Optison

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/0075/G	This was an application for a group of variations.	27/06/2022	n/a		
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2022		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).

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N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/10/2021		PL	
IAIN/0070/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	16/06/2021	n/a		
IA/0071	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/06/2021	n/a		
IA/0069/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	05/11/2020	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IAIN/0068	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	08/07/2020	n/a		
IA/0067/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/02/2020	n/a		
IAIN/0066/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	08/11/2019	n/a		
PSUSA/2350/ 201812	Periodic Safety Update EU Single assessment - perflutren	05/09/2019	n/a		PRAC Recommendation - maintenance

IAIN/0064	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	15/08/2019	n/a		
IAIN/0065/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/08/2019	n/a		
IB/0062/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/11/2018	21/10/2019	SmPC, Annex II, Labelling and PL	
IAIN/0061	B.V.a.1.d - PMF - Inclusion of a new, updated or	26/06/2018	n/a		

	amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IB/0060	B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP	24/04/2018	n/a		
IB/0059/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	31/08/2017	n/a		
IAIN/0058	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	28/04/2017	n/a		
IB/0056	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	02/03/2017	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IA/0055/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	28/02/2017	n/a		
IAIN/0057	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	27/02/2017	n/a		
PSUSA/2350/ 201512	Periodic Safety Update EU Single assessment - perflutren	02/09/2016	n/a		PRAC Recommendation - maintenance
IAIN/0054	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/06/2016	n/a		
IAIN/0052	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes	13/05/2015	n/a		

	do not affect the properties of the FP				
IA/0051	A.7 - Administrative change - Deletion of manufacturing sites	20/10/2014	n/a		
IA/0050/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	10/09/2014	n/a		
IB/0049	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	08/05/2014	04/07/2014	SmPC	
IAIN/0048	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/04/2014	n/a		
IAIN/0047	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	30/10/2013	n/a		

IAIN/0046/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	28/08/2013	n/a		
IAIN/0045	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	16/08/2013	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IB/0043/G	This was an application for a group of variations. 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)	26/07/2013	n/a		
IB/0044	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/07/2013	04/07/2014	SmPC, Annex II, Labelling and PL	
IA/0041/G	This was an application for a group of variations. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters	03/07/2013	n/a		

	and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
II/0039/G	This was an application for a group of variations. This was an application for a group of variations to add a manufacturing site for the drug product, and to make changes to the drug product manufacturing process, batch size and in-process tests and limits. B.II.a.3.b.6 - Changes in the composition (excipients) of the finished product - Other excipients - Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a	30/05/2013	n/a		

	manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size 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 tests and limits 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.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				
IB/0040	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	05/04/2013	n/a		
II/0037	Update of section 4.2 and 5.1 of the Summary of Product Characteristics (SPC) further to the request of the CHMP following the assessment of paediatric data submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended (P45-012). C.I.3.b - Implementation of change(s) requested	18/11/2010	20/12/2010	SmPC and PL	In accordance with Article 45 of the Paediatric Regulation 1901/2006, the Marketing Authorisation Holder (MAH) submitted available paediatric data. Following the assessment of these paediatric data, the CHMP concluded that although demonstrating an effect that appears to be similar to that seen in adults, the submitted study does not allow any conclusions on posology in children and adolescents.

	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				However, safety data is available in 42 children, aged 8 months to 19 years. The data indicate that the safety profile of Optison is similar in this age group when compared to adults. This information could be of use to the prescriber and CHMP recommended that sections 4.2 and 5.1 were amended with these observations.
IA/0038	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	18/11/2010	n/a		
IB/0036	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	20/09/2010	n/a	SmPC and PL	To include nausea and tachycardia in section 4.8 in the SmPC as common and rare adverse reactions respectively. The PL has been updated accordingly. Furthermore section 4.6 was updated according to QRD to include Fertility in the heading.
IB/0035	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	20/09/2010	n/a	SmPC and PL	To update SPC and PL to include warning on transmissible agents. Also section 4.4 and PL were updated to include wording required for albumin. Furthermore the MAH applied to update the addresses of local representatives for Sweden, Spain, Greece, Belgium, Luxembourg and Denmark and to add the statement that "Not all pack size may be marketed" in section six of the PL to reflect the text already present in the SPC.
IA/0034	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	19/05/2010	n/a		

