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EU Risk Management Plan (RMP) for Sulphur Hexafluoride
For European Medicines Agency (EMA)

RMP Version number:	10.0
Data lock point (DLP) for this RMP:	30 June 2025
Date of final sign off:	30 September 2025
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Summary of significant changes in this RMP:	Removal of "potential for off-label use in paediatrics" as a safety concern, transfer to latest EU RMP template
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Qualified Person Responsible for Pharmacovigilance (QPPV) name	Letizia Vitali
QPPV signature	The content of this RMP has been reviewed and approved by the marketing authorisation holder (MAH)/applicant's QPPV. The QPPV signature is provided with this RMP as a separate document.

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Abbreviations and Definition of Terms

ACS	acute coronary syndrome
ADR	adverse drug reaction
CAD	coronary artery disease
CDS	Core Data Sheet
CEUS	contrast-enhanced ultrasound
CI	confidence interval
DLP	data lock point
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FLL	focal liver lesion
HCC	hepatocellular carcinoma
IBD	International Birth Date
LV	left ventricular
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NSTE	non-ST-segment elevation
PEG	polyethylene glycol
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RR	reporting rate
SF_6	sulphur hexafluoride
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
STEMI	ST-segment elevation myocardial infarction
UTI	urinary tract infection
VUR	Vesicoureteral Reflex
VUS	Voiding Ultrasonography

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Sulphur hexafluoride
Pharmaco-therapeutic group (ATC Code)	V08DA05
Marketing Authorisation Holder or Applicant	Bracco International B.V. Strawinskylaan 3051 NL - 1077 ZX Amsterdam The Netherlands
Medicinal product(s) to which this RMP refers	1 (one)
Invented name(s) in European Economic Area (EEA)	SonoVue®
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Inert gas
	Intravenously administered sulphur hexafluoride (SF_6)-filled microbubbles , enhance blood echogenicity and thus increase contrast between the blood and the surrounding tissues. Intravesically administered SF_6 microbubble increases signal intensity of fluids within the urethra, bladder, ureters, and renal pelvis.
Hyperlink to the Product Information	Link to product information.
Indications in EEA	Current: Diagnostic use only in patients to enhance the echogenicity of the blood or of fluids in the urinary tract, which results in an improved signal to noise ratio, for the following ultrasound imaging studies: Echocardiography: Provides opacification of cardiac chambers and enhance left ventricular endocardial border delineation in adult patients with suspected or established cardiovascular disease. Doppler of Macrovasculature: Increases accuracy in detection or exclusion of abnormalities of cerebral arteries and extra cranial carotid or peripheral arteries in adult patients. SonoVue increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment in adult patients. Doppler of Microvasculature: Improves display of the vascularity of liver and breast lesions during Doppler sonography in adult patients, leading to more specific lesion characterisation. Ultrasonography of the excretory urinary tract: is indicated for use in ultrasonography of the excretory tract in paediatric patients, from newborn to 18 years, to detect vesicoureteral reflux (VUR).

Indications in EEA (cont'd)	Proposed: Not Applicable
Dosage in EEA	Current: Intravenous administration: Cardiac imaging: 2 mL Vascular imaging: 2.4 mL A second intravenous injection of the recommended dose can be administered during a single examination when deemed necessary by a physician. Intravesical administration: Ultrasonography of the paediatric urinary tract: 1 mL
	Proposed : Not Applicable
Pharmaceutical form(s) and strengths	Current: Lyophilised powder and sodium chloride solution solvent for dispersion for intravenous injection When reconstituted as directed, 1 mL of the dispersion contains 8 µL (45 µg) sulphur hexafluoride in microbubbles.
	Proposed: No change.
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SonoVue is a diagnostic imaging agents approved for use with ultrasound imaging including echocardiography, Doppler of macrovasculature, and Doppler of microvasculature in adult patients; SonoVue is also approved in pediatric patients for ultrasonography of the urinary tract. Therefore, the target population for SonoVue is very diverse in terms of the demographic profile as well as the different types of diseases and pathology that may include cardiovascular conditions such as degenerative changes or congenital malformations, tumors (both benign and malignant), and vesicoureteral reflux (VUR).

As SonoVue is a diagnostic agent, it is not used for treating any disease; it is rather used during ultrasound imaging in patients with a known clinical condition/disease to confirm the presence of abnormalities, evaluate the evolution of the disease, or define its severity. For this reason, it is difficult to describe the incidence, prevalence, and mortality of the wide variety of diseases and conditions that are investigated using contrast-enhanced ultrasound (CEUS). Epidemiology data for the currently approved indications of SonoVue and relevant main target populations is provided below.

SI.1 Echocardiography

Coronary Artery Disease and Echocardiography with SonoVue

SonoVue is a transpulmonary echocardiographic contrast agent for use in adult patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular (LV) endocardial border delineation. Accurate assessment and quantification of LV function and detection of regional wall motion abnormalities are dependent on visualising the entire endocardium in cross section.

Coronary artery disease (CAD) represents an important socio-epidemiologic problem being the main cause of death in developed countries. As reported by the American Heart Association in the 2025 update of heart disease and stroke statistics,[1] it is estimated that roughly 127.9 million Americans (48.6%) ≥20 years of age have cardiovascular disease, including coronary heart disease, heart failure, stroke, or hypertension. Similarly, in 2021 there were 1.71 million deaths in the EU resulting from diseases of the circulatory system, which was equivalent to 32.4% of all

[1] Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Committee. 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2025 Feb 25;151(8):e41-e660. Erratum in: Circulation. 2025 Jun 24;151(25):e1096.

deaths.[2] Establishing the diagnosis, extent, and severity of CAD and determining the potential risk of cardiovascular events are crucial steps toward improving patient outcomes.

Acute Coronary Syndromes

Coronary artery disease (CAD) associated with Acute Coronary Syndromes (ACS), which include unstable angina and myocardial infarction (MI) with ST segment elevation (STEMI) or without (NSTEMI), are life-threatening disorders which still remain the leading cause of morbidity and mortality worldwide despite advances in treatment. Each year, an estimated 1.2 million individuals in the United States are hospitalised with ACS. [1] STEMI accounts for about 30% of these hospitalizations, while NSTEMI, or NSTE-ACS, accounts for the remaining 70%. [1] The economic burden of ACS is also high, costing Americans more than $150 billion, according to American Heart Association estimates.[3,4] Approximately 20% of the ACS patients are re-hospitalised within 1 year, and a significant portion of the costs related to ACS result from re-hospitalisation.

At the beginning of the 20th century, cardiovascular diseases accounted for less than 10% of all deaths worldwide. At the beginning of the 21st century they account for 25% in the developing world and nearly half of all deaths in the developed world.[5] From 1990 to 2006 the proportion with NSTEMI increased exponentially in North America from 14.2% to 59.1%.[6]. And among patients with acute MI, the proportion of those presenting with NSTEMI increased from 52.8% in 2002 to 68.6% in 2011).[7]

With respect to National Registry of Myocardial Infarction, the largest registry in the United States which involve voluntary participation of 1600 hospitals and more than 2.2 million patients, overall acute MI has improved over the last few years, [8] with timely diagnosis and implementation of acute therapies.

In 1997 in European countries the risk of dying from cardiovascular diseases was 5 times higher in Eastern European countries than in Western European countries such as France, Italy or Spain.[9] This major difference in prevalence of cardiovascular diseases may be explained by

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2 https://ec.europa.eu/eurostat/statistics-explained/index (2024)

3 Kolansky DM. Acute Coronary Syndromes: Morbidity, Mortality, and Pharmacoeconomic Burden. Am J Manag Care. 2009; 15:S36-S41.

4 Lloyd-Jones D, Adams RJ, Brown TM, et.al.; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010, 23 (7): e46-e215.

5 Murray CJL, Lopez AD. The Global Burden of Disease. Cambridge, MA, Harvard School of Public Health. 1996.

6 Rogers WJ, Frederick PD, Stoehr E, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008; 156:1026-34.

7 Khera S, Kolte D, Aronow WS, et.al. Non-ST-elevation myocardial infarction in the United States: contemporary trends in incidence, utilization of the early invasive strategy, and in-hospital outcomes. J Am Heart Assoc. 2014 Jul 28;3(4):e000995.

8 Gibson CM: NRMI and current treatment patterns for ST-Elevation myocardial infarction Am Heart Journal 2004; 148:S29-S33.

9 Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe. Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. Eur Heart J. 1997; 18;1231-48.

higher prevalence of risk factors in Eastern Europe such as smoking, hypertension, obesity and diabetes as well as unfavourable economic conditions.

The prevalence rate of NSTE-ACS is difficult to estimate due to challenges in the diagnosis of NSTE-ACS compared to STEMI. The annual incidence of hospital administration for NSTE-ACS varies widely in Europe, resulting in the highest incidence in Central and Eastern Europe in comparison to Western Europe. While the rate of NSTE-ACS has been increasing, compared to STEMI, the higher proportion of hospitalisation is related to NSTE-ACS.

Similarly, surveys have indicated that the prognosis of NSTE-ACS also varies with a lower death rate within the first 30 days compared to STEMI, but the death rate appears to be the same for both ACS.

The clinical utility of the use of contrast ultrasound in acute unstable cardiac patients has been described in numerous clinical papers, including the American Society of Echocardiography consensus statement[10] on the clinical applications of ultrasound contrast agents published in November 2008 in the Journal of the American Society of Echocardiography. These guidelines provide the rationale for contrast use, and specifically highlight a number of clinical scenarios in which contrast should always be considered. These include the 1) assessment of LV systolic function-especially when quantitative LV volumes and ejection fraction, or serial assessments are required, and during stress echocardiography; 2) evaluation of the LV apex; 3) evaluation of mechanical complications of MI; 4) evaluation of suspected intracardiac mass; and 5) to enhance Doppler signals in the systemic circulation.

Furthermore, contrast echocardiography is the only technique that allows immediate bedside simultaneous assessment of wall motion and perfusion and, in this regard, can offer a unique role in the diagnosis and management of ACS patients. Contrast transthoracic echocardiography has been shown to be particularly useful in the assessment of LV function in patients ventilated in intensive care, reducing the time required to obtain diagnostic information and obviating the need for transoesophageal echocardiography.[11]

Rest and stress echocardiography are widely used in the diagnosis, monitoring, follow-up, risk stratification and assessment of prognosis of patients with CAD).[10,12,13,14,15,16] Patients with known or suspected CAD may be in stable or unstable conditions, such as patients with ACS.

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10 Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, et al; American Society of Echocardiography. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. J Am Soc Echocardiogr. 2008; 21:1179-1201.

11 Reilly JP, Tunick PA, Timmermans RJ. Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients. J Am Coll Cardiol. 2000; 35:485-90.

12 Pellikka PA. American Society of Echocardiography: Recommendations for Performance, Interpretation, and Application of Stress Echocardiography. J Am Soc Echocardiogr. 2007; 20:1021-41.

13 Senior R. et al. Contrast echocardiography: evidence-based recommendations by European Association. European Journal of Echocardiography 2009; 10:194-212.

14 Douglas PM, Khandheria B, Stainback RF,. Weissman NJ, Peterson E, Hendel RC, Stainback RF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008Appropriateness Criteria for Stress Echocardiography A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear

Stress echocardiography

Stress echocardiography is a key imaging modality for the detection of CAD. SonoVue is an ultrasound contrast agent approved for use in stress echocardiography, i.e., in conjunction with the use of pharmacological stressors like dobutamine (a cardiac inotrope and chronotropic agent that increases heart rate and myocardial oxygen demand), or dipyridamole (a vasodilator that increases blood velocity and flow rate in normal vessels and less of a response in stenotic vessels). Both types of stressors induce local myocardial ischaemia in CAD patients that may be visible on the echocardiogram as a regional wall motion abnormality.[13,17,18,19] To accurately detect wall motion abnormalities, proper visualisation of the entire endocardium in cross section, with complete delineation of the endocardial border, is critical. [10,12,13]

The use of SonoVue is particularly useful when associated with stress echocardiography, where this agent minimises the degradation of image quality, induced by tachycardia, excessive contraction of normal walls and hyperventilation, which may lead to higher interobserver variability and lower diagnostic accuracy.[20] SonoVue has become a quite useful tool in the stress echo laboratory for improving image quality and diagnostic interpretation. Converting a diagnostically non-interpretable image into one which can be interpreted may reduce more costly and/or more invasive downstream diagnostic testing for cardiac function assessments. It has to be noted that the alternative imaging methods for cardiac function assessment are not without risk. For transoesophageal echocardiography, upper gastrointestinal haemorrhage has been reported in 0.03% of cases and oesophageal perforations have been reported in 0.01% and in comparison the risk of major complications during a diagnostic cardiac catheterization procedure is usually less than 1%, and the mortality risk is 0.05% for diagnostic procedures.[21,22,23]

Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine Journal of the American College of Cardiology. 2008; 51 doi:10.1016/j.jacc.2007.12.005.

