SonoVue

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
IB/0051	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/12/2022	n/a		
II/0049	Update of Annex II of the SmPC based on final results from study BR1-145 listed as a PAES in the Annex II; this is an observational, retrospective, multicentre, comparative study conducted in patients below 18 years of age who had undergone a VUS exam with intravesically administered	10/11/2022		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).

	SonoVue/Lumason or a VCUG exam as part of their standard of care for evaluation of known or suspected VUR. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0050	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	01/06/2022	n/a		
IA/0048/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - 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.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-	16/03/2022	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
PSUSA/2822/202009	Periodic Safety Update EU Single assessment - sulfur hexafluoride	24/06/2021	26/08/2021	Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2822/202009.
IB/0046	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	25/08/2021	n/a		
IA/0045	A.7 - Administrative change - Deletion of manufacturing sites	26/07/2021	n/a		
IB/0044	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/05/2021	26/08/2021	Annex II	
II/0039/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.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	02/04/2020	n/a		

	aseptically manufactured) excluding biological/ immunological medicinal products 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 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 B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products				
II/0041	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/03/2020	09/03/2021	SmPC and PL	
II/0040	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	12/03/2020	09/03/2021	Annex II	
PSUSA/2822/ 201709	Periodic Safety Update EU Single assessment - sulfur hexafluoride	17/05/2018	n/a		PRAC Recommendation - maintenance
II/0037/G	This was an application for a group of variations. Grouped variation application in order to align with	26/04/2018	17/04/2019	SmPC and PL	Use caution when treating anaphylaxis with epinephrine in patients on beta blockers since response may be poor or promote undesired alpha-adrenergic and vagotonic effects

	Company Core Data Sheet (CCDS): • Update of section 4.4 of the SmPC in order to reword the warning on hypersensitivity reactions. • Update of section 4.4 of the SmPC in order to reword the warning for patients with unstable cardiopulmonary status • Update of section 4.4 of the SmPC in order to delete the warning for patients on mechanical ventilation or with unstable neurological diseases • Update of section 4.4 of the SmPC in order to delete the warning for patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease • Update of section 4.8 of the SmPC in order to revise the table of Adverse Drug Reactions. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes/corrections in sections 4.8 and 4.9 of the SmPC. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to				(hypertension, bradycardia). It should be emphasised that stress echocardiography not only can induce an ischaemic episode but also the stressors may induce predictable, dose-dependent effects on the cardiovascular system (e.g., increase in heart rate, blood pressure and ventricular ectopic activity for dobutamine, or decrease in blood pressure for adenosine and dipyridamole) as well as unpredictable, hypersensitivity reactions.

	new quality, preclinical, clinical or pharmacovigilance data				
X/0034/G	This was an application for a group of variations. Annex I_2.(e) Change or addition of a new route of administration C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/06/2017	22/08/2017	SmPC, Annex II, Labelling and PL	Please refer to the published assessment report for SonoVue X/0034/G.
IA/0036	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	23/06/2017	n/a		
IB/0035/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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	15/03/2017	n/a		
N/0031	Update of the package leaflet in line with results of a user testing.	24/05/2016	22/08/2017	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0033/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	26/04/2016	n/a		
IA/0032	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	14/04/2016	n/a		
PSUSA/2822/ 201409	Periodic Safety Update EU Single assessment - sulfur hexafluoride	23/04/2015	19/06/2015	SmPC, Annex II and PL	Please refer to SonoVue - 000303 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IAIN/0030	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	30/04/2015	n/a		
IA/0027	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	07/05/2014	n/a		
II/0025	These changes involve the deletion in Section 4.3 of the contraindications for use in patients with acute coronary syndrome or clinically unstable ischaemic	25/04/2014	13/04/2015	SmPC and PL	Please refer to the CHMP AR for SonoVue II/0025.

	cardiac disease and the insertion of these patient populations into Section 4.4 Special warnings and precautions for use, with editing of the wording as appropriate. These changes are also reflected in revised wording for the PIL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
PSUV/0026	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IA/0024	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/06/2013	n/a		
IB/0023	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	08/01/2013	n/a		
II/0021	Update of sections 4.4, 4.5 and 4.8 of the SmPC. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/09/2012	24/10/2012	SmPC and PL	The MAH proposed the update of sections 4.4 and 4.5 of the SmPC in order to add a warning about the concommitent use of beta blockers and the update of section 4.8 of the SmPC to add a table of adverse events of "hypotension". The Package Leaflet was proposed to be updated in accordance.
IA/0022/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding	17/10/2012	n/a		

	manufacturer for batch release) B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
IA/0020/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	03/05/2011	n/a		
II/0017	Update of Summary of Product Characteristics and Package Leaflet. The MAH has applied to amend section 4.8 of the SPC in order to be in line with the Company Core Data Sheet (September 2009). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update Annex II in line with the standard DDPS wording and to reflect the latest RMP version agreed with the CHMP. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	24/01/2011	SmPC, Annex II and PL	The integrated clinical trial database for SonoVue, from which the adverse events table in the new SPC is derived, contains 58 studies (8 healthy volunteer studies, 13 cardiac studies, 9 macrovasculature studies (i.e., Doppler sonography studies of arteries), 25 microvasculature studies (i.e., Doppler sonography studies of tissue microcirculation), and 3 special population studies). The database includes a total of 4653 subjects of whom 128 were healthy volunteers and 38 were special population patients. Safety data from myocardial perfusion studies (a total of 423 patients) were excluded from analysis since this indication is not approved in Europe. The MAH has applied to amend section 4.8 of the SPC in order to be in line with the Company Core Data Sheet (September 2009).

IA/0019	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	24/11/2010	n/a		
IB/0018/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation 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.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	24/08/2010	n/a		
IA/0016	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	22/04/2009	n/a		
II/0015	The MAH applied for replacement of an analytical procedure. Update of or change(s) to the pharmaceutical documentation	20/11/2008	26/11/2008		
II/0014	The MAH applied for additional manufacturing sites	25/09/2008	02/10/2008		

	for manufacture, testing and secondary packaging. Update of or change(s) to the pharmaceutical documentation				
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/01/2008	n/a	PL	
IA/0012	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	29/01/2008	n/a	Annex II and PL	
IA/0010	IA_47_c_Deletion of a pack size(s)	08/06/2006	n/a	SmPC, Labelling and PL	
R/0008	Renewal of the marketing authorisation.	23/02/2006	24/04/2006	SmPC, Annex II, Labelling and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	27/09/2004	SmPC and PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/03/2003	24/03/2003	PL	
II/0004	Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	04/12/2002	SmPC and PL	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/03/2002	29/04/2002	PL	
N/0002	Minor change in labelling or package leaflet not	13/12/2001	19/02/2002	PL	

	connected with the SPC (Art. 61.3 Notification)				
II/0001	Change(s) to the manufacturing process for the active substance	27/06/2001	04/07/2001		