information on breastfeeding following the PRAC Recommendation (EMEA/H/C/PSUSA/00002609/202010) based on a cumulative assessment of pre-clinical studies, pharmacokinetic data, published literature and post-marketing spontaneous reports. The Package Leaflet is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the	15/09/2022	09/11/2022	SmPC and PL	SmPC new text SmPC Section 4.6 It is unknown whether Lucentis is excreted in human milk. Based on very limited data, ranibizumab may be excreted in human milk at low levels. The effect of ranibizumab on a breast-fed infant is unknown. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis. PIL Pregnancy and breast-feeding /…./

	assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				Small amounts of Lucentis may pass into breast milk, therefore Lucentis is not recommended during breast-feeding because it is not known whether Lucentis passes into human milk. Ask your doctor or pharmacist for advice before Lucentis treatment. The benefit-risk balance of Lucentis remains positive. For more information, please refer to the Summary of Product Characteristics.
IA/0099	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/04/2022	n/a		
IB/0097	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	01/02/2022	n/a		
IB/0096/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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished	01/02/2022	n/a		

	product - Deletion of a non-significant in-process test 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 B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished 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.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.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				
IB/0095/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - 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	29/11/2021	09/11/2022	SmPC, Annex II, Labelling and PL	
IB/0093/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	01/06/2021	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IAIN/0094/G	This was an application for a group of variations. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	07/05/2021	n/a		
PSUSA/2609/ 202010	Periodic Safety Update EU Single assessment - ranibizumab	06/05/2021	n/a		PRAC Recommendation - maintenance
IB/0092	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/04/2021	n/a		
II/0090/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.I.e.2 - Introduction of a post approval change management protocol related to the AS	21/01/2021	n/a		
IB/0089	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/10/2020	n/a		

II/0088	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	15/10/2020	n/a		
IA/0087	A.7 - Administrative change - Deletion of manufacturing sites	05/08/2020	09/12/2020	Annex II	
II/0086	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	23/07/2020	09/12/2020	SmPC, Annex II, Labelling and PL	
II/0085	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/07/2020	n/a		
PSUSA/2609/ 201910	Periodic Safety Update EU Single assessment - ranibizumab	14/05/2020	n/a		PRAC Recommendation - maintenance
IA/0083	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	12/12/2019	09/12/2020	SmPC, Labelling and PL	
II/0076	Extension of Indication to include treatment of proliferative diabetic retinopathy (PDR) in adults for	19/09/2019	21/10/2019	SmPC and PL	Please refer to the Scientific Discussion in the AR for

	Lucentis; as a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated with the safety information. The Package Leaflet is updated in accordance. RMP version 19.0 is also being submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				/II/0076.
IB/0081/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.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	18/10/2019	n/a		
IA/0082/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 approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	17/10/2019	n/a		

	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				
II/0074/G	This was an application for a group of variations. Extension of Indication to include: A new indication for Lucentis vial presentation: treatment of retinopathy of prematurity (ROP) in preterm infants; as a consequence, sections 2, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, RMP version 18.0 is also submitted. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2019	03/09/2019	SmPC, Labelling and PL	
II/0075/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	28/03/2019	12/06/2019	Annex II and PL	

	product and any of the test methods at the site is a biol/immunol method B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter 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) 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.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation				

IB/0080/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	28/02/2019	n/a		
IA/0079	B.I.d.1.b.1 - Stability of AS - Change in the storage conditions - Change to more restrictive storage conditions of the AS	29/01/2019	n/a		
IA/0078/G	This was an application for a group of variations. 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification 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	16/01/2019	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0077	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	18/12/2018	n/a		
IB/0073/G	This was an application for a group of variations. B.IV.z - Quality change - Change in Medical Devices - Other variation B.IV.z - Quality change - Change in Medical Devices - Other variation	24/10/2018	n/a		
II/0069	Update of section 5.1 of the SmPC in order to include information on the diabetic retinopathy severity score (DRSS) in diabetic macular edema patients (DME) based on pooled data from studies RFB002D2301 (RESTORE), RFB002D2303 (REVEAL) and RFB002D2305 (REFINE). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/07/2018	12/06/2019	SmPC	
II/0070/G	This was an application for a group of variations. 1. Type II- C.I.13: Submission of the final report from study LUMINOUS study (CRFB002A2406), an observational, multicentre study to assess the long term safety and effectiveness of ranibizumab in	12/07/2018	12/06/2019	Annex II	