15 Gaibazzi N, Squeri A, Reverberi C, Molinaro S, Lorenzoni V, Sartorio D, et al. Contrast stress-echocardiography predicts cardiac events in patients with suspected acute coronary syndrome but nondiagnostic electrocardiogram and normal 12-hour troponin. J Am Soc Echocardiogr. 2011; 24:1333-41.

16 Becher H, Helfen A, Michels G, Gaibazzi N, Senior R, Dietrich CF. How to Perform Cardiac Contrast-Enhanced Ultrasound (cCEUS): Part I. Diagnostics. 2025; 15(14):1743.

17 Kim C, Kwok YS, Heagerty P, Redberg R. Pharmacologic Stress testing for Coronary Disease diagnosis: A Meta-analysis. Am Heart J. 2001; 142:934-44.

18 Porter TR; Xie F. Contrast Echocardiography: How Will It Be Used? ACC Current Journal Review Nov/Dec 2001; 43-47.

19 Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Polderman D, et al. EAE GUIDELINES. Stress echocardiography expert consensus statement. European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008; 9:415-37.

20 Rainbird AJ, Mulvagh SL, Oh JK, et al. Contrast dobutamine stress echocardiography: Clinical practice assessment in 300 consecutive patients. J Am Soc Echocardiogr. 2001; 14: 378-85.

21 KallmeyerIJ, Collard CD, Fox JA, Body SC, Shernan SK. The safety of intraoperative transesophageal echocardiography: a case series of 7200 cardiac surgical patients. Anesth Analg. 2001; 92:1126-30.

22 Pepine CJ, Hill JA, Lambert CR (editors). Diagnostic and therapeutic cardiac catheterization: Risks of cardiac catheterization. 1989, Williams & Wilkins, Baltimore, Maryland, USA.

23 Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. Glob J Health Sci. 2012 Jan 01;4(1):65-93.

Incorrect diagnostic assessments may furthermore cause inadequate therapeutic decisions. For stress echocardiography, it must be considered that the examination may be inconclusive due to limited image quality in a percentage of patients ranging from 15% to 30%. An unenhanced but non-diagnostic stress echocardiography poses the patient at a 1/1000 risk for a serious adverse drug reaction (ADR), with cardiac deaths reported. [24,25] This risk of stress testing is greater than that being reported for SonoVue and on its own is a reason for seeking to ensure with the greatest certainty that the examination can be useful. To subject a patient to the risk of a repeat stress is not warranted. In addition a non-diagnostic stress echocardiography is in many cases followed by further downstream diagnostic testing with stress-single-photon emission computed tomography, which not only exposes the patient to a relevant amount of X-ray radiation but it has a rate of life-threatening adverse events varying from 0.26% to 0.48%.[26,27]

In the literature, several studies compared and reported the safety of different echocardiography stress procedures with and without contrast.

A survey from the International Stress Echo Complication Registry evaluated the types and numbers of complications during various modalities of stress unenhanced echocardiographic testing in 85,997 patients.[28] Adverse effects were defined in 3 different procedures used for cardiac stress studies: dobutamine (35,103 patients), dipyridamole (24,599 patients), and physical exercise as cardiac stressor (26,295 patients). The type and rate of complications during stress testing are shown in Part II SI Table 1.

[24] Lowenstein J, Varga A, Rodriguez GM, Picano E. Safety of stress echocardiography. The results of the international stress echo complication registry. Echocardiography. 2004; 21:208.

[25] Picano E, Mathias W Jr, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. Lancet. 1994; 344:1190-92.

[26] Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, et al. Safety of dipyridamole testing in 73,806 patients: the Multicenter Dipyridamole Safety Study. J Nucl Cardiol. 1995; 2:3-17.

[27] Ranhosky A, Kempthorne-Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Intravenous Dipyridamole Thallium Imaging Study Group. Circulation. 1990; 81:1205-09.

[28] Varga A, Garcia MAG, Picano E. Safety of stress echocardiography (from the International Stress Echo Complication Registry). Am J Cardiol. 2006; 98:541-43.

Part II SI Table 1: Types and Numbers (%) of Complications during Stress Echocardiographic Testing Without Contrast Reported in a Registry Analysis

Complications	Dobutamine N = 35,103	Dipyridamole N = 24,599	Exercise (Treadmill or Bicycle) N = 26,295
Death	5 (0.01)	1 (0.004)	0
Acute myocardial infarction	11 (0.03)	5 (0.02)	1 (0.004)
Sustained ventricular tachycardia	27 (0.08)	1 (0.004)	2 (0.008)
Ventricular fibrillation	11 (0.03)	2 (0.008)	0
Cardiac rupture	5 (0.01)	0	1 (0.004)
Asystolic	2 (0.006)	4 (0.02)	0
Transient ischaemic attack/stroke	3 (0.009)	3 (0.01)	0
Hypotension/shock	2 (0.006)	4 (0.02)	0
Third-degree atrioventricular block	2 (0.006)	0	0
Data source: Varga et al. 2006[28]			

Life-threatening events occurred in 86 patients. Thirty-four percent (34%) of the patients with complications had previous infarctions, 20% were studied after recent (in 15 days window) infarctions, and 46% had no previous documentation of ischaemic heart disease. Over half of the patients had a history of serious disease. The overall safety of stress echocardiography in this analysis was 1 life-threatening event for every 1000 examinations: during exercise in 4 patients (event rate: 1 in 6574), during dobutamine infusion in 63 patients (event rate: 1 in 557), and during dipyridamole stress testing in 19 patients (event rate: 1 in 1294). Of the 86 patients with complications evaluated in this study, 5 died during dobutamine testing and 1 after dipyridamole testing. The event rate for fatal events was 1 in 14,332 tests, including all types of stressors.

The concomitant use of stressors may represent an important confounding factor in the assessment of cases of serious adverse reactions to SonoVue in echocardiography. 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.[29] In general the risks of major complications with stressors is low and has been described to be in the range of ~0.015% to 0.04% with exercise, ~0.2% with dobutamine and ~0.08% with vasodilatory agents.[30]

[29] Lattanzi F, Picano E, Adamo E, Varga A. Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. Drug Saf. 2000; 22:251-62.

[30] Lee C, Dow S, Shah K, Henkin S, Taub C. Complications of exercise and pharmacologic stress echocardiography. Front Cardiovasc Med. 2023 Aug 3;10:1228613.

SI.2 Doppler of Macrovasculature

Steno-occlusive Vascular Disease

Clinical manifestations of atherosclerosis, including CAD, cerebrovascular disease, and peripheral arterial disease, will occur in 2 of 3 men and 1 in 2 women after age 40.[31] Atherosclerosis is a chronic, progressive disease with a long asymptomatic phase.[32] Subclinical atherosclerosis is a latent precursor of clinical cardiovascular disease, including MI and stroke.[33]

The prevalence of peripheral artery disease in the United States is estimated to be ≈7%, affecting 8.5 million adults. However, we should note that this estimate is predominantly based on data collected in the 1990s.[34] Although atherosclerotic narrowing can affect virtually any artery in the body, the greatest burden of disease falls on the lower extremity.[35]

Patients with peripheral vascular disease may present with an acute limb threatening event, a chronically threatened limb (i.e., rest pain, tissue loss, cellulitis, or ulceration) most frequently in diabetics manifesting with distal small vessel disease, or merely intermittent claudication, a lifestyle-modifying disease predominantly affecting proximal large vessels. However, the most common manifestation of peripheral vascular disease is a markedly increased risk of cardiovascular morbidity and mortality.[36] Traditionally rates of lower extremity amputations are 15 to 46 times higher in diabetic patients when compared to non-diabetic patients.[37]

However a decline in the rate of nontraumatic lower extremity amputation in the United States has been reported from the 1990s to the beginning of the 2000s.[38] Despite an overall decrease in amputation rates among all patients with peripheral artery disease, high-risk populations remain disproportionally affected. Specifically, patients in rural areas, African-American and Native-American patients, and those of low socioeconomic status carry the highest risk of amputation.[39] Most affected patients have diffuse disease at many sites, and the location and severity of

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31 Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart Disease and Stroke Statistics--2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.

32 Toth PP. Subclinical atherosclerosis: what it is, what it means and what we can do about it. Int J Clin Prac. 2008; 62:1246-54.

33 Faxon DP, Creager MA, Smith SC, Pasternak RC, Olin JW, Bettman MA, et al, American Heart Association: Atherosclerotic vascular disease conference: executive summary. Circulation. 2004; 109:2595-2604.

34 Allison MA, Cushman M, Solomon C, Aboyans V, McDermott MM, Goff DC, et al. Ethnicity and risk factors for change in the ankle-brachial index: the Multi-Ethnic Study of Atherosclerosis. J Vasc Surg. 2009;50:1049–56.

35 Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1991; 20:384-92.

36 Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol. 1999; 19:538-45.

37 Armstrong D, Lavery L. Diabetic foot ulcers: prevention, diagnosis and classification. Am Fam Physician. 1998; 57:1325-78.

38 Goodney PP, Tarulli M, Faerber AE, Schanzer A, Zwolak RM. Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among medicare patients. JAMA Surg. 2015;150:84–86.

39 Eid MA, Mehta KS, Goodney PP. Epidemiology of peripheral artery disease. Semin Vasc Surg. 2021 Mar;34(1):38-46.

stenoses show significant variations from patients to patient that ultimately impacts clinical decision making.

Doppler ultrasonography, in particular colour and power Doppler imaging, is a useful imaging tool for detection or exclusion of vascular abnormalities in large vessels, including cerebral, carotid, peripheral, renal and portal blood vessels. Doppler examinations are performed to gather haemodynamic information for increasing the accuracy of disease assessment and for improving patient management. However, the use of unenhanced Doppler ultrasound in assessing disease has a number of limitations, including the overall low reflectivity of blood in comparison with the strong Doppler effect from the motion of surrounding solid tissue. The depth and size of a lesion can also reduce the sensitivity of Doppler imaging data.

The development of ultrasound contrast agents is based on the underlying principle of increasing the acoustic impedance mismatch from blood/tissue interfaces. The extremely high reflectivity of SonoVue microbubbles for sound frequencies in the medically relevant 2 to 10 MHz ultrasonography range increases the Doppler signal and acts over a sufficiently long duration to provide a strong increase in the signal-to-noise ratio. This in turn improves the quality and quantity of data from the Doppler scan by enhancing the display of flow and by detecting flow in areas that were not visible before contrast.

SonoVue is the only ultrasound contrast agent approved for use in Doppler sonography of macrovasculature. In patients with known or suspected large vessels pathology, SonoVue-enhanced ultrasound also provides significant improvement of global quality and diagnostic accuracy of Doppler assessments when compared to baseline examinations, thus reducing the potential need for more invasive and expensive diagnostic procedures.

Conventional unenhanced ultrasound techniques are limited in demonstrating slow flow, especially in small vessels such as collaterals, and flow in critical stenoses. Ultrasound contrast agents help to overcome some of these limitations. As reported in the guidelines and recommendations on the use of CEUS on non-hepatic applications issued in 2017 by the European Federation of Societies on Ultrasound in Medicine and Biology,[40] CEUS improves the sensitivity of Doppler ultrasound and can be used for distinguishing occlusion from tight sub-occlusive stenosis, even with conventional ultrasound equipment.[41]

SonoVue-enhanced macrovascular imaging results in improved assessment of blood flow from a Doppler evaluation in patients investigated for large vessel pathology Higher accuracy in detection or exclusion of abnormalities in the anatomic areas of the cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal-to-noise ratio can be achieved by contrast-enhanced vascular imaging.

[40] Sidhu PS, Cantisani V, Deganello A, Dietrich CF, Duran C, Franke D, et al. Role of contrast-enhanced ultrasound (CEUS) in paediatric practice: an EFSUMB position paper. European Journal of Ultrasound. 2017; 38 33-43.

[41] Piscaglia F, Nolsoe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschall Med. 2012; 33:33-59.

SI.3 Doppler of Microvasculature

In the characterisation of focal parenchymal lesions, the final diagnosis is based on a number of parameters and investigations in a step-by-step process, among which histology and cytology investigations are the most reliable methods for differentiating between benign and malignant lesions. However, these techniques are invasive and are not devoid of risk for the patient. Doppler ultrasound has the potential to reveal the presence of altered vascularity within a parenchymal lesion that has acoustic properties similar to those of the surrounding normal parenchyma, and therefore would not be visible by conventional imaging. However, in assessing low velocity blood flow and small volume flow rates in tissue microcirculation, which characterise small focal parenchymal lesions, the strong Doppler effect from solid tissue motion supersedes that of the weaker Doppler echoes from blood flow in small blood vessels.

