Eylea

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
PSUSA/10020 /201811	Periodic Safety Update EU Single assessment - aflibercept (ophthalmological indication(s))	14/06/2019	n/a		PRAC Recommendation - maintenance
II/0052	Update of section 5.1 of the SmPC in order to reflect the final results from ALTAIR (SN17668) study; Overall, the long term results at week 96 are consistent with the outcomes at week 52 and suggest a maintenance of the benefice over the time.	29/05/2019		SmPC	

[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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0050	Submission of the final report from Study 16995, PLANET. This is a category 4 international randomized, double-masked, sham-controlled phase 4 study to evaluate the efficacy and safety of intravitreal aflibercept (IVT-AFL) monotherapy compared with IVTAFL with rescue PDT (photodynamic therapy) in patients with Polypoidal Choroidal Vasculopathy (PCV), subtype of neovascular age-related macular degeneration (wAMD). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/01/2019	n/a		
IB/0049/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.3.z - 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 assessment done under A 45/46 - Other variation	13/11/2018		Annex II	
IB/0047	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/09/2018	n/a		

II/0045	Update of sections 4.2 and 5.1 of the SmPC in order to add information for the Health Care Professional related to earlier treatment extension and related increments intervals based on final results from phase 4 study ALTAIR. The Package Leaflet is updated accordingly. The RMP version 24.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/06/2018	30/07/2018	SmPC and PL	Earlier treat-and-extend regimens in the first year of treatment with one injection per month for three consecutive doses and one injection 2 months later is agreed and reflected in section 4.2 of the SmPC. Supported evidence came from extrapolated data from the ALTAIR study (conducted in Japanese subjects) to the Caucasian population and associated these results to an Ethnic Sensitivity Report. The ALTAIR study was an interventional study evaluating the efficacy and safety of repeated doses of intravitreal (IVT) aflibercept with variable treatment intervals in Japanese subjects with neovascular AMD. The Ethnic Sensitivity Report concluded that IVT aflibercept is ethnically insensitive for Asians and Caucasians. Section 5.1 of the SmPC reflects the results at week 52of the ALTAIR study.
II/0046	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	26/07/2018	n/a		
IA/0048	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	20/07/2018	n/a		
PSUSA/10020 /201711	Periodic Safety Update EU Single assessment - aflibercept (ophthalmological indication(s))	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0043/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	20/04/2018	n/a		

	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.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.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.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.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				
II/0041/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.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.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	19/04/2018	n/a		

II/0040/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	19/04/2018	n/a		
II/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/04/2018	n/a		
IB/0042/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.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	28/03/2018	n/a		
IB/0037	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	28/09/2017	n/a		
IB/0038	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/09/2017	30/07/2018	Annex II	

R/0033	Renewal of the marketing authorisation.	18/05/2017	13/07/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Eylea in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10020 /201611	Periodic Safety Update EU Single assessment - aflibercept (ophthalmological indication(s))	09/06/2017	n/a		PRAC Recommendation - maintenance
T/0036	Transfer of Marketing Authorisation	30/03/2017	12/04/2017	SmPC, Labelling and PL	
IAIN/0035/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/03/2017	12/04/2017	Annex II and PL	
IB/0032	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	24/01/2017	n/a		

