Zaltrap

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0067/G	This was an application for a group of variations. 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	15/12/2022		Annex II	

[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).

	method at the site is a biol/immunol method 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.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 B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the 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.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where				

	batch control/testing takes place B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
T/0068	Transfer of Marketing Authorisation	31/10/2022	21/11/2022	SmPC, Labelling and PL	
IB/0065	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	19/07/2022	n/a		
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2022	21/11/2022	PL	
PSUSA/10019 /202108	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	10/03/2022	n/a		PRAC Recommendation - maintenance
IB/0064/G	This was an application for a group of variations. 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.d.1.z - Stability of AS - Change in the re-test	14/12/2021	n/a		

	period/storage period or storage conditions - Other variation				
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2021	21/11/2022	PL	
IB/0061/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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	18/06/2021	n/a		
PSUSA/10019 /202008	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	11/03/2021	n/a		PRAC Recommendation - maintenance
IB/0060/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.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	26/02/2021	n/a		

	applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
II/0058/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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 B.I.a.1.k - Change in the manufacturer of AS or of a	14/01/2021	n/a		

	starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB				
WS/1829	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2020	09/12/2021	SmPC, Annex II and PL	
II/0055/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 control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.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 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	02/04/2020	n/a		

	material/intermediate				
IB/0056/G	This was an application for a group of variations. B.I.a.z - Change in manufacture of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	11/03/2020	n/a		
PSUSA/10019 /201908	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	13/02/2020	n/a		PRAC Recommendation - maintenance
IB/0054	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	06/02/2020	n/a		
IAIN/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/10/2019	15/10/2020	SmPC, Annex II and PL	
II/0051	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2019	n/a		
PSUSA/10019 /201808	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	14/02/2019	n/a		PRAC Recommendation - maintenance
IB/0049/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	09/01/2019	n/a		

	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.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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0050	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	04/01/2019	n/a		
IA/0047	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/10/2018	n/a		

IA/0046	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/10/2018	n/a		
IB/0045	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	04/05/2018	n/a		
PSUSA/10019 /201708	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	08/03/2018	n/a		PRAC Recommendation - maintenance
II/0044	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/02/2018	n/a		
IB/0043	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	15/12/2017	n/a		
II/0040	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	07/12/2017	n/a		
IB/0042/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or	04/12/2017	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure 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				
II/0038	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	28/09/2017	n/a		
IB/0039	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	25/09/2017	n/a		
R/0037	Renewal of the marketing authorisation.	20/07/2017	21/09/2017	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Zaltrap in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0036/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	25/04/2017	n/a		

	or addition) for the AS or a starting material/intermediate				
IB/0033/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	01/03/2017	n/a		
II/0035	Update the Product Information (SmPC, section 5.1 Pharmacodynamic properties) to reflect the results of the biomarker programme encompassing the EFC10262, EFC10668 and EFC11338 studies in order to fulfil the Annex II condition of Zaltrap, aflibercept 25 mg/ml, Concentrate for solution for infusion (EMEA/H/C/002532). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2017	21/09/2017	SmPC and Annex II	
II/0034	Submission of the final results of the Drug Utilisation	23/02/2017	n/a		

	Study monitoring the use of Zaltrap in cancer patients including potential off-label use and evaluating the potential for intravitreal use. This fulfils the post authorisation commitment MEA 03. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10019 /201608	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	09/02/2017	n/a		PRAC Recommendation - maintenance
IB/0032	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	17/11/2016	n/a		
II/0025/G	This was an application for a group of variations. B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	10/11/2016	n/a		
IB/0030	B.I.a.1.k - Change in the manufacturer of AS or of a	09/11/2016	n/a		

	starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB				
II/0026	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add the adverse reactions cardiac failure and ejection fraction decreased and to recommend the discontinuation of Zaltrap in case these adverse reactions occur. This update reflects the results of a safety cumulative review. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	24/10/2016	SmPC and PL	Cardiac failure and ejection fraction decreased have been reported in patients treated with Zaltrap. Baseline and periodic evaluations of left ventricular function should be considered while the patient is receiving Zaltrap. Patients should be monitored for signs and symptoms of cardiac failure and ejection fraction decreased. Discontinue ZALTRAP in patients who experience cardiac failure and ejection fraction decreased.
IA/0029	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	21/07/2016	n/a		
IB/0028	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/06/2016	n/a		
IA/0027/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/05/2016	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
PSUSA/10019 /201508	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	25/02/2016	28/04/2016	SmPC and PL	Please refer to Zaltrap-PSUSA/00010019/201508 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IB/0023	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	15/03/2016	n/a		
IB/0022	B.I.c.3.z - Changes in the test procedure for the immediate packaging of AS - Other variation	05/02/2016	n/a		
IB/0021/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	21/12/2015	n/a		
PSUSA/10019 /201502	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	10/09/2015	n/a		PRAC Recommendation - maintenance

N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/08/2015	28/04/2016	PL	
IB/0017/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	16/06/2015	n/a		
IB/0016/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	26/02/2015	n/a		

	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.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.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 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 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 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 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 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 material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
IB/0015/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 changes to an approved test procedure	23/02/2015	n/a		

IB/0014	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/02/2015	n/a		
PSUSA/10019 /201408	Periodic Safety Update EU Single assessment - aflibercept (oncological indication(s))	12/02/2015	n/a		PRAC Recommendation - maintenance
IB/0013/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.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	29/01/2015	n/a		
II/0005	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	18/12/2014	n/a		
PSUV/0009	Periodic Safety Update	25/09/2014	19/11/2014	SmPC	Please refer to Zaltrap-EMEA-H-C-2532-PSUV-0009 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IB/0012/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	12/11/2014	n/a		

	batch control/testing takes place 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				
IG/0454	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	17/07/2014	n/a		
PSUV/0008	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
II/0007	Update of section 4.4 of the SmPC in order to amend the existing warnings on proteinuria in line with a proposed amendment to the CCDS. Moreover, a minor rewording of the recommendation regarding recurrent hypertension is introduced in section 4.2 of the SmPC and the warning on hypertension in section 4.4 of the SmPC is amended accordingly. In addition, the MAH took the opportunity to update Annex II in line with the QRD template version 9 and to update the details of the local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/12/2013	27/06/2014	SmPC, Annex II and PL	Proteinuria occurring during aflibercept treatment should be monitored by urine dipstick analysis and/or urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria before each aflibercept administration. Patients with a dipstick of ≥2+ for protein or a UPCR >1 should undergo a 24 hour urine collection. In case of recurrent medically significant or severe hypertension despite optimal treatment, ZALTRAP should be suspended until the hypertension is controlled and the dose reduced to 2 mg/kg for subsequent cycles. Aflibercept should be permanently discontinued if hypertension cannot be adequately managed with appropriate anti hypertensive therapy or aflibercept dose reduction, or if hypertensive crisis or hypertensive encephalopathy occurs.
IB/0006	B.I.d.1.b.3 - Stability of AS - Change in the storage	05/11/2013	n/a		

	conditions - Change in storage conditions of the AS				
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/09/2013	27/06/2014	PL	
IAIN/0004	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
IA/0001	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	21/06/2013	27/06/2014	SmPC	