Therefore, the major benefit of contrast in Doppler imaging of focal parenchymal lesions is that it allows a more complete display of vessels with very slow flow and vessels of small volume flow rates. With the acquisition of long-lasting and clear images of anatomy and pathologic structure at this level of detail, contrast-enhanced Doppler imaging can provide qualitative and quantitative assessment of haemodynamic characteristics of microcirculation in focal lesions.

The efficacy of SonoVue in producing clinically useful enhancement of Doppler signals in investigations of the vascularisation of focal lesions in different organs has been established.[42,43]

Based upon review and evaluation of these data, the approved indication is for the use of SonoVue for improving the assessment of vascularity of focal parenchymal lesions by enhancing the Doppler signal of the microvasculature of lesions in two anatomical areas, breast and liver.

Liver cancer

Focal hepatic lesions constitute a daily challenge in the clinical setting. Due to the high prevalence of benign focal hepatic lesions in adults, liver lesion characterisation is an important objective of diagnostic imaging. Incidental liver masses are often discovered in healthy adults during routine imaging procedures as well as during staging of a known malignancy, and they need to be characterised. In the figure below, the incidence of incidentally identified liver lesions is presented.[44]

[42] Westwood M, Joore M, Grutters J, Redekop K, Armstrong N, Lee K, et al. Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of liver metastases: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2013; 17:1-243.

[43] Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver—Update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultraschall Med. 2013; 34:11-29.

[44] Little JM, Richardson A, Tait N. Hepatic dystychoma: a five year experience. HPB Surg. 1991; 4:291-97.

Table 2–1. FINAL DIAGNOSES OF INCIDENTALLY IDENTIFIED HEPATIC LESIONS IN OTHERWISE WELL PATIENTS

Lesion	Incidence (%)
Benign	
Hemangioma	52
FNH	11
Adenoma	8
Fatty infiltrate	8
Other	4
Total	83
Malignant	
HCC	6
Metastasis	11
Total	17

FNH = focal nodular hyperplasia; HCC = hepatocellular carcinoma.
Adapted from Little JM, Richardson A, Tait A. Hepatic dystychoma: a five-year experience. HPB Surg 1991;4:291–7.

Contrast-Enhanced Ultrasound (CEUS) should be considered as the first-line contrast imaging modality to differentiate benign from malignant incidentally found focal liver lesions (FLLs). Common benign liver masses include cysts and haemangiomas; common malignant tumours are metastases and hepatocellular carcinoma (HCC). Less common liver tumours include focal nodular hyperplasia, hepatic adenoma, fibrolamellar HCC, intrahepatic cholangiocarcinoma, biliary cystadenoma and cystadenocarcinoma, lymphoma, stromal tumours, a variety of sarcomas, haemangioendothelioma, and hepatoblastoma in children. On occasion, nontumourous masses seen as focal fat sparing, abscess, or haematoma, may mimic liver tumours. Patients with cirrhosis are a special group in whom certain benign (regenerating nodules), premalignant (dysplastic nodules), malignant (HCC), and nontumourous (confluent hepatic fibrosis) masses are more prevalent.

Prevalence of various liver lesions has marked differences across geographic regions and ethnic groups.[45] In general, hepatic metastases are 18-40 times more common than primary liver tumours.[46] Focal liver lesion (FLL) is more likely to represent a metastatic deposit than primary malignancy in Europe and United States; however, hepatocellular carcinoma is a much more prevalent common hepatic disorder in Asia.

The American Cancer Society's estimates for primary liver cancer and intrahepatic bile duct cancer in the United States for 2025 are:

- About 42,240 new cases (28,220 in men and 14,020 in women) will be diagnosed
- About 30,090 people (19,250 men and 10,840 women) will die of these cancers.

[45] Méndez-Sánchez N, Villa AR, Chávez-Tapia NC, Ponciano-Rodriguez G, Almeda-Valdés P, González D, et al. Trends in liver disease prevalence in Mexico from 2005 to 2050 through mortality data. Annals of Hepatology. 2005; 4:52-55.

[46] Namasivayam S, Martin DR, Saini S. Imaging of liver metastases: MRI. Cancer Imaging. 2007; 7:2-9.

Liver cancer incidence rates have more than tripled since 1980, while the death rates have more than doubled during this time. An average man's lifetime risk of getting liver or intrahepatic bile duct cancer is about 1 in 85, while an average woman's risk is about 1 in 204. Most cases occur in people with certain risk factors including but not limited to chronic (long-term) infection with hepatitis B virus or hepatitis C virus and alcohol abuse.

The average age at diagnosis of liver cancer is 62. More than 90% of people diagnosed with liver cancer are older than 45 years of age. About 3% are between 35 and 44 years of age and less than 3% are younger than 35.

Liver cancer is much more common in countries in sub-Saharan Africa and Southeast Asia than in the United States. In many of these countries it is the most common type of cancer. More than 800,000 people are diagnosed with this cancer each year throughout the world. Liver cancer is also a leading cause of cancer deaths worldwide, accounting for more than 700,000 deaths each year.[47]

SonoVue is the only agent approved for characterisation of liver lesions with ultrasonography, and is approved for this application in both adults and children in the United States (under the trade name Lumason), while in all the other countries where SonoVue is registered it is approved only in adults. In children the two main types of liver cancer are hepatoblastoma and HCC. Hepatoblastoma is the most common type, occurring mainly in infants and children under 3 years of age. HCC occurs most frequently in children aged 10-16 years. Together, these liver cancers account for about 1% to 2% of all cancers in children.

Over the years, SonoVue has been proven to improve the accuracy of liver lesion characterization and several guidance documents have provided recommendations on when to use the product in the management of patients with known or suspected liver lesions. [43,48]

Breast cancer

In 2022, about 2.3 million women were diagnosed with breast cancer worldwide and 670,000 died. Every 14 seconds, somewhere in the world, a woman is diagnosed with breast cancer.[49] Female breast cancer incidence rates vary considerably, with the highest rates in Europe and the lowest rates in Africa and Asia.[50] Globally, 2.3 million new cases and 670,000 deaths from female breast cancer occurred in 2022. Annual rates increased by 1% to 5% in half of examined countries. Mortality rates decreased in 29 countries with very high Human Development Index.[51] Unfortunately, the global incidence has constantly increased in the last years in all age groups, with some regional and age group differences.[52]

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47 https://cancerstatisticscenter.cancer.org/.

48 SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast enhanced ultrasound imaging of the liver. Issued: August 2012. NICE diagnostics guidance 5. Available at www nice.org.uk/dg5

49 https://www.bcrf.org/breast-cancer-statistics-and-resources/

50 Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet] Lyon, France: International Agency for Research on Cancer; 2010. Available at: http://globocan.iarc fr

51 Kim J, Harper A, McCormack V, Sung H, Houssami N, Morgan E, et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. Nat Med. 2025 Apr;31(4):1154-1162.

The lifetime risk of developing breast cancer is 1 in 8 for women (i.e., approximately 12% to 13%), but can be approximately 20% to 25% or greater ("high risk" women).[47,50] Several factors are known to increase the risk of breast cancer; however, a familial history of breast cancer increases the risk by a factor of two or three. Some gene mutations, particularly in Breast Cancer genes one and two (BRCA[1], BRCA[2]) and p53, increase the risk of breast cancer considerably. Reproductive factors associated with prolonged exposure to endogenous oestrogens, such as early menarche, late menopause, late age at first childbirth are among the most important risk factors for breast cancer.[53,54] Exogenous hormones also exert a higher risk for breast cancer. Oral contraceptive and hormone replacement therapy users are at higher risk than non-users.[53,54] Breastfeeding has a protective effect.

Breast cancer survival rates vary greatly worldwide. The 5-year survival rate for patients with breast cancer reported by the American Cancer Society in 2015 varied from 53% in South Africa to 89% in the United States.[55] Prognosis in breast cancer relates to the stage of the disease at presentation.[56]

When an invasive breast cancer is diagnosed, the extent of the disease should be assessed and the tumour staged. Staging classification will influence patient management. Most patients have a combination of local treatments to control local disease and systemic treatment for any micro-metastatic disease. Local treatments consist of surgery and radiotherapy. Surgery can involve excision of the tumour with surrounding normal breast tissue (breast conservation surgery) or mastectomy. [56]

According to the European Society of Breast Imaging,[57] implementation of mammographic screening has contributed to a reduction in breast cancer mortality of at least 20% over the last 30 years. Screening programs usually include all women irrespective of their risk of developing breast cancer and with age being the only determining factor. This approach has recognized limitations, including underdiagnosis, false positive cases, and overdiagnosis. Breast cancer remains a major cause of cancer-related deaths in women undergoing cancer screening. Supplemental imaging modalities, including ultrasound, breast magnetic resonance imaging, and, more recently, contrast-enhanced mammography, are available and have already shown potential to further increase the diagnostic performances. SonoVue is the only agent approved for use in

52 Lima SM, Kehm RD, Terry MB. Global breast cancer incidence and mortality trends by region, age-groups, and fertility patterns. EClinicalMedicine 2021;38:100985.

53 IARC (2008). World cancer report 2008. Lyon, International Agency for Research on Cancer. Available at http://www.iarc fr/en/publications/pdfs-online/wcr/2008/

54 Lacey JV Jr. et al. Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort. BMC Cancer. 2009; 9:84.

55 Maajani K, Jalali A, Alipour S, Khodadost M, Tohidinik HR, Yazdani K. The Global and Regional Survival Rate of Women With Breast Cancer: A Systematic Review and Meta-analysis. Clin Breast Cancer. 2019 Jun;19(3):165-177.

56 Sainsbury JRC, Anderson TJ, Morgan DAL. ABC of breast diseases. Breast Cancer. BMJ. 2000; 321:745-51.

57 Marcon M, Fuchsjäger MH, Clauser P, Mann RM. ESR Essentials: screening for breast cancer - general recommendations by EUSOBI. Eur Radiol. 2024 Oct;34(10):6348-6357.

ultrasonography of breast. Several studies have shown how SonoVue can improve the characterisation of breast masses.[58,59,60]

SI.4 Vesicoureteral Reflux

Vesicoureteral reflux (VUR) is a common urinary tract abnormality in children which may lead to non-obstructive chronic nephropathy.[61,62,63] The presence of VUR is associated with an increased risk of renal scarring after urinary tract infection (UTI) with potential for nephrovascular hypertension and renal failure.[61,63,64] UTI is the most frequent serious bacterial infection during childhood, affecting approximately 2% of boys and 8% of girls by the age of 7 years, and represents a frequent indication for diagnostic imaging in children.[63] The prevalence of VUR in children with UTIs is 30% to 40% and increases in children with recurrent UTIs.

Although VUR is common in childhood, its exact prevalence is unknown since invasive diagnostic procedures are performed only when clinically indicated.[61,65] The estimated prevalence of VUR in “well” children is between 0.4 and 1.8%; the prevalence of disease is higher (up to 16.2%) among infants with hydronephrosis detected on antenatal ultrasound and in siblings of children with VUR (11%-67% in a review of 10 papers).[61,65] Case series of children with UTI who underwent voiding cystourethrogram have reported an incidence of VUR between 25% and 50%.[61,65] Considering that the cumulative incidence of UTI in children is 6%, it is estimated that 1.5% to 2.4% of all children will be diagnosed with VUR after UTI.[61]

SonoVue is currently the only ultrasound contrast agent approved for intravesical use in children (newborn to 18 years old) to evaluate known or suspected VUR. Over the years, a number of clinical studies have been published on the use of SonoVue for assessment of VUR[66,67,68,69,70] and

58 Saracco A, Szabó BK, Aspelin P, Leifland K, Wilczek B, Celebioglu F, Axelsson R. Differentiation between benign and malignant breast tumours using kinetic features of real-time harmonic contrast-enhanced ultrasound. Acta Radiol. 2012; 53:382-88.

59 Zhao H, Xu R, Ouyang Q, Chen L, Dong B, Huihua Y. Contrast-enhanced ultrasound is helpful in the differentiation of malignant and benign breast lesions. Eur J Radiol. 2010; 73:288-93.

60 Liu H, Jiang YX, Liu JB, Zhu QL, Sun Q, Chang XY. Contrast-enhanced breast ultrasonography: imaging features with histopathologic correlation. J Ultrasound Med. 2009; 28:911-20.

61 Williams G, Fletcher JT, Alexander SI, Craig JC. Vesicoureteral reflux. J Am Soc Nephrol. 2008; 19:847-62.

62 Zimbaro G, Ascenti G, Visalli C, Bottari A, Zimbaro F, Martino N, Mazziotti S. Contrast-enhanced ultrasonography (voiding urosonography) of vesicoureteral reflux: state of the art. Radiol Med. 2007; 112:1211-24.