II/0028	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	10/11/2016	n/a		
IA/0031	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	25/10/2016	n/a		
PSUSA/10020 /201511	Periodic Safety Update EU Single assessment - aflibercept (ophthalmological indication(s))	23/06/2016	16/08/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10020/201511.
II/0027/G	This was an application for a group of variations. Update of section 5.1 of the Summary of Product Characteristics (SmPC) to provide data on an independent comparative trial (Protocol T). The Marketing Authorization Holder (MAH) took the opportunity to condense Anti-Platelet Trialists' collaboration (APTC) text in section 4.8 of the SmPC as recommended during procedure II-18; to shorten section 5.1 of the SmPC as recommended during procedure II-21, and to implement minor changes within wet age related macular degeneration (AMD) and Diabetic Macular Oedema (DME) in section 4.2 of the SmPC. Update of section 5.1 of the SmPC to provide 3-year data of the pivotal trials VIVID-DME and VISTA-DME as recommended during procedure II-09. Furthermore, the PI is brought in line with the QRD template version 9.1 A revised RMP version 23.1 was agreed during this procedure.	26/05/2016	30/06/2016	SmPC, Annex II and PL	DRCR.net Protocol T An independent comparative trial (DRCR.net Protocol T) utilised a dosing regimen based on strict OCT and vision re-treatment criteria. In the aflibercept treatment group (n = 224) at week 52, this treatment regimen resulted in patients receiving a mean of 9.2 injections, which is similar to the administered number of doses in the Eylea 2Q8 group in VIVID DME and VISTA DME, while overall efficacy of the aflibercept treatment group in Protocol T was comparable to the Eylea 2Q8 group in VIVID DME and VISTA DME. A 13.3 mean letter gain with 42% of patients gaining at least 15 letters in vision from baseline was observed in Protocol T. Ocular and systemic safety profiles (including ATEs) were similar to VIVID DME and VISTA DME. Diabetic macular oedema The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with DME (VIVID DME and VISTA DME). A total of 862 patients were treated and evaluable for efficacy, 576 with Eylea. Patient ages ranged from 23 to 87 years with a mean of 63 years. In the DME studies, approximately 47%

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				(268/576) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older. The majority of patients in both studies had Type II diabetes. In both studies, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) Eylea administered 2 mg every 8 weeks following 5 initial monthly injections (Eylea 2Q8); 2) Eylea administered 2 mg every 4 weeks (Eylea 2Q4); and 3) macular laser photocoagulation (active control). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the Eylea groups could receive laser and patients in the control group could receive Eylea. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 and both Eylea 2Q8 and Eylea 2Q4 groups demonstrated statistical significance and were superior to the control group. This benefit was maintained through week 100.
IB/0029/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	02/05/2016	n/a		

	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.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0020	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	19/11/2015	n/a		
II/0018	Update of sections 4.8 and 5.1 of the SmPC to reflect full 2-year efficacy and safety data from the ongoing studies VIVID-DME and VISTA-DME; post-authorisation measures (RECs) agreed as part of II-09. The Package Leaflet has been revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. A revised RMP version 19.1 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	19/11/2015	30/06/2016	SmPC and PL	Diabetic macular oedema In the VIVID- DME and the VISTA- DME studies the mean decreases in central retinal thickness (CRT) at week 52 were -192.4 and -183.1 microns for the 2Q8 Eylea groups and -66.2 and -73.3 micronsfor the control groups, respectively. At week 100 the decrease was maintained with -195.8 and -191.1 microns for the 2Q8 Eylea groups and -85.7 and -83.9 microns for the control groups, in the VIVID-DME and VISTA-DME studies, respectively. A ≥ 2 step improvement in DRSS was assessed in a

	data				pre-specified manner in VIVID-DME and VISTA-DME. The DRSS score was gradable in73.7% of the patients in VIVID-DME and 98.3% of the patients in VISTA-DME. At week 52, 27.7% and 29.1% of the Eylea 2Q8 groups, and 7.5% and 14.3% of the control groups experienced a ≥2 step improvement in the DRSS. At week 100, the respective percentages were 32.6% and 37.1% of the Eylea 2Q8 groups and 8.2% and 15.6% of the control groups. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both Eylea 2Q8 and Eylea 2Q4 groups were shown to have efficacy that was statistically significantly superior to the control group. This benefit was maintained through week 100. Please refer to SmPC section 5.1, table 5, for the detailed efficacy results.
II/0021	Extension of Indication to include a new indication for adult for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated, including the warning on populations with limited data to inform healthcare professionals that no data were available for non-Asian and non-treatment naïve myopic CNV patients as well as patients with extrafoveal lesions. In addition, sections 5.1 and 6.6 of the SmPC have been updated to further condense the description of the pharmacodynamic effects and to clarify the instructions for use including improved pictograms. The Package Leaflet has been updated accordingly.	24/09/2015	28/10/2015	SmPC, Annex II and PL	The review of the data from the MYRROR trial showed a beneficial effect of Eylea in the treatment of adult patients with impaired vision due to formation of abnormal and leaky blood vessels in the choroid layer of the eye caused by pathologic myopia, where the axial length of the eyeball is abnormally elongated. The safety profile remained unchanged and the benefit-risk profile of Eylea in this new indication was considered positive.