	routine clinical practice, in fulfilment of the post-authorisation measures MEA 036, MEA 048 and MEA 054. Consequentially, the RMP has been updated to reflect these changes. 2. Type II-C.I.11: Submission of an updated RMP version 17.2 (RMP template Rev. 2) according to GVP Module V to include changes not consequential to LUMINOUS study. In addition, the MAH is proposing the removal of the physician educational material and the targeted follow-up checklists. Furthermore, the patient education material has been reviewed to reflect the safety identified risks 'intraocular inflammation', 'retinal detachment and retinal tear' and 'infectious endophthalmitis'. The additional risk minimisation measures section in Annex II has been updated accordingly. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
T/0072	Transfer of Marketing Authorisation	20/03/2018	26/04/2018	SmPC, Labelling and PL	

IB/0071/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.a.2.z - Changes in the manufacturing process 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.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.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	12/04/2018	n/a		
IB/0068/G	This was an application for a group of variations.	30/10/2017	n/a		

	B.II.z - Quality change - Finished product - Other variation B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
IA/0067/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.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	25/08/2017	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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 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 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				
IAIN/0066	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	01/08/2017	n/a		
PSUSA/2609/201610	Periodic Safety Update EU Single assessment - ranibizumab	05/05/2017	n/a		PRAC Recommendation - maintenance

IB/0063	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/02/2017	n/a		
IB/0065	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	05/01/2017	n/a		
II/0061	Extension of Indication to include treatment of visual impairment due to choroidal neovascularization (CNV) based on data from the pivotal study CRFB002G2301 (MINERVA). Consequential changes have been implemented in SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and the Package Leaflet has been updated accordingly. An updated RMP version 16.2 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	13/10/2016	14/11/2016	SmPC and PL	For further information, please refer to the scientific discussion "Lucentis-H-C-715-II-61".
R/0062	Renewal of the marketing authorisation.	15/09/2016	11/11/2016	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Lucentis in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/2609/ 201510	Periodic Safety Update EU Single assessment - ranibizumab	14/04/2016	n/a		PRAC Recommendation - maintenance

II/0059	Update of sections 4.4 and 5.1 of the SmPC in order to reflect information from the long-term clinical studies E2401 and E2402 in Retinal Vein Occlusion (RVO) patients. This addresses post-authorisation measure MEA 055. An updated RMP version 15 is also proposed to reflect the completion of the studies. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	08/09/2016	SmPC	The long-term (24 months) clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO were assessed in the BRIGHTER (BRVO) and CRYSTAL (CRVO) studies. In both studies, subjects received a 0.5 mg ranibizumab PRN dosing regimen driven by individualised stabilisation criteria. BRIGHTER was a 3-arm randomised active-controlled study that compared 0.5 mg ranibizumab given as monotherapy or in combination with adjunctive laser photocoagulation to laser photocoagulation alone. After 6 months, subjects in the laser arm could receive 0.5 mg ranibizumab. CRYSTAL was a single-arm study with 0.5 mg ranibizumab monotherapy. In BRIGHTER, ranibizumab 0.5 mg with adjunctive laser therapy demonstrated non-inferiority versus ranibizumab monotherapy from baseline to Month 24. In both studies, a rapid and statistically significant decrease from baseline in central retinal subfield thickness was observed at Month 1. This effect was maintained up to Month 24. The effect of ranibizumab treatment was similar irrespective of the presence of retinal ischaemia. The effect in terms of visual improvement was observed in all patients treated with 0.5 mg ranibizumab monotherapy regardless of their disease duration in both BRIGHTER and CRYSTAL. Treatment initiation at the time of diagnosis should be considered. There are insufficient data to conclude on the effect of Lucentis in patients with RVO presenting irreversible ischaemic visual function loss. The long term safety profile of ranibizumab observed in the 24 month studies is consistent with the known Lucentis safety profile. For more information, please refer to the Summary of