63 Montini G, Tullus K, Hewitt I. Febrile urinary tract infections in children. New Engl J Med. 2011; 365:239-250.

64 Karmazyn B, Coley BD, Binkovitz LA, Dempsey-Robertson ME, Dillman JR, Dory CE, et al. American College of Radiology Appropriateness Criteria® Urinary Tract Infection - Child. [online publication]. Reston (VA): American College of Radiology, 1995. Updated 2012. Available at: https://acsearch.acr.org/docs/69444/Narrative/

65 Tekgül S, Riedmiller H, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, Stein R, Dogan HS, European Assoc. Urology. EAU guidelines on vesicoureteral reflux in children. Eur Urol. 2012; 62:534-42.

66 Ascenti G, Zimbaro G, Mazziotti S, Chimenz R, Fede C, Visalli C, Scribano E. Harmonic US imaging of vesicoureteric reflux in children: usefulness of a second generation US contrast agent. Pediatr Radiol. 2004; 34:481-87.

67 Wong LS, Tse KS, Fan TW, Kwok KY, Tsang TK, Fung HS, et al. Voiding urosonography with second-generation ultrasound contrast versus micturating cystourethrography in the diagnosis of vesicoureteric reflux. Eur J Pediatr. 2014; 173:1095-1101.

several guidance documents have provided recommendations on when to use the product in the management of paediatric patients with suspected VUR.[71,72, 40]

Part II: Module SII - Non-clinical part of the safety specification

A summary of the important non-clinical safety findings is reported in Part II Module SII Table 1 below.

Part II Module SII Table 1: Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Toxicity ***Single dose toxicity*** Single-dose toxicity studies were performed in rats and monkeys using a dose of 20 mL/kg, equivalent to more than 600 times the human dose in mL/kg. No deaths nor clinical findings, changes in body weight, food consumption, blood pressure or lesions in the internal organs, attributable to SonoVue were observed in these studies.	No relevance to human usage. The dose of 20 mL/kg was selected as the highest volume that can reasonably be injected in these animals. This dose corresponds to more than 600 times the human dose in mL/kg and to 114 times the human dose in mL/m^2 in the rat and 275 times in the monkey. For human use the approved dose of SonoVue in the final formulation is very small so that the expected dosage for human use (0.03 mL/kg) is well below the dose used in animals in single-dose studies.

[68] Ključevšek D, Battelino N, Tomažič M, Kersnik Levart T. A comparison of echo-enhanced voiding urosonography with X-ray voiding cystourethrography in the first year of life. Acta Paediatr. 2012; 101:e235-9.

[69] Kis E, Nyitrai A, Várkonyi I, Máttyus I, Cseprekál O, Reusz G, Szabó A. Voiding urosonography with second-generation contrast agent versus voiding cystourethrography. Pediatr Nephrol. 2010; 25:2289-93.

[70] Papadopoulou F, Anthopoulou A, Siomou E, Efremidis S, Tsamboulas C, Darge K. Harmonic voiding urosonography with a second-generation contrast agent for the diagnosis of vesicoureteral reflux. Pediatr Radiol. 2009; 39:239-44.

[71] Piscaglia F, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, et al. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschall Med. 2012; 33:33-59.

[72] Riccabona M, Vivier P-H, Ntoulia A, Darge K, Avni F, Papadopoulou F, Damasio B, et al. ESPR uroradiology task force imaging recommendations in paediatric uroradiology, part VII: standardised terminology, impact of existing recommendations, and update on contrast-enhanced ultrasound of the paediatric urogenital tract. Pediatr Radiol. 2014; 44:1478-84.

Part II Module SII Table 1: Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Repeat-dose toxicity Four-week repeat-dose toxicological studies were performed in rats and monkeys using daily doses of 0.2, 1.0 and 5.0 mL/kg. There were no changes or consistent pattern of changes indicating an adverse effect of SonoVue in vital signs, body weights, food consumption, ophthalmoscopy, haematology, clinical chemistry, urine analysis, or organ weights during the studies, except for 3 deaths in one study with rats, all in animals in the 5 mL/kg cohort (1 control and 2 treated). These deaths were considered related to the stress of a large volume injection and not related to the test article. The only treatment-related change observed was inflammation in the cecum and sometimes colon in one study with rats when the animals were sacrificed at the end of the 28-day repeat-dose treatment. The finding was observed in all treated groups, but appeared to be dose-related only in females and not in males. However, the cecum or colon lesions were not observed in the rats that were assigned to the group with a treatment-free period after the 28-day treatment and could not be reproduced in a second repeated-dose study in rats designed to verify the occurrence of these lesions. No other findings related to the repeated administration of SonoVue to rats and monkeys for 28 days were observed in internal organs by microscopic examinations.	No relevance to human usage. Since SonoVue is a diagnostic agent for ultrasound imaging it will not be administered on a daily basis in patients. SonoVue is a transpulmonary echocardiographic contrast agent that does not diffuse into the extravascular compartment, but remains within the vasculature until the gas dissolves in the blood and is eliminated in the expired air. Therefore even if repeated SonoVue-enhanced ultrasound exams are needed in a short time frame no cumulative or carry over effects of SonoVue are expected. This phenomenon of microbubble size enlargement depends very much on the intestinal wall thickness, which scales with animal size. The phenomenon of local microbubble aggregation and accumulation and the subsequent microbubble size enlargement depends very much on the intestinal wall thickness, which scales with animal size. The studies reported that the phenomenon occurred in mice and rats, but not in rabbits, dogs, guinea pigs, or humans.[73,74,75]
Local Tolerance – Intravenous administration No adverse effects of SonoVue were observed in a local tolerance study performed in rabbits after intravenous injection of 10 mL/animal or after paravenous injection of 0.5 mL/animal.	No relevance to human usage. The recommended dose of SonoVue is 2-2.4 mL administered as an intravenous bolus injection. During a single examination, a second injection may be administered to prolong contrast enhancement. Each SonoVue injection is followed with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection. No findings in clinical trials or post-marketing surveillance data have revealed any signs of potential local toxicity in humans following an intravenous injection of SonoVue. As a relatively small volume of the contrast agent is injected in humans (0.03 mL/kg body weight) and the product osmolality is that of the physiologic saline used to reconstitute the product, the local effects in case of paravascular application are negligible. Minimal space occupying effects but not osmotic effects may occur. These effects are mild in intensity and usually do not require local or symptomatic measures for treatment. They mostly concern pain or an unusual sensation at the site of injection.

[73] Rasmussen H, Dirven HA, Grant D, Johnsen H, Midtvedt T. Etiology of cecal and hepatic lesions in mice after administration of gas-carrier contrast agents used in ultrasound imaging. Toxicol Appl Pharmacol 2003;188:176–184.

[74] Dirven HA, Rasmussen H, Johnsen H, Videm S, Walday P, Grant D. Intestinal and hepatic lesions in mice, rats, and other laboratory animals after intravenous administration of gas-carrier contrast agents used in ultrasound imaging. Toxicol Appl Pharmacol 2003;188:165–175.

[75] Wong KK, Huang I, Kim YR, Tang H, Yang ES, Kwong KK, Wu EX. In vivo study of microbubbles as an MR susceptibility contrast agent. Magn Reson Med. 2004 Sep;52(3):445-52.

Part II Module SII Table 1: Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Local tolerance - Intravesical administration Local tolerance was evaluated in rats after intravesical administration via catheterisation of the urethra. A single-dose study and a repeat-dose study, both followed by a treatment-free period, were performed in female rats divided into 3 dose groups of 10 animals (5 animals per sacrifice time points). The high dose group was administered 1 mL of native SonoVue into the urinary bladder. Macroscopic and histopathological examination of both kidneys and ureters, the urinary bladder and the urethra did not reveal any test item-related lesions in any of the examined organs, in particular in the urinary bladder, in both the single-dose and the repeat-dose studies.	No relevance to human usage. SonoVue was well tolerated in the rat after intravesical administration.
Reproductive and Developmental Toxicity SonoVue did not demonstrate any reproductive/developmental toxicity in studies in rats and rabbits at daily doses of 0.2, 1.0 and 5.0 mL/kg equivalent to more than 6, 30 and 160 times, respectively, the human dose in mL/kg. In rats, 5 mL/kg correspond to approximately 20 times the human dose based on body surface area. In rabbits, 5 mL/kg correspond to approximately 40 times the human dose based on body surface area. However, after repeated administration of SonoVue in pregnant rats in a pre- and post-natal study, a low incidence of caecal lesions was observed at the end of the lactation period. The finding was considered to be species-specific, not related to SonoVue and not relevant to human. Similar findings were observed in rodents treated with other approved gas carrier ultrasound contrast agents, such as Optison® and Levovist®.[73,74,75]	No relevance to human usage. SonoVue did not exert any adverse effect on reproduction as demonstrated by the fertility and embryo-toxicity studies performed in rats and in rabbits at the same doses as the repeated dose studies. The finding of low-incidence caecal lesions observed after repeated administration of SonoVue was considered to be species-specific to rodents, not related to SonoVue and not relevant to human. Since SonoVue is a diagnostic agent for ultrasound imaging it will not be administered on a daily basis in humans in clinical routine. This additionally enlarges the safety margin demonstrated in animal testing.
Nephrotoxicity Potential nephrotoxicity was assessed by clinical evaluation, organ and body weight, haematology, clinical chemistry, urinalysis, macroscopic and microscopic examination during the 4-week repeat-dose toxicity studies in rats and monkeys, as mentioned above. There was no evidence of nephrotoxicity related to SonoVue. In addition, a study on renal function in rats showed that SonoVue at doses of both 0.3 and 1 mL/kg had no significant effects on urine volume and the amount of urinary electrolytes (Na+, K+ and Cl-).	No relevance to human usage. The product does not undergo any elimination path dependent upon renal function. There is no evidence of potential nephrotoxicity related to SonoVue in humans.
Hepatotoxicity Potential hepatotoxicity was assessed by clinical evaluation, organ and body weight, haematology, clinical chemistry, urinalysis, macroscopic and microscopic examination during the 4-week repeat-dose toxicity studies in rats and monkeys, as mentioned above. There was no evidence of hepatotoxicity related to SonoVue.	No relevance to human usage.
Genotoxicity In the in vitro bacterial reverse mutation assays and chromosomal aberration assays, SonoVue did not demonstrate any mutagenic or clastogenic potential.	No relevance to human usage. SonoVue has been shown to be non-mutagenic in all test systems investigated in animals.

Part II Module SII Table 1: Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
General safety pharmacology: ***Central Nervous System*** An Irwin test performed in rats showed that SonoVue evaluated up to the dose level of 3 mL/kg intravenously did not produce biologically relevant effects on behaviour, physiological state and on body temperature. In addition, SonoVue, at doses up to 3 mL/kg, did not have any significant effects on the acetic acid writhing test, a test used in rats to evaluate peripheral analgesic activity. In a series of studies in mice, it was shown that SonoVue at 0.3 and 1 mL/kg had no effect on spontaneous locomotor activity or on body temperature, no synergistic or anticonvulsive effect on pentylenetetrazole-induced convulsion, no effect on pentobarbital-induced anaesthesia and no effect on intestinal transit time.	No relevance to human usage.
Cardiovascular (including potential for QT interval prolongation) Single-dose studies in the rat and in the rabbit demonstrated that SonoVue at doses of 0.3 or 1 mL/kg had no effect on heart rate, blood pressure or arterial blood gases. Studies in the dog showed that SonoVue at a dose of 0.3 mL/kg did not induce any changes in systemic arterial pressure or haematology parameters. At the dose of 1 mL/kg, hypotension and thrombocytopenia/leucopenia was observed in some of the animals. The effect was transient and the dogs recovered quickly (10 minutes and 2 hours, respectively).	No relevance to human usage.
A study measuring the effects on electrocardiogram (ECG) and ultrasound exposure at various mechanical index (acoustic pressure) values was performed in the dog at dose levels of 0.1, 0.3 and 1 mL/kg of SonoVue. In seven out of eight treated animals no effect was observed on ECG parameters, i.e., RR, PR, QT, QTc and QRS complex duration, whatever the dose of SonoVue and the intensity of the ultrasound exposure. There were no treatment-related microscopic findings in the heart of these animals. A study was performed in a canine model of pulmonary hypertension. Cumulative doses of SonoVue (0.1, 0.3 and 1 mL/kg) administered at 15 min intervals had no effects on arterial blood pressure, heart rate and on QT and QTc intervals of the ECG. Additionally, myocardial and pulmonary functions were not modified. At the highest dose, a transient increase in pulmonary arterial pressure was observed between 5 to 7 minutes after the administration. A review of the microscopic findings of the toxicology studies did not indicate a pulmonary safety concern at high multiples of human exposure. A study examined the effects of SonoVue (1, 2 or 5 mL/kg) on clinical signs, arterial blood pressure, heart rate, locomotor activity, parameters of the ECG (RR, PR, QT, QTc and QRS complex duration) and body temperature in the cynomolgus monkey monitored by telemetry. No treatment-related effects were observed.	No relevance to human usage.

