



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
IAIN/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/10/2019		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

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).



IB/0049/G	<p>This was an application for a group of variations.</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>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</p> <p>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</p> <p>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)</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p>	09/01/2019	n/a		
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	18/10/2018	n/a		

	the AS				
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.	04/12/2017	n/a		

	<p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>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</p>				
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	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p>	25/04/2017	n/a		

IB/0033/G	<p>This was an application for a group of variations.</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p>	01/03/2017	n/a		
II/0035	<p>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 (EMA/H/C/002532).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	23/02/2017	21/09/2017	SmPC and Annex II	
II/0034	<p>Submission of the final results of the Drug Utilisation 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.</p>	23/02/2017	n/a		

	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 starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	09/11/2016	n/a		
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	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

	<p>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.</p> <p>In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>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.</p>
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	<p>This was an application for a group of variations.</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p>	11/05/2016	n/a		
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	16/06/2015	n/a		

	<p>the AS</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p>				
IB/0016/G	<p>This was an application for a group of variations.</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting</p>	26/02/2015	n/a		

<p>material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</p> <p>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion</p>				
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<p>of an obsolete parameter)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p>				
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	<p>B.1.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.1.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation</p>				
IB/0015/G	<p>This was an application for a group of variations.</p> <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p>	23/02/2015	n/a		
IB/0014	B.1.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	<p>This was an application for a group of variations.</p> <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an</p>	29/01/2015	n/a		

	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/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-EMA-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 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	12/11/2014	n/a		
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	<p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	19/12/2013	27/06/2014	SmPC, Annex II and PL	<p>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 $\geq 2+$ for protein or a UPCR > 1 should undergo a 24 hour urine collection.</p> <p>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.</p>
IB/0006	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	05/11/2013	n/a		
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	