					Product Characteristics.
IA/0058	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	09/12/2015	n/a		
II/0055	Update of section 5.1 of the SmPC, upon request by the CHMP following the assessment of variation II-47, in order to shorten the overall clinical trial section and to implement minor editorial changes for increased clarity. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	08/09/2016	SmPC	N/A
IA/0057/G	This was an application for a group of variations. A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS A.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS	17/08/2015	n/a		
IB/0056	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/04/2015	n/a		
PSUV/0049	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance

IAIN/0054	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/12/2014	n/a		
IAIN/0052	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	12/12/2014	20/07/2015	SmPC, Labelling and PL	
IAIN/0053	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	11/12/2014	n/a		
IB/0051/G	This was an application for a group of variations. To extend shelf life and correct manufacturing address. 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 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	28/11/2014	20/07/2015	SmPC	
IAIN/0050	A.1 - Administrative change - Change in the name and/or address of the MAH	29/09/2014	20/07/2015	SmPC, Labelling and PL	

II/0047	Update of section 4.2 of the SmPC in order to harmonise the administration instructions for Lucentis across indications in line with the available clinical evidence, relevant guidelines and treatment recommendations as well as clinical practice. The proposed posology recommendations for diabetic macular oedema are further supported by the final report of the RETAIN study. In addition, SmPC sections 4.5 and 5.1 were proposed to be updated to reflect RETAIN study data including data on the concomitant treatment with thiazolidinediones. The information in SmPC section 5.1 on the RESTORE study was also proposed to be updated with data from the 2-year extension phase. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	04/09/2014	SmPC and PL	In this variation the company updated the information on dosing of Lucentis in all the indications based on the analysis of all available clinical data. Furthermore, information related to interaction with a group of antidiabetic medication called thiazolidinediones has been added to the product information.
IB/0048	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	20/08/2014	20/07/2015	SmPC and PL	
II/0044	Update of section 4.4 of the SmPC in order to revise the warning on bilateral use of Lucentis. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	04/09/2014	SmPC	In this variation the company has updated the product information section on warnings to include more information pertinent to the administration of Lucentis to both eyes.
II/0043	Update of section 4.2 of the SmPC in order to	23/01/2014	04/09/2014	SmPC, Annex	A review of the risk of serious eye infections

	remove the recommendation to use topical antibiotics before and after intravitreal injection of Lucentis and to advice on the use of local microbicides for disinfection in accordance with local practice. Consequential changes to Annex II and the RMP were introduced to remove the related information from the educational material. In addition, SmPC sections 5.1 and 6.6 were amended to reflect that the mechanism of action applies to all approved indications, to harmonise information on availability of clinical data and to include more specific disposal instructions for the vial kit and vial only presentations of the product. The Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			II and PL	(endophthalmitis) following injection of Lucentis or other anti-VEGF inhibitors in the eye with and without prophylactic use of antibiotic eye drops was performed based on post-marketing data including data from the scientific literature. Results from studies comprising collectively almost 30,000 injections showed no beneficial effect of the use of antibiotic eye drops immediately before and/or after intravitreal injection. However, frequent and periodic use of antibiotic eye drops has been demonstrated to cause antimicrobial resistance. Therefore, the CHMP agreed to no longer recommend prophylactic antibiotics with injections of Lucentis but rather to advise to follow local clinical practice. Other minor changes to the SmPC and changes to the educational materials (physicians' information) were also agreed.
PSUV/0042	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IA/0046/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	16/12/2013	n/a		