Part II Module SII Table 1: Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
General safety pharmacology (cont'd): ***Cardiovascular*** (including potential for QT interval prolongation) (cont'd) In addition, cardiovascular parameters were studied in cynomolgus monkeys during the single and repeat-dose toxicity studies. No changes in systemic arterial blood pressure, heart rate were noted at doses up to 20 mL/kg and no effects on ECG parameters were seen at doses up to 5 mL/kg.	
Respiratory System Single-dose studies in the rat and in the rabbit showed that SonoVue at doses of 0.3 or 1 mL/kg did not cause significant changes of pulmonary parameters, namely airways resistance and lung compliance.	No relevance to human usage.
Microcirculation The effect of SonoVue (3.8 or 7.6 mL/kg) on microcirculation was studied using the hamster cheek pouch model. No apparent interruption of the microvascular blood flow, no apparent modification of the diameter of the arterioles, no microvascular permeability to macromolecules and no tendency for leukocytes to adhere to vessels were noticed.	No relevance to human usage. Microbubbles in SonoVue have a mean diameter of 2.5 µm with 90% of them being smaller than 8 µm and 99% having a diameter of less than 10 µm. Mean bubble size is very stable over time after reconstitution. Therefore, the majority of the microspheres, which are smaller than a red blood cell, can pass through the pulmonary vasculature and are small enough to prevent trapping in the capillary vasculature and any risk of gas microembolism.
SonoVue (1 mL/kg) did not induce any cerebral ischaemic lesion after intracarotid injection in the rat, as assessed by histology and the neuron-specific enolase (a marker of neuronal degeneration) assay. The microvascular behavior of SonoVue microbubbles and the extent of microbubble retention were evaluated in a *spinotrapezius* microcirculation study. There were no substantial changes in arteriolar, venular and capillary blood flow. A small number of microbubbles were transiently retained in capillaries, but not in postcapillary venules. All bubbles were dislodged and/or dissolved within 20 min after administration. There was no evidence of red blood cell modification or of leukocyte or platelet adhesion at the site of retainment, nor of thrombosis. In addition, there were no effects on microvasculature in histological samples from any of the toxicology studies, including repeat-dose rat and monkey studies.	No relevance to human usage. Due to the very small total bubble volume in SonoVue administered to humans (the total volume of sulphur hexafluoride in the bubbles is around 5 µL/mL), the quantity of gas bubbles administered remains extremely low even at the highest doses, typically less than 12 µL per subject which applies to 2.4 mL standard dose and 25 µL for the 5 mL maximum dose.
Mechanisms for drug interactions Single-dose studies were performed in rats to investigate possible interactions of SonoVue with drugs that might be commonly used by patients undergoing contrast ultrasound examinations. The drugs studied were propranolol, captopril, nifedipine, isosorbide dinitrate, heparin and digoxin. No drug-drug interactions were observed. Additionally, SonoVue did not interact with the anti-platelet activity of aspirin in an in vitro study	No relevance to human usage. No effect of SonoVue on concomitantly administered medications is to be expected as: - SonoVue dosing in man occurs on one day only and as a single administration - The kinetics studies conducted in humans showed very rapid clearance (a few minutes) of SonoVue following its intravenous administration

Part II Module SII Table 1: Summary of Key Safety Findings from Non-clinical Studies

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Mechanisms for drug interactions (cont'd)	- There was no apparent relationship with respect to occurrence of adverse events in clinical studies for patients receiving various categories of the most common concomitant medications. Neither signs nor trends showing a potential safety hazard could be identified in the clinical study database for patients who concomitantly received other commonly used drugs.
Effects on the Complement System Animal and in vitro studies suggest that complement activation may represent a possible mechanism for hypersensitivity reactions to SonoVue. However, detailed pathological pathway by which complement activation triggers the reaction is unclear. In animal model, pulmonary intravascular macrophages and thromboxane are possibly involved but not in humans where transient changes in mast-cell/basophil susceptibility may be involved in development of the reactions. Functional in vitro tests are performed to mimic in vitro the contact between allergens and the cells responsible for symptoms of anaphylaxis, i.e., those possessing the ability to release histamine. Basophils are considered as equivalent to symptoms of anaphylaxis, i.e., those possessing the ability to release histamine.	The mechanism for hypersensitivity reactions to SonoVue has not been elucidated, however hypersensitivity to any of the components of SonoVue, as for other contrast agents, cannot be excluded, and there is potential for unpredictable, hypersensitivity reactions, as evident from the clinical trial and postmarketing experience.
Basophils are considered as equivalent to tissue mast cells since they play, by themselves, a pivotal role in the immediate allergic reaction. Consequently, functional in vitro tests for allergic reactions are focused on circulating basophils. An in vitro study using human blood samples to identify biomarkers of immediate hypersensitivity reaction to SonoVue demonstrated that SonoVue induced no basophil activation in the 5 to 455 µg/mL concentration range. Only 5 out of the 100 donor blood samples displayed repeatable, significant basophil activation in both the primary and secondary assays at the highest concentration of SonoVue (10% of the blood volume), which is over 200 times the concentration achieved in the clinical situation (0.048% or 2.4 mL SonoVue in about 5 L blood). No basophil activation was observed at concentrations of 1% or 0.1% of the blood volume. This study shows that any hypersensitivity reaction to SonoVue administration is not caused by a direct activation of basophils.	
Special Population A study was conducted in a model of acute pulmonary hypertension in anesthetised dogs. In this study, SonoVue did not have any adverse effects on arterial blood pressure, heart rate and QT/QTc intervals and did not modify myocardial or pulmonary functions. Only transient increase in pulmonary arterial pressure at 5 to 7 minutes post-dosing was observed.	Intravenous use of SonoVue is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome.

Non-clinical toxicology studies performed with SonoVue demonstrated that this product is well tolerated following single and repeated intravenous injections. The only remarkable finding in animals following intravenous administration of SonoVue was a reversible inflammation of the

cecum in rats in a 28 day repeat-dose study. This observation was considered related to the unique anatomy/physiology of this organ in rodents and has also been reported with other microbubble contrast agents. The findings in rats were also not reproduced in a second 28-day toxicology study in this species. SonoVue was devoid of genetic toxicity, did not show reproductive or developmental toxicity and did not induce histopathological findings in the immune system during the 4 weeks of repeated dose toxicity studies. A venous and paravenous injection study in rabbits demonstrated that SonoVue had a good local tolerance.

SonoVue was also well tolerated in the rat after single and repeated intravesical administrations.

The available non-clinical data document the effects in animals and additional non-clinical studies are not required. Non-clinical data reveal no special hazard for humans based on conventional safety pharmacology and toxicity studies. Indeed, pre-clinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure so as to indicate little relevance to clinical use.

A summary of the important non-clinical safety findings is reported in Part II Module SII Table 2 below.

Part II Module SII Table 2: Safety concerns

Safety concerns	
Important identified risks (confirmed by clinical data)	• Hypersensitivity to any of the excipients of SonoVue
Important potential risks (not refuted by clinical data or which are of unknown significance)	• None
Missing information	• None

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

SonoVue is an ultrasound contrast agent developed by Bracco International B.V., the product's Marketing Authorisation Holder (MAH) for intravenous use in echocardiography, Doppler sonography of arterial and venous vessels, Doppler sonography of tissue microcirculation, and the evaluation of known or suspected VUR in paediatric patients after intravesical administration of SonoVue.

SonoVue was first approved under the centralised procedure in the EU on 26 March 2001 (International Birth Date; IBD) by the European Commission; this marketing authorisation is also valid for EEA countries, which as of 01 January 2021 following Brexit excludes Great Britain but includes United Kingdom (Northern Ireland).

Outside the EEA, SonoVue has been registered in Switzerland, Singapore, China, Hong Kong, Republic of Korea, Canada, India, Russian Federation, Brazil, the United States, Israel, Mexico, Taiwan, and United Kingdom.

SonoVue is currently registered in 44 countries worldwide. The indications registered in all countries are presented below.

EEA countries (comprises United Kingdom [Northern Ireland])	Adult population Echocardiography, Doppler of macrovasculature, and Doppler of microvasculature. Paediatric population Ultrasonography of the urinary tract in paediatric patients from newborn to 18 years for the detection of suspected or known VUR.
United Kingdom	Adult population Echocardiography, Doppler of macrovasculature, and Doppler of microvasculature. Paediatric population Ultrasonography of the urinary tract in paediatric patients from newborn to 18 years for the detection of suspected or known VUR.
China, Republic of Korea	Adult population Echocardiography, Doppler of macrovasculature, Doppler of microvasculature, Hysterosalpingo-contrast sonography. Paediatric population Ultrasonography of the urinary tract in paediatric patients from newborn to 18 years for the evaluation of suspected or known VUR.
India	Adult population Echocardiography, Doppler of macrovasculature, and Doppler of microvasculature.
Singapore	Adult population Echocardiography, Doppler of macrovasculature, and Doppler of microvasculature. Paediatric population Ultrasonography of the urinary tract in paediatric patients from newborn to 18 years for the detection of suspected or known VUR.
Hong Kong, Israel, Russia, Brazil	Adult population Echocardiography, Doppler of macrovasculature, and Doppler of microvasculature.
Switzerland	Adult population Echocardiography, Doppler of macrovasculature, and Doppler of microvasculature. Paediatric population Ultrasonography of the urinary tract in paediatric patients from newborn to 18 years for the detection of suspected or known VUR.
Taiwan	Echocardiography: SonoVue is indicated for use in adult patients with suboptimal (2 or more adjacent segments cannot be visualised) echocardiograms to opacify the LV chamber and to improve the delineation of the LV endocardial border. Ultrasonography of the Liver: SonoVue is indicated for use with ultrasound of the liver in adult patients to characterise focal liver lesions.

Canada	Adult population Echocardiography and Doppler of macrovasculature. Paediatric population Assessment of VUR indicated for use in ultrasonography of the urinary tract in paediatric patients for the evaluation of suspected or known VUR.
United States (trade name “Lumason”)	Adult and paediatric population Suboptimal echocardiograms to opacify the LV chamber and to improve the delineation of the LV endocardial border. Adult and paediatric population Ultrasound of the liver to characterise focal liver lesions. Paediatric population Ultrasonography of the urinary tract in paediatric patients for the evaluation of suspected or known VUR.
Mexico	Echocardiography SonoVue is a transpulmonary echocardiographic contrast product for use in patients with cardiovascular disease established or suspected to provide opacity of the cardiac chambers and highlight border delineation LV endocardiac. Macrovasculature Doppler SonoVue increases accuracy in detecting or excluding abnormalities in the cerebral and carotid arteries extracranial or peripheral arteries improving the Doppler signal-to-noise ratio. SonoVue increases the quality of the Doppler flow image and the duration of this improved and clinically useful signal in examination of the portal vein. Microvasculature Doppler SonoVue improves the vision of the vascularisation of liver lesions (in adult and paediatric patients) and breast during Doppler ultrasound, providing a more specific characterisation of the lesion. Ultrasonography (sonography) of the excretory urinary tract SonoVue is indicated for use in urinary tract ultrasonography in paediatric patients from newborns up to 18 years for evaluation of suspected or known VUR.

The overall clinical development programme performed in Europe, North America and Asia to assess the safety and diagnostic efficacy of SonoVue in the above indications comprises a total of 80 clinical studies which had been completed by 30 June 2025 and are pooled for purposes of safety data presentations.

Most of these studies (29 studies) were conducted in cardiologic indications (including delineation of endocardial borders in patients undergoing B-mode transthoracic echocardiography, myocardial perfusion evaluation in patients with ischaemic heart disease, enhancement of left chamber Doppler echocardiography in patients with mitral regurgitation, and cardiac electrophysiology assessments in patients with CAD undergoing enhanced B-mode echocardiography) or for Doppler diagnostic assessment of parenchymal focal lesions, i.e. microvasculature, (30 studies) including characterisation of FLLs and monitoring of response to local treatment of FLLs as well as detection and characterisation of breast lesions microcirculation. In addition, special population studies were conducted in patients with

congestive heart failure, chronic obstructive pulmonary diseases, diffuse interstitial pulmonary fibrosis and pulmonary hypertension, respectively.