2PMF/0033	Inclusion of the updated or amended Plasma Master File (CSL Behring EMEA/H/PMF/000001/04) in the marketing authorisation dossier	15/12/2009	n/a		
Z/0032		25/06/2009	08/10/2009		Please refer to Assessment Report (Optison-H-166-Z-32-AR) for further information.
R/0031	Renewal of the marketing authorisation.	19/03/2008	12/06/2008	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Optison continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity. However, due to limited exposure and in light of the ongoing discussions with the US FDA regarding the changes to the USPI in the context of the safety concern on micro-bubble contrast agents, the CHMP is of the opinion that the MAH should continue to provide annual PSURs. Notwithstanding the above, the CHMP noted that the MAH was not able to present an authorised importer for Optison to ensure the supply of the medicinal product at the EU/EEA market and to proof GMP compliance of the manufacturing process at the US manufacturing site at the time of this Renewal. Therefore, the CHMP recommends that the marketing authorisation of Optison should be suspended. The following changes were included to Section 4.4 and Section 4.8 of the SPC including corresponding changes to the package leaflet: Section 4.4 was amended in that the warning on

					hypersensitivity was made broader and is no longer linked to human albumin and protein allergy. Furthermore, the recommended time for monitoring of severely ill patients with certain conditions (with cardiac, pulmonary, renal, hepatic diseases) was extended to during and after administration of Optison. Finally, a recommendation to use end-diastolic triggering to avoid biological side effects of the contrast agent due to interaction with the ultrasound beam was included. In the Section 4.8, the term anaphylactoid shock was included.
MF/0030	2PMF (2nd step of PMF certification procedure)	17/10/2007	n/a		
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2006	n/a	PL	
IA/0028	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	09/10/2006	n/a	SmPC, Annex II, Labelling and PL	
A20/0027	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 11 April 2006 the opinion of the Committee for Medicinal Products for Human Use (CHMP) on whether further action is necessary with respect to OPTISON, in the light of a Class I Rapid Alert and subsequent suspension of the import authorisation of the manufacturer responsible for batch release in the EU/EEA.	01/06/2006	07/08/2006		Decision: To maintain the MA following untoward findings of a GMP inspection of the manufacturing site.

IB/0026	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	10/05/2005	n/a		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/02/2005	n/a	Labelling and PL	
II/0024	Update of Summary of Product Characteristics and Package Leaflet	23/06/2004	12/08/2004	SmPC and PL	
II/0023	Change(s) to the test method(s) and/or specifications for the active substance	25/09/2003	26/09/2003		
R/0022	Renewal of the marketing authorisation.	20/02/2003	15/05/2003	SmPC, Annex II, Labelling and PL	
I/0021	Change in manufacturing site for outer packaging and batch release in the EEA. 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/01/2003	17/03/2003	Annex II and PL	
II/0020	Change(s) to the manufacturing process for the finished product Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	20/11/2002	SmPC, Labelling and PL	
T/0019	Transfer of Marketing Authorisation	19/03/2002	29/04/2002	SmPC, Labelling and	

				PL	
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/03/2002	18/04/2002	PL	
I/0015	01_Change following modification(s) of the manufacturing authorisation(s)	17/01/2002	07/02/2002		
I/0016	02_Change in the name of the medicinal product (either invented name of common name)	14/05/2001	n/a	SmPC, Labelling and PL	
II/0011	Update of Summary of Product Characteristics and Package Leaflet	27/07/2000	29/11/2000	SmPC and PL	
I/0014	01_Change in the name of a manufacturer of the medicinal product	09/08/2000	14/08/2000		
I/0013	The Marketing Authorisation Holder applied for the use of an alternative rubber stopper for the 3 ml cartridge and for an extension of the shelf life of the finished product as packaged for sale, from 2 years to 3 years, for the current and proposed alternative container closure system of the 3 ml cartridge presentations. 17_Change in specification of the medicinal product	30/05/2000	n/a		
I/0012	12_Minor change of manufacturing process of the active substance	26/05/2000	29/05/2000		
I/0010	15_Minor changes in manufacture of the medicinal	08/05/2000	12/05/2000		

	product				
I/0009	19_Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines)	08/05/2000	12/05/2000		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/01/2000	23/10/2000	PL	
I/0007	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	19/08/1999	23/09/1999		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/1999	29/06/1999	PL	
I/0006	15a_Change in IPCs applied during the manufacture of the product	04/05/1999	n/a		
I/0004	17_Change in specification of the medicinal product	18/12/1998	02/03/1999		
I/0002	01_Change following modification(s) of the manufacturing authorisation(s)	05/11/1998	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/09/1998	19/11/1998	PL	