	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 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				
IA/0045/G	This was an application for a group of variations. 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification 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.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	13/12/2013	n/a		
II/0040/G	This was an application for a group of variations.	24/10/2013	04/09/2014	SmPC, Annex II, Labelling	

	To add a pre-filled syringe presentation for Lucentis 10 mg/mL. 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.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.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.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.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.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.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			and PL	

	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 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.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale				
IAIN/0041	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	09/09/2013	04/09/2014	SmPC, Labelling and PL	
II/0034	Extension of Indication to include treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia for Lucentis.	30/05/2013	04/07/2013	SmPC, Annex II, Labelling and PL	Please refer to scientific discussion H-C-715-II-34-AR-variation.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0039	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	01/03/2013	04/07/2013	Annex II and PL	
IB/0038	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	01/03/2013	n/a		
IA/0037	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	08/02/2013	n/a		
II/0031	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information to add a revised class warning in relation to the theoretical risk of systemic adverse events following intravitreal injection of VEGF inhibitors and to include stroke and myocardial infarction to the product-class-related adverse reactions as an example of arterial thromboembolic events. In addition, the conditions for the safe and effective use of Lucentis in Annex II were updated to reflect the three main safety concerns, endophthalmitis, traumatic cataract and transient increase in intraocular pressure, in the educational material. Furthermore, the PI was	17/01/2013	04/07/2013	SmPC and Annex II	Based on a request by the CHMP following the 8th Periodic Safety Update Report (PSUR 8), cumulative data from clinical trials as well as from the post-marketing setting and the scientific literature were reviewed to assess the risk of cardiac and non-cardiac arterial thromboembolic events under treatment with ranibizumab. There was limited evidence for a causal relationship between these events and the use of ranibizumab. However, as a causal relationship could not be excluded, the section in the product information informing about product-class-related adverse reactions was updated to add stroke and myocardial infartion as examples for the potential risk of arterial thromboembolic events. In addition, based on a

	brought in line with the latest QRD template version 8.2. 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				class labelling agreed for intravitreal anti-VEGF treatments, a revised warning was included to inform health care providers that systemic adverse events in general and also including non-ocular haemorrhages have been observed after intravitreal injection of VEGF inhibitors.
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	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		
IB/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/07/2012	29/10/2012	SmPC, Labelling and PL	Update of annex I (SmPC) and annex III (Labelling and Package Leaflet) in order to adapt the declaration of the medical devices included in the Lucentis kit to the current QRD template, the Medical Device Directive 93/42/EEC and industry norms, such as ISO 7864 and ISO 7886. The medical devices in the Lucentis kit remain unchanged and there is no update in Module 3. Furthermore, additional minor amendments were added in

					section 4.2 (in order to ensure language specific consistency in the medical device wording), concerning the translations in the following countries: DE, ES, ET, FR, IS, LT and PL.
II/0029	Additional site for the manufacture and control of the active substance 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	24/05/2012	27/06/2012	Annex II	
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		
IA/0028	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	09/01/2012	n/a		

R/0024	Renewal of the marketing authorisation.	20/10/2011	14/12/2011	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Lucentis remains positive, but considers that its safety profile is to be closely monitored for the following reasons: - The recently approved new indications, treatment of visual impairment due to DME and macular oedema secondary to RVO, imply that the population receiving Lucentis treatment will be broader and may include patients at potentially higher risk of cardiovascular systemic adverse events; - There are at present ongoing safety issues concerning systemic adverse events such as the EPITT signal hypertensive crisis; - The data quality issues related to Ranibizumab Reimbursement Scheme and Patient Support Program adverse event reporting introduce uncertainty to the assessment of post-marketing safety data.
II/0023	Changes to the dosing recommendations in wet Age-related Macular Degeneration (AMD). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	02/09/2011	SmPC and PL	With this variation the posology for Lucentis in wet AMD was revised. The originally approved posology in wet AMD, based on three initial monthly injections and re-treatment in case of a 5-letter loss of VA, was not optimal. Analyses of the currently available monotherapy data from completed AMD studies (MARINA, ANCHOR, PIER, EXCITE, SUSTAIN, MONT BLANC, DENALI) were carried out. This was the basis for an update of the SPC and Package Leaflet with an alternative posology for the ranibizumab treatment of patients with wet AMD following a concept of an individualised PRN treatment which is driven by monitoring of the stability.