The SonoVue clinical trial programme also includes 1 completed study (BR1-026) involving re-challenge dosing in subjects who had received SonoVue in previous clinical trials, 1 completed case-control study (BR1-124) in subjects who experienced hypersensitivity reactions after being administered with SonoVue in post-marketing clinical use. One additional clinical study (BR1-146) evaluating the diagnostic performance of SonoVue in Hysterosalpingo-Contrast Sonography for the assessment of fallopian tube occlusion using laparoscopy with chromotubation as the truth standard has been completed but is not yet integrated into the safety database.

In addition, one Phase III clinical study is currently being conducted to evaluate bolus versus continuous infusion of Lumason (SonoVue) in healthy volunteer patients with sub-optimal unenhanced echocardiography in the United States.

The 80 completed studies included in the current safety summary are listed in Part II Module SIII Table 1 below. Synopses of these studies, the one clinical study not yet integrated in the safety database, and the one ongoing clinical study are presented in Annex 4.

Part II Module SIII Table 1: Clinical Studies Completed in the SonoVue Clinical Development Programme as of 30 June 2025

Population	No. of Studies	No. of Treated Subjects		
		SonoVue[a]	Control Only	Total
All Completed Studies[b]	80	7341	162	7503
Healthy Volunteers[c]	8	128	30[d]	158
All Patients	72	7213	132	7345
Cardiac Population	29	2819	126[e]	2945
Macrovascular Population	9	555	0	555
Microvascular Population	30	3765	0	3765
Special Patient Populations	4	74	6[d]	80

[a] Received SonoVue only or SonoVue plus control in crossover studies; included as SonoVue subjects in all summary data displays.
[b] Completed studies are those for which a final clinical trial report was available as of 30 June 2025 and included in the Integrated Safety Database.
[c] Clinical PK and pilot efficacy studies in non-patient volunteers.
[d] Saline.
[e] Albunex/saline.

SIII.2 Clinical trial exposure

As for all contrast media for ultrasound examinations, SonoVue dosing in humans occurs over 1 day only, mostly as a single administration. Therefore data on duration of exposure are not applicable for this product.

A total of 7341 subjects were exposed to SonoVue in the 80 clinical studies included in the Integrated Safety Database. Of these subjects, 128 were adult healthy volunteers (or with no

disease in the area of interest) and 7201 were adult and 12 were paediatric patients with medical conditions referred for a CEUS examination, namely: 2819 subjects underwent a SonoVue-enhanced echocardiographic examination, 555 underwent Doppler sonography of arterial and venous vessels with SonoVue, 3765 underwent Doppler sonography of tissue microcirculation with SonoVue, and 74 who were examined in the Special Patient Population. In addition, in these clinical trials, 162 subjects have been exposed either to a comparator drug (Albunex) or to placebo (saline).

Safety data were pooled and evaluated in a total of 7341 subjects who were studied in Phase I to Phase IV clinical trials with SonoVue in Europe, North America and Asia. These studies were undertaken to assess the safety, pharmacokinetics, and efficacy of SonoVue at doses from less than 1 mL to over 50 mL. The majority of the subjects (over 76%) received a cumulative dose up to 10 mL while the remaining received cumulative doses up to 50 mL (22%) or over (2%).

The patients included in the pooled clinical trial safety database are representative of the conditions of use of an ultrasound contrast agent. The pooled data consists of adverse event data for 14 patients from age 0 to 17 years (0.2%), 4306 adult patients between the age of 18 and 65 years (59%) and 2817 patients above 65 years of age (38%). Two patients were of unknown age. Besides patients, also 128 (2.0%) adult healthy volunteers are included in the pooled clinical database since they represent a portion of the population that is exposed to SonoVue to confirm or exclude a diagnosis of disease. Finally, the SonoVue Integrated Clinical Trials Safety Database also includes studies performed in special populations with congestive heart failure, chronic obstructive pulmonary diseases, diffuse interstitial pulmonary fibrosis and pulmonary hypertension, respectively (0.2%).

The exposure data from clinical trials with SonoVue are provided for all patients (both blinded and open label studies are included) and by indication in Part II Module SIII Table 2 to Part II Module SIII Table 6 below.

Part II Module SIII Table 2: Exposure by Age Group and Gender (by Indication)

	Number (%) of Subjects			
Overall population	**Males**	**Females**	**Unknown**	**Total**
Age group (indication: Echocardiography)	**1998 (70.9)**	**821 (29.1)**	**0**	**N**=2819 [a]
Children (0 to 5 years)	0	0	0	0
Children (6 to 11 years)	0	1 (<0.1)	0	1 (<0.1)
Adolescents (12 to 17 years)	5 (0.2)	6 (0.2)	0	11 (0.4)
18-40 years	66 (2.3)	26 (0.9)	0	92 (3.3)
41-64 years	1085 (38.5)	360 (12.8)	0	1445 (51.3)
65-74 years	614 (21.8)	309 (11.0)	0	923 (32.7)
75-84 years	216 (7.7)	112 (4.0)	0	328 (11.6)
≥85 years	12 (0.4)	7 (0.3)	0	19 (0.7)
Unknown	0	0	0	0

Part II Module SIII Table 2: Exposure by Age Group and Gender (by Indication)

	Number (%) of Subjects			
Overall population	**Males**	**Females**	**Unknown**	**Total**
Age group (indication: Macrovasculature)	**341 (61.4)**	**213 (38.3)**	**1 (0.2)**	**N=555** [a]
<18 years	0	0	0	0
18-40 years	25 (4.5)	14 (2.5)	0	39 (7.0)
41-64 years	157 (28.3)	85 (15.3)	0	242 (43.6)
65-74 years	103 (18.6)	57 (10.3)	0	160 (28.8)
75-84 years	49 (8.8)	54 (9.7)	0	103 (18.6)
≥85 years	7 (1.3)	3 (0.5)	0	10 (1.8)
Unknown	0	0	1 (0.2)	1 (0.2)
Age group (indication: Microvasculature)	**2182 (58.0)**	**1583 (42.0)**	**0**	**N=3765** [a]
<18 years	0	2 (0.1)	0	2 (0.1)
18-40 years	157 (4.2)	334 (8.9)	0	491 (13.0)
41-64 years	1163 (30.9)	834 (22.2)	0	1997 (53.0)
65-74 years	652 (17.3)	287 (7.6)	0	939 (24.9)
75-84 years	201 (5.3)	117 (3.1)	0	318 (8.5)
≥85 years	8 (0.2)	9 (0.2)	0	17 (0.5)
Unknown	1 (<0.1)	0	0	1 (<0.1)

NOTE: This table excludes Healthy Volunteers and Patients included in studies performed in Special Patient Populations.
[a] Denominator for percentages by indication.

Part II Module SIII Table 3: Exposure by Age Group and Gender (Total Population)

	Number (%) of Subjects			
Overall population	**Males**	**Females**	**Unknown**	**Total**
Total	**4521 (63.3)**	**2617 (36.7)**	**1 (<0.1)**	**N=7139**[a]
Paediatric Population (<18 years)	**5 (0.1)**	**9 (0.1)**	**0**	**N=14**
Children (0 to 5 years)	0	0	0	0
Children (6 to 11 years)	0	1 (<0.1)	0	1 (<0.1)
Adolescents (12 to 17 years)	5 (<0.1)	8 (0.1)	0	13 (0.2)
Unknown	0	0	0	0
Adult Population (≥18 years)	**4516 (63.3)**	**2608 (36.5)**	**1 (<0.1)**	**N=7125**
Adults (18 to 40 years)	248 (3.5)	374 (5.2)	0	622 (8.7)
Adults (41 to 64 years)	2405 (33.7)	1279 (17.9)	0	3684 (51.6)
Elderly (≥ 65 years)	1862 (26.1)	955 (13.4)	0	2817 (39.5)
65-74 years	1369 (19.2)	653 (9.2)	0	2022 (28.3)
75-84 years	466 (6.5)	283 (4.0)	0	749 (10.5)
85+ years	27 (0.4)	19 (0.3)	0	46 (0.6)
Unknown	1 (<0.1)	0	1 (<0.1)	2 (<0.1)

NOTE: This table excludes Healthy Volunteers and Patients included in studies performed in Special Patient Populations.
[a] Denominator for percentages.

Part II Module SIII Table 4: Exposure by Dose and Population (by Indication)

Dose of exposure	Number (%) of Subjects
Dose of exposure (indication: Echocardiography)	**N=2821**[a]
≤1 mL	61 (2.2)
>1 –5 mL	828 (29.4)
>5 –10 mL	828 (29.4)
>10 –50 mL	1000 (35.4)
>50 mL	101 (3.6)
Unknown	3 (0.1)
Dose of exposure (indication: Doppler of Macrovasculature)	**N=555** [b]
≤1 mL	2 (0.4)
>1 –5 mL	437 (78.7)
>5 –10 mL	86 (15.5)
>10 –50 mL	29 (5.2)
>50 mL	1 (0.2)
Unknown	0
Dose of exposure (indication: Doppler of Microvasculature) [c]	**N=3733** [b]
≤1 mL	163 (4.4)
>1 –5 mL	2344 (62.8)
>5 –10 mL	704 (18.9)
>10 –50 mL	509 (13.6)
>50 mL	13 (0.4)
Unknown	0

NOTE: This table excludes Healthy Volunteers and Patients included in studies performed in Special Patient Populations.

[a] Denominator for total population (includes paediatric and adult subjects)

[b] Denominator for total population (includes only adult subjects)

[c] Excludes Study BR1-129 (n=30), as the study design had multiple visits, 2-8 weeks apart, which made it very different from all the other studies being summarised. All patients in this study received between one and two 2.4-mL bolus injections of SonoVue per study visit.

Part II Module SIII Table 5: Exposure by Dose (Total Population)

Cumulative Dose	Number (%) of Subjects
TOTAL POPULATION [a]	**N=7109** [b]
≤1 mL	226 (3.2)
>1 – 5 mL	3609 (50.8)
>5 – 10 mL	1618 (22.8)
>10 – 50 mL	1538 (21.6)
>50 mL	115 (1.6)
Unknown	3 (<0.1)

Part II Module SIII Table 5: Exposure by Dose (Total Population)

TOTAL PAEDIATRIC (<18 years) POPULATION	**N=14** [c]
≤1 mL	1 (7.1)
>1 – 5 mL	13 (92.9)
>5 – 10 mL	0
>10 – 50 mL	0
>50 mL	0
Unknown	0
TOTAL ADULT (≥18 years) POPULATION [a]	**N=7095** [d]
≤1 mL	225 (3.2)
>1 – 5 mL	3596 (50.7)
>5 – 10 mL	1618 (22.8)
>10 – 50 mL	1538 (21.7)
>50 mL	115 (1.6)
Unknown	3 (<0.1)

NOTE: This table excludes Healthy Volunteers and Patients included in studies performed in Special Patient Populations.

[a] Excludes Study BR1-129 (n=30), as the study design had multiple visits, 2-8 weeks apart, which made it very different from all the other studies being summarised. All patients in this study received between one and two 2.4-mL bolus injections of SonoVue per study visit.

[b] Denominator for all patients (paediatric and adult)

[c] Denominator for paediatric population

[d] Denominator for adult population

Part II Module SIII Table 6: Special Populations

	Number (%) of Subjects in Total Population (N=7341 [a]**)**
Special population	
Congestive heart failure study	13 (0.2)
Chronic obstructive pulmonary disease study	12 (0.2)
Diffuse interstitial pulmonary fibrosis study	13 (0.2)
Pulmonary hypertension study	36 (0.5)
Pregnant women	Not included in clinical trials
Elderly Patients (age ≥65 years)	2817 (38.4)
Paediatric Patients (age <18 years)	14 (0.2)

Note: The age groups exclude Healthy Volunteers and Patients included in studies performed in Special Patient Populations.

[a] Denominator for percentages.

Part II: Module SIV - Populations not studied in clinical trials

SonoVue was first approved in March 2001. Clinical trials have been conducted both pre-approval and post-approval. This section represents the knowledge on the patients studied up to 30 June 2025.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion 1, Any known allergy to one or more of the ingredients of the investigational product

Reason for exclusion: According to **Section 4.3** of the Summary of Product Characteristics (SmPC), SonoVue should not be administered to patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue such as polyethylene glycol (PEG).

Included as missing information?: No

Rationale: Serious hypersensitivity reactions have been observed during or shortly following SonoVue administration in patients with no prior exposure to sulphur hexafluoride microbubble products, including patients with prior hypersensitivity reaction(s) to macrogol, also known as PEG.

SonoVue contains PEG. There may be increased risk of serious reactions in patients with prior hypersensitivity reaction(s) to PEG.

It is recommended to keep all patients under close medical supervision during and for at least 15 minutes following the administration of SonoVue to monitor the risk of serious hypersensitivity reactions.

Criterion 2, Known right-to-left shunts

Reason for exclusion: Section 4.3 of the SmPC indicates that SonoVue is contraindicated in patients known to have right-to-left shunts.