	Annex II was amended to indicate that an updated physician information pack should be distributed after introduction of the new indication. Minor editorial and typographical amendments were made throughout the Product Information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0022	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	17/09/2015	n/a		
IB/0025/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.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.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	08/09/2015	n/a		

IB/0026/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.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	28/07/2015	n/a		
II/0023	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	23/07/2015	n/a		
IB/0024	Addition of the Ph. Eur. gel clot method as alternative method for Endotoxin testing of Eylea drug product in vials and prefilled syringes. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	09/07/2015	n/a		
PSUSA/10020 /201411	Periodic Safety Update EU Single assessment - aflibercept (ophthalmological indication(s))	11/06/2015	n/a		PRAC Recommendation - maintenance
II/0013	Extension of the indication for the treatment of adult patients with visual impairment due to macular oedema secondary to branch retinal vein occlusion	22/01/2015	24/02/2015	SmPC and PL	Review of the data of the VIBRANT phase III study showed that Eylea was able to improve vision and reduce macular oedema in patients with visual impairment due to macular

	(BRVO); Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were updated to add the new indication and related dosing recommendations, as well as in order to include information on the data supporting the application and resulting updates to the safety information. Section 4.4 was updated to harmonise the warnings for intravitreal injection-related reactions and concomitant use with anti-VEGF inhibitors across the class of anti-VEGF inhibitors. The Package Leaflet was updated in accordance. Furthermore, Annex II was updated to clarify the patient population (age related macular degeneration) for one of the studies and to update the due date as agreed during review of the study protocol. Additional amendments were made throughout the product information to condense the information as well as to make editorial changes. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				oedema secondary to BRVO. The safety profile remained largely unchanged and the benefit-risk balance was considered favourable.
PSUV/0016	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
IB/0017	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	15/10/2014	n/a		
PSUV/0011	Periodic Safety Update	26/06/2014	26/08/2014	SmPC and PL	Please refer to Eylea PSUV-11 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the

					marketing authorisation.
IB/0015	B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	14/08/2014	n/a		
II/0009	Extension of indication to add a new indication for the treatment of visual impairment due to diabetic macular oedema. As a consequence, updates of sections 4.2, 4.4, 4.8, 5.1 and 5.2 in order to add dosing recommendation for DME patients, update the safety information and provide a summary of relevant clinical data in DME. SmPC section 4.8 was furthermore updated to introduce a joint summary of the safety profile across all indications. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/06/2014	06/08/2014	SmPC, Annex II and PL	Upon review of the data of two phase 3 clinical trials as well as one supportive phase 2 study investigating the safety and efficacy of Eylea in the treatment of visual impairment due to diabetic macular oedema, the CHMP considered that Eylea had been shown to improve vision and reduce macular oedema in a relevant patient population in a significant and clinically meaningful manner. The safety profile remained largely unchanged and the benefit-risk balance was considered favourable.
IB/0014	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	17/07/2014	n/a		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/04/2014	06/08/2014	PL	
PSUV/0008	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IA/0010	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	25/11/2013	n/a		
IB/0007/G	This was an application for a group of variations.	14/10/2013	n/a		

	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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IB/0006/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch	16/09/2013	n/a		

	control/testing takes place 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				
II/0001	Extension of indication for the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2013	26/08/2013	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion Eylea-H-002392-II-0001-AR
IB/0005/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/07/2013	n/a		
IB/0003/G	This was an application for a group of variations. 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	23/04/2013	n/a		

	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				
IAIN/0004	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/04/2013	n/a		
IB/0002	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	17/01/2013	n/a		