					The SPC was brought in line with the recommendations for DME and RVO-indications, based on a 'stability concept' (i.e. monthly injections administered until no further improvement is observed and re-treatment initiated when there is a loss of Visual Acuity due to disease activity). The new section 4.2 of the SPC (posology) for wet AMD reads: "In wet AMD, the recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. Treatment is given monthly and continued until maximum visual acuity is achieved i.e. the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month." This variation also affected section 3 of the PL.
IA/0025	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	26/07/2011	n/a		
IG/0088/G	This was an application for a group of variations.	11/07/2011	n/a		

	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/0022	Extension of indications to include treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/03/2011	27/05/2011	SmPC, Annex II and PL	The revised CHMP variation assessment report will be published as part of the EPAR, following review/deletion of confidential information.
II/0020	Update of the SPC (sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3) to include information on treatment of visual impairment due to diabetic macular oedema (DME). Sections 1, 2, 3 and 4 of the Package Leaflet have been updated accordingly. In addition, Annex IIB was updated. The MAH also took the opportunity to update the contact details of the local representatives in Estonia, Slovenia, Finland, Cyprus and Latvia. Extension of Indication	21/10/2010	06/01/2011	SmPC, Annex II and PL	Please refer to the Scientific Discussion Lucentis-H-715-II-20-AR.

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 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	21/12/2010	n/a		
IB/0021	Update of the section 4.4 of the SmPC following the assessment of the PSUR 6 and RMP 5 to include information on increased risk of retinal pigment	20/08/2010	n/a	SmPC and Annex II	With this variation the MAH proposes to amend SmPC section 4.4, following the assessment of the PSUR 6 and RMP 5, to include information on risk factors associated

	epithelial detachment after the intravitreal injection of anti-VEGF. 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				with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD including a large and/or high pigment epithelial retinal detachment. In addition, two administrative changes were proposed i.e. inclusion of an explanation of VEGF (vascular endothelial growth factor) in section 4.4 of the SPC and an update of the version identifier for the current RMP (version 5) in Annex II.
II/0019	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 (core version 8.0 and product specific version 7.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
II/0018	Changes to batch release testing of the drug product Change(s) to the test method(s) and/or specifications for the finished product	17/12/2009	04/01/2010		
IA/0017	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/09/2009	n/a		
IB/0016	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	14/08/2009	n/a		
II/0014	Update of the Detailed Description of the Pharmacovigilance system (DDPS) in Module 1.8.1 of the Lucentis Marketing Authorisation to version 6 dated 30 March 2009, in accordance with the current Pharmacovigilance guideline. Consequently, Annex II	25/06/2009	06/08/2009	Annex II	With this variation the MAH submitted an updated DDPS (version 6.0). After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. The CHMP accepted an update of Annex II to include an updated wording of the section "other

	has been updated with the new version number of the agreed DDPS. Update of DDPS (Pharmacovigilance)				conditions" to include the version numbers of the latest submitted DDPS and Risk Management Plan.
IB/0015	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	01/07/2009	n/a		
II/0013	Change to the control of the drug substance. Change(s) to the test method(s) and/or specifications for the active substance	29/05/2009	08/06/2009		
II/0012	Change to ranibizumab reference material specifications. Change in the drug product facility. Change(s) to the test method(s) and/or specifications for the finished product	22/01/2009	27/01/2009		
II/0011	Changes to the storage conditions of the Master Cell Bank and Working Cell Bank. Minor changes to the manufacture and control of the drug substance. Change(s) to the manufacturing process for the active substance	22/01/2009	27/01/2009		
II/0009	Update of section 5.1 of the Summary of Product Characteristics to include 9-month safety data from	23/10/2008	24/11/2008	SmPC and Annex II	The review of the final results of the clinical study PROTECT with the same day administration of ranibizumab 0.5 mg