Included as missing information?: No

Rationale: Risk of systemic embolisation with SonoVue has not been studied in humans with right-to-left, bi-directional, or transient right-to-left cardiac shunts.

Criterion 3, Renal or hepatic impairment

Reason for exclusion: Section 4.4 of the SmPC recommends caution when administering the product to patients with, among other diseases, end-stage renal or hepatic disease, as the numbers of patients with those conditions who were exposed to SonoVue in the clinical trials were limited.

Included as missing information?: No

Rationale: There are no studies in these patient populations as these special populations are not relevant for SonoVue, because the kidney and liver are organs that are not involved in the elimination of the product after intravenous or intravesical injection.

Criterion 4, **Pregnancy and lactation**

Reason for exclusion: Pregnant or lactating women were excluded from all SonoVue clinical trials, as they are from most drug trials, due to the potential risk of harm to the foetus or nursing infant.

Included as missing information?: Yes

Rationale: There are no clinical data for the use of SonoVue in pregnant or lactating women. Reproduction studies have been performed in animals at doses up to at least 20 and 40 the human dose based on body surface area in rats and rabbits, respectively (see Part II Module SII Table 1). These studies revealed no evidence of impaired fertility or harm to the foetus due to SonoVue. Because animal reproduction studies are not always predictive of human response, **Section 4.6** of the SmPC states that as a precautionary measure, it is preferable to avoid the use of SonoVue during pregnancy.

It is not known whether SonoVue is excreted in human milk. However, **Section 4.6** of the SmPC underlines that, based on its rapid elimination from the body via the expired air, it is considered that the breastfeeding can be resumed two to three hours after administration of SonoVue.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical trial development programme for SonoVue may be unable to detect certain kinds of adverse reactions, due to the following particular conditions (Part II Module SIV Table 1).

Part II Module SIV Table 1: Limitations to detect adverse reactions in the clinical trial development programme for SonoVue

Ability to detect adverse reactions	Limitation of trial programme	Implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	7341 patients were exposed to SonoVue in clinical trials	With 7341 patients studied, rare ADRs with an incidence greater than 1 in could be 6627 patients (0.0151%) detected with more than 85% power if there were no background incidence.
Due to prolonged exposure	Prolonged exposure is not applicable to SonoVue as it is a diagnostic product used for an imaging examination and it is normally administered as a single dose. More than 80% of the administered SF_6, the active ingredient of SonoVue, is recovered in exhaled air within 2 minutes after injection and almost 100% after 15 minutes.	Based on the fast elimination and the negligible likelihood that multiple consecutive contrast-enhanced exams are performed in a very short time, there are no real implications for the target populations.
Due to cumulative exposure	SonoVue is a contrast agent for diagnostic ultrasound and therefore administered as a single dose. During a single examination, a second injection of the recommended dose can be made when deemed necessary by the physician. In patients with chronic disease, CEUS might be repeated after days, weeks or months to follow up or to monitor therapy response. For this reason repeated doses might be needed.	Due to the very short elimination half-life of SF_6 in patients with normal pulmonary and cardiac function (5 minutes for males and 7 minutes for females) it can be assumed that the contrast agent is eliminated completely from the body within 15 minutes. In such patients even repeated examinations with SonoVue will not lead to cumulative effects. In patients with Impaired Pulmonary Function or Pulmonary Hypertension the elimination of SF_6, the active ingredient of SonoVue, is not modified. In patients with diffuse interstitial pulmonary fibrosis, the percentage of dose recovered in expired air averaged 100% and the terminal half-life was similar to that measured in healthy volunteers. Therefore there are no real implications for the target populations.
Which have a long latency	Not applicable	Not applicable

SIV.3 Limitations with respect to populations typically under-represented in clinical trial development programmes

Certain populations are often excluded or under-represented in clinical trials. Representation of these populations in the clinical trial programme for SonoVue is provided in Part II Module SIV Table 2**.**

Part II Module SIV Table 2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not excluded from clinical trials in the development program
• Patients with renal impairment	Not excluded from clinical trials in the development program. Of note, SonoVue is not eliminated through the kidney.
• Patients with cardiovascular impairment	Subjects with various degrees of cardiovascular impairment have been studied in clinical trials, including patients with New York Heart Association class IV.
• Immunocompromised patients	Not explicitly excluded in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	SonoVue was widely studied in patients with various disease states. In many cases, subjects enrolled in medical imaging trials are quite ill or debilitated with numerous primary disease processes and co-morbidities. It is considered that patients included in clinical trials with SonoVue adequately represents the severity of disease expected in the intended patient population for this agent.
Subpopulations carrying relevant genetic polymorphisms	Possibly included in the clinical development program, but information not in database
Other **Paediatric subjects**	Paediatric patients were included in an observational study for the evaluation of suspected or known VUR.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Worldwide cumulative exposure data for SonoVue is reported from 26 March 2001 to the data lock point (DLP) of this RMP (30 June 2025).

SV.1.1 Method used to calculate exposure

SonoVue administration in a person occurs over one day, and generally as a single dose. Therefore, the estimate of patient exposure is calculated based upon the number of single dose vials sold from when SonoVue was first introduced into the market through 30 June 2025. By

Company convention, the estimate of sales/exposure figures of the DLP month is considered to be identical to that of the month immediately prior. The total number of sold vials represents an approximation of the number of patients exposed to the agent.

SV.1.2 Exposure

Cumulatively, since the IBD of SonoVue (26 March 2001), 17,702,882 single vials have been sold, which includes 5,253,418 vials in Europe and 12,449,464 vials outside EU. The geographical region distribution of sales and estimated patient exposure cumulatively from IBD to RMP DLP is summarised in Part II Module SV Table 1.

Part II Module SV Table 1: Distribution of sales and patients exposure to SonoVue from the introduction into the market (26 March 2001) to the RMP DLP (30 June 2025)

Geographical Region	Number of Patients Exposed
EU	5,253,418
Extra-EU	12,449,464
TOTAL	17,702,882

It is not possible to provide the actual breakdown of SonoVue exposure by indication.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

SonoVue is administered in controlled healthcare environment; the chemical property of the product and its lack of physiological effect indicate minimal likelihood of illegal use. No misuse of SonoVue for illegal purposes has been suspected or observed to date.

Part II: Module SVII - Identified and potential risks

Overall, the safety concerns identified for SonoVue at the DLP of this RMP are listed in Part II Module SVII Table 1 and described in detail in the following sections.

Part II Module SVII Table 1: Summary of safety concerns at the DLP of this RMP

Important identified risks	• Anaphylactic/anaphylactoid reactions
Important potential risks	• Potential for off-label use in paediatrics
Missing information	• Pregnant or lactating women • Paediatric patients (intravenous administration and use in echocardiography and vascular Doppler imaging)

Note: Safety concerns as presented in the last approved SonoVue RMP, V9.4 (2017)

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns were identified from either clinical trials, scientific literature or post-marketing sources since RMP **Version 9.4** was submitted (22 June 2017).

This RMP is being submitted to reclassify “Potential risk for off-label use in paediatric patients” as no longer being a safety concern.

As agreed with competent authorities during the Procedure EMEA/H/C/PSUSA/00002822/202309, the important potential risk “Potential for off-label use in paediatrics” was removed and gathered with the missing information ‘paediatric patients’ since an overlap was noticed between these two safety concerns and there is a need to characterise the use in children, regardless the approved indications (i.e., on label use and off-label use). Off-label use in paediatrics will be discussed in the remaining safety concern “paediatric patients” including the analysis by region and by therapeutic indication.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

SVII3.1.1 Presentation of important identified risk: Anaphylactic/anaphylactoid reactions

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

MedDRA terms	Standardized MedDRA Query (SMQ) for Anaphylactic Reaction and SMQ Hypersensitivity
Potential Mechanisms	Detailed pathological pathway by which these reactions occur is not clear yet, for SonoVue as well as for any other injectable contrast agent. Drug provocation test has not been routinely recommended for diagnosis of contrast-induced anaphylaxis because it is not risk free and, therefore, negative predictive value of skin test has not been widely established. Basophil activation test proved a valuable promising method for diagnosis and may complement the in-vivo tests;[76] however, the use is limited by the fact that its positivity depends upon involvement of an IgE-mediated mechanism, which has not been demonstrated to be involved in all cases of contrast-induced anaphylaxis. Specifically, animal and in-vitro studies conducted to elucidate the possible mechanisms of hypersensitivity reactions to SonoVue show that such reactions are not caused by a direct activation of basophils.[77]
Evidence source(s) and strength of evidence:	Integrated clinical trial database, post-marketing safety database, literature searches
Characterisation of the risk: Frequency with 95 % Confidence Interval (CI)	In the cumulative integrated clinical trial database including 7,341 subjects dosed with SonoVue, there were 58 cases, of which 3 serious and 55 non-serious, extracted via the SMQ Hypersensitivity. The incidence rate of adverse events potentially indicative of hypersensitivity is 58/7,341 (0.7900%; 95% CI: 0.6005%, 1.0202%), equivalent to less than 1 in 100 exposed patients. Specifically, querying the integrated clinical trial database using the SMQ Anaphylactic reaction, there were 7/7,341 cases (0.0954%; 95% CI: 0.0383%, 0.1964%), corresponding to about 1 in 1,000 exposed patients. There was only 1 confirmed case of anaphylactic/anaphylactoid reaction related to SonoVue, which corresponds to an incidence rate of 0.0136% (95% CI: 0.0003%, 0.0759%), equivalent to about 1 in 10,000 exposures. The integrated clinical trial database contains limited comparator information on only 162 subjects; based on the available data, no cases were reported in those subjects exposed to a comparator agent. No anaphylactic/anaphylactoid reactions have been reported in the post-marketing prospective non-interventional studies. Cumulatively, during post-marketing surveillance, the estimated number of patients exposed to SonoVue based on sales is 17,702,882 patients from 01 April 2001 to 30 June 2025.

[76] Salas M, Gomez F, Fernandez TD, Doña I, Aranda A, Ariza A, et al. Diagnosis of immediate hypersensitivity reactions to radiocontrast media. Allergy. 2013;68:1203-1206.

[77] Report No. BRACCO-0903. Submitted to European Medicines Agency in December 2009.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

Characterisation of the risk: Frequency with 95 % CI (cont'd)	In the same period, based on spontaneous reports received from post-marketing surveillance extracted by running the SMQ Anaphylactic reaction, there were 1,013 cases with the estimated reporting rate (RR) for anaphylactic reaction cases of 0.0072% (95% CI: 0.0068%, 0.0076%), corresponding to approximately 7 in 100,000 exposed patients. When the MedDRA SMQ Hypersensitivity was used, 1,690 cases were retrieved with an estimated RR of 0.0120% (95% CI: 0.0114%, 0.0126%), corresponding to approximately 10 in 100,000 exposed patients. The number of patients cumulatively exposed to SonoVue during echocardiography examinations was estimated as 5,784,606 based on Bracco SonoVue sell-out database (as 35% of the total number of all examinations reported each period from 01 April 2001 to 30 September 2004, 20% of the total number of all examinations reported each period from 01 October 2004 to 30 September 2013, 33% of the total number of all examinations reported for the period 01 October 2013 to 30 September 2014, 30% of the total number of all examinations reported for the period 01 October 2014 to 30 September 2017, 37.3% of the total number of all examinations reported each period from 01 October 2017 to 30 September 2020, 46.8% of the total number of all examinations reported for the period 01 October 2020 to 30 September 2023 and 34.4% of the total number of all examinations reported for the period 01 October 2023 to 30 September 2024). Of note, the increase in cardiac use (from 30% in the SONO21 PSUR to 46.8%) is due to the increasing volume sold in the United States where echocardiography is the dominant indication. The cumulative estimated RR of serious adverse reactions potentially indicative of anaphylactic/anaphylactoid reactions in the indication echocardiography is as follows: for the SMQ Anaphylactic reaction 547/5,784,606 (0.0095%; 95% CI: 0.0087%, 0.0102%) and for the SMQ Hypersensitivity 704/5,784,606 (0.0122%; 95% CI: 0.0113%, 0.0131%). No meaningful estimate of the anaphylactic/anaphylactoid reactions RR in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease can be calculated from post-marketing surveillance since these patients cannot be identified with certainty due to often missing cardiovascular history details and because no reliable data are available or can be extrapolated on the denominator (i.e., total number of patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease exposed to SonoVue for echocardiography).
Absolute Risk	For anaphylactic/anaphylactoid reaction approximately 7 in 100,000 exposed patients; for hypersensitivity: 10 in 100,000 exposed patients
Relative Risk	3.2-68.4 per 100,000 patient-years (please refer to section Background incidence/prevalence section of this table).
Severity	Severity of anaphylactic/anaphylactoid reactions ranges from mild to severe life-threatening and fatal. The symptoms could include skin erythema, bradycardia, hypotension, dyspnoea, loss of consciousness, cardiac/cardio-respiratory arrest, and anaphylactic shock. More severe events can occur rapidly and require full and aggressive cardiopulmonary resuscitation. Other signs and symptoms typically occurring during anaphylactic reactions, such as urticaria and symptoms of acute gastrointestinal distress are very rare. In patients with underlying coronary artery disease, myocardial ischaemia and/or myocardial infarctions have been reported. In very rare cases, fatal outcomes have been reported in temporal association with the use of SonoVue in patients with a high underlying risk for major cardiac complications. Primary circulatory collapse can occur as the only and/or initial presentation without respiratory symptoms or without other signs or symptoms outlined above. Treatment of anaphylaxis/anaphylactoid reaction include: close monitoring of blood pressure, pulse, and respirations, proper intravenous cannulation, adrenalin 1:1000 intramuscularly if hypotension or bronchospasm are severe (the intratracheal route may be used for severe bronchospasm), bronchodilators to treat bronchospasm, oxygen through nasal tube, sedation, intravenous fluids, and corticosteroids. H1 and H2 antihistamines by intravenous administration have a limited role in treatment of anaphylaxis but are often used for relief of mucocutaneous symptoms.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