	the PROTECT study following CHMP conclusions for FUM 006. Additionally, the Detailed Description of the Pharmacovigilance System (DDPS) in Module 1.8.1 of the Lucentis Marketing Authorisation has been updated to version 5.0 (dated June 25, 2008), in accordance with the current pharmacovigilance guideline. Update of Summary of Product Characteristics				and verteporfin/PDT showed that although the safety data are from a limited number of subjects (32), the combination treatment did not give rise to any new concerns regarding the frequency, or the adverse event profile. Therefore, as recommended by the CHMP, section 5.1 of the SPC was revised to include the final 9-month safety data from the study. The text included reads as follows: "Data from an open label study (PROTECT) in 32 patients followed for 9 months in which the safety of same-day administration of verteporfin PDT and Lucentis 0.5mg was evaluated showed that the incidence of intraocular inflammation following the initial treatment was 6.3% (2 of 32 patients)".
IB/0010	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	19/11/2008	n/a	SmPC	
II/0006	Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	27/10/2008	SmPC and PL	In broader terms the changes to the product information were as follows: Section 4.8 of the SPC The following terms were added based on the data provided: Retinal haemorrhage, blindness, eye haemorrhage, eyelid irritation, uveitis, iritis, iridocyclitis, vitritis, hypopyon, tetinal pigment epithelial tear, detachment of the retinal pigment epithelium, allergic conjunctivitis, corneal deposits, eye discharge, eyelid pain, hyphaema, iris adhesion, photopsia, anxiety, allergic reactions (urticaria, pruritus, erythema and rash) and hypersensitivity. The following terms were removed supported by the data provided: Nuclear cataract, angle closure glaucoma, dellen,

					maculopathy, retinal exudates, subretinal fibrosis, hypertension, atrial fibrillation, bronchitis, lichenoid keratosis and wheezing In addition the paragraph on arterial thromboembolic events (ATEs) was updated based on the 2-year results in the pooled data and a paragraph was included with the observations of an increase of extra-ocular haemorrhage in ranibizumab-treated subjects. Section 4.9 of the SPC: A description of the most common AEs (intraocular pressure increased, eye pain, transient blindness and corneal oedema) following an overdose were included. Section 5.1 of the SPC: Inclusion of 2-year data from the ANCHOR and PIER studies and from an analysis of non-responders in MARINA and ANCHOR studies including addition of information that continued treatment may be beneficial also for patients that experience a loss of ? 15 letters and information that early initiation of treatment may be associated with a better preservation of vision. Section 5.2 of the SPC: The vitreous and apparent serum half-life was corrected to 9-days. Based on the changes to the SPC the Package Leaflet was subsequently updated.
II/0008	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of DDPS (Pharmacovigilance)	24/07/2008	02/09/2008	Annex II	With this variation the MAH submitted an updated DDPS (version 4.0). After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. The CHMP accepted an update of Annex II to include an updated wording of the section "other

					conditions" to include the version numbers of the current DDPS and Risk Management Plan.
II/0007	Change(s) to the test method(s) and/or specifications for the active substance	30/05/2008	05/06/2008		
IB/0005	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	04/02/2008	n/a	SmPC	
II/0004	Change(s) to the manufacturing process for the finished product	15/11/2007	19/12/2007	SmPC, Annex II, Labelling and PL	
IA/0003	IA_06_a_Change in ATC code: Medicinal products for human use	15/06/2007	n/a	SmPC	
II/0001	Quality changes	26/04/2007	07/05/2007		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	27/04/2007	n/a	SmPC	