Severity (cont'd)	Treatment of anaphylactic shock include: safeguarding the airways (intubation and assisted ventilation if needed, oxygen up to 10 L/minute, fluids, and plasma expanders, 1:1000 adrenalin intramuscularly (intravenous adrenalin at 1:10,000 strength is used for cardiac arrest, intravenous corticosteroids; in case of cardiac arrest, standard treatment protocols include cardiopulmonary resuscitation reanimation, defibrillation, adrenalin intravenously 1:10,000, sodium bicarbonate intravenously, and other intravenous cardiac medications such as lidocaine and calcium chloride. The use of diagnostic contrast media, such as SonoVue, should be restricted to hospitals or clinics staffed for intensive care emergencies and where cardiopulmonary resuscitation equipment is readily available.
Reversibility	Normally, hypersensitivity is a reversible reaction after treatment. Very rarely, as reported in section "Precautions", in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease the clinical course of the hypersensitivity may lead to life-threatening conditions.
Long Term Outcomes	Hypersensitivity generally manifest as immediate reaction.
Impact on Quality of Life	There is no effect on the patient's quality of life, as anaphylactic/anaphylactoid reactions are acute reactions which in the large majority of cases are mild to moderate in intensity and promptly recover upon treatment without sequelae. More rarely, serious reactions may lead to life-threatening conditions involving the cardiac and/or respiratory system and require aggressive emergency treatment. For example, upper respiratory tract oedema, dyspnoea progressing even to the point of respiratory distress or respiratory arrest can be caused by spasm and/or oedema of the airways as manifested by a number of symptoms: wheezing, stridor, hoarseness, dysphonia, sensation of throat closure, dysphagia, chest tightness (especially in asthmatics), tachypnea, hypoxia, and/or cyanosis. Hypotension (which may be experienced by the patient as faintness, dizziness, lightheadedness, sense of impending doom, near-syncope, pallor, and/or cold sweat/diaphoresis), tachycardia (which may be suppressed by beta-blocker medications or by an underlying heart condition that involves bradycardia), or other arrhythmia and cardiac arrest can occur. In most severe cases, shock (cardiovascular collapse) may develop. It is acute circulatory failure – a *haemodynamic collapse* – marked by a fall in blood pressure and loss of perfusion of vital organs leading to their failure and damage. In this situation, the severe hypotension leads to tissue hypoxia, manifested by reduced temperature and cyanosis, and potentially ultimately resulting in the very dangerous condition of lactic acidosis. The reduction of blood return to the heart and consequent reduction of intracardiac pressures leads to reduced cardiac output, and may ultimately result in pulseless electrical activity and cardiac/cardio-respiratory arrest. Because of decreased perfusion to the brain, shock may be accompanied by acutely altered mental status, resulting in various states of decreased consciousness (somnolence, stupor, coma, syncope), unresponsiveness, eyes rolling, tongue protrusion, mouth foaming, convulsions/seizures, and/or incontinence. In these situations, the patient's quality of life is affected temporarily due to hospitalisation.
Background incidence/prevalence	Data on the incidence of anaphylactic/anaphylactoid reactions induced by ultrasound contrast media are limited. Provided below are epidemiologic data on anaphylaxis extracted from the literature: • Studies estimate a lifetime prevalence of anaphylaxis between 0.05% and 2% and an incidence of 3.2-68.4 per 100,000 patient-years.[78,79]

[78] Lieberman P, Camargo CA Jr, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol. 2006;97:596-602.

[79] Koplin JJ, Martin PE, Allen KJ. An update on epidemiology of anaphylaxis in children and adults. Curr Opin Allergy Clin Immunol. 2011;11:492-496.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

Background incidence/prevalence (cont'd)	• In the United Kingdom, the incidence of anaphylaxis from all causes was reported to be 21.28 (95% CI: 17.64-25.44)/100,000 person-years[80] and it accounts for 1 per 1,500 emergency room visits.[81] • In the United States, it is estimated that anaphylaxis affects between 1.21% and 15.04% of the general population. Incidence rate in in-patients is 1/3,000 and risk of death is 15 for 500 to 1,000 deaths annually.[82] • A relatively low risk of anaphylaxis following drug exposure during hospitalisation has been demonstrated for most non-steroidal anti-inflammatory drugs (incidence of 2-7/100,000 patients for paracetamol and aspirin and 16/100,000 for diclofenac) and antibacterials (from 5 to 14/100,000 exposed patients). An intermediate risk was shown for dextran and parenteral penicillin (36 and 32/100,000, respectively), while streptokinase and plasma were associated with a higher incidence (>250/100,000 patients).[83] In another published paper, the rate of penicillin-induced fatal anaphylaxis is 2/100,000 or 20 per million (0.002%) and this drug accounts for 75% of fatal anaphylaxis in the United States.[82] • Radiocontrast-induced anaphylaxis rate is 0.22% to 1%, but is lower for non-ionic low-osmolar contrast agents (0.01% to 0.04%) that have been introduced since 20 years and almost replaced the older ionic agents.[82,84,85,86] Available data with other ultrasound contrast agents: - Optison™: in clinical trials, <0.5% of patients experienced hypersensitivity.[87] - Definity®: in a large multicentre retrospective study, a total of 8 serious reactions were reported as being probably related to Definity, 4 of which were consistent with anaphylactic reactions with a rate of 0.006%.[88] - Definity®: from the Food and Drug Administration Advisory Committee information of 2008 and 2011 – 2008 information has 106 cases of serious hypersensitivity reactions with total exposure of approximately 2 million patients and 2011 information has 23 cases of serious anaphylaxis reactions with total exposure of 1,083,000 patients, together

80 Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. J Allerg Clin Immunol. 2010;125:1098-1104.

81 Rusznak C, Peeles SR Jr. Anaphylaxis. Postgrad Med. 2002;111:101-114.

82 Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in United States: an investigation into its epidemiology. Arch Intern Med. 2001;161:15-21.

83 Kaufman DW, Kelly JP. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. Pharmacoepidemiol Drug Saf. 2003;12:195-202.

84 Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiol. 1990;175:621-628.

85 Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. AJR. 1991;156:825-832.

86 Joint Task Force on Practice Parameters. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol. 1998;101:S465-S528.

87 Optison prescribing information, August 2012.

88 Wei K, Mulvaugh SL, Carson L, Davidoff R, Gabriel R, Grimm RA, et al. The safety of Definity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr. 2008;21:1202-1206.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

	129/3,083,000 resulting rate of 0.0042%.[89,90]
Background incidence/prevalence (cont'd)	No sufficient data about the overall incidence and prevalence of anaphylactic/anaphylactoid reactions in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease unexposed to SonoVue are currently available.
Risk groups or risk factors	No particular group could be identified in the clinical safety database to be at increased risk of developing anaphylactic/anaphylactoid reactions to SonoVue. As there are very few cases of anaphylactic/anaphylactoid reactions, meaningful assessment of correlation with age, gender, or other factors is precluded. There is literature evidence that patients who are on concomitant treatment with beta-blockers are at higher risk of occurrence of anaphylactic reactions induced by contrast agents in general. Beta-blockers may worsen the outcome of the reaction. In the event of an anaphylactic reaction, beta-blockers (including eye drop preparations) may aggravate the reaction. Patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions. Beta-adrenoceptor antagonists are used in patients with hypertension as well as in patients with history of myocardial infarction, cardiac arrhythmia, and heart failure, and the risk associated with avoiding beta-blocker treatment may outweigh the risk of anaphylaxis or the risk of its unfavourable outcome. The decision of avoiding beta-blockers in cardiac patients undergoing SonoVue ultrasound procedures has to be taken on an individual basis. Data from post-marketing surveillance indicate that in patients with underlying coronary artery disease, the significant drop in blood pressure during an anaphylactoid reaction may lead to life-threatening conditions including myocardial ischaemia and/or myocardial infarctions. Patients with high underlying risk for major cardiac complications may be at increased risk of developing anaphylactic/ anaphylactoid reactions with a serious outcome. Cumulatively, in post-marketing surveillance, the overall RRs of serious adverse reaction cases (across the time periods from 2001 to 2024) in patients undergoing SonoVue-enhanced ultrasound for non-cardiac examinations are between 0% (no cases during the first post-authorisation year) and 0.0088% for SMQ Anaphylactic reaction and from 0% (no cases during the first post-authorisation year) to 0.0105% for SMQ Hypersensitivity. Cumulatively in patients undergoing SonoVue-enhanced ultrasound for echocardiographic examinations, the overall RRs are between 0% and 0.0930% (3 cases during the first post-authorisation year) for SMQ Hypersensitivity. It is acknowledged in the scientific literature that patients with history of allergy and asthma are at higher risk of developing contrast media allergy. It is unknown if previous exposure to SonoVue increases a patient's probability of developing anaphylactic/anaphylactoid reactions. In patients who undergo echocardiography because of suspected or known cardiac disease, often a stressor is used for these examinations. 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. [91] The FDA alerted to the potential risk for patients allergic to polyethylene glycol (PEG) to develop hypersensitivity reactions after SonoVue administration. The potential for rare

89 2008 Advisory Committee Meeting Briefing Package: Definity® (Perflutren Lipid Microsphere). From FDA website: http://www fda.gov/ohrms/dockets/AC/08/briefing/2008-4369b1-04.pdf. Accessed 26 April 2011.

90 Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. United States FDA. 02 May 2011.

91 Lattanzi F, Picano E, Adamo E, Varga A. Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. Drug Saf. 2000; 22:251-62.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

Risk groups or risk factors (cont'd)	immunoglobulin E-mediated type I hypersensitivity reactions to PEG components has been recently recognised after publication of case reports implicating PEG allergy.[92,93] These reactions are extremely rare while ultrasound contrast agents provide vital information that improves patient outcomes arising from their ability to detect or exclude life-threatening conditions or to stratify patients to lifesaving therapies.[94] **Section 4.4** (Special warnings and precautions for use) of the SonoVue Core Data Sheet (CDS) indicates serious hypersensitivity reactions have been observed during or shortly following SonoVue administration in patients with no prior exposure to sulphur hexafluoride microbubble products, including patients with prior hypersensitivity reaction(s) to macrogol, also known as PEG. SonoVue contains PEG. There may be increased risk of serious reactions in patients with prior hypersensitivity reaction(s) to PEG. It is recommended to keep all patients under close medical supervision during and for at least 15 minutes following the administration of SonoVue to monitor the risk of serious hypersensitivity reactions. Moreover, extreme caution should be taken in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease because in these patients' allergy-like and/or vasodilatory reactions may lead to life-threatening conditions. Additionally, it is recommended to 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 (hypertension, bradycardia). **Section 4.8** Undesirable effects of CDS reads that some of the hypersensitivity cases, mostly in patients with underlying coronary artery disease, myocardial ischemia and/or myocardial infarctions were also reported in post-marketing experience. In very rare cases, fatal outcomes have been reported in temporal association with the use of SonoVue. Most of these patients had a high underlying risk for major cardiac complications, which could have led to the fatal outcome.
Preventability	Anaphylactic/anaphylactoid reactions to contrast media are idiosyncratic in nature and, therefore, are NOT predictable and cannot be prevented, although patients with certain factors (e.g., history of allergy, asthma, concomitant beta-blocker therapy, etc.) are at higher risk of developing contrast media allergy.[95,96,97] Upon appropriate and immediate treatment and patient management the reactions are reversible.

92 Krantz MS, Liu Y, Phillips EJ, Stone CA Jr. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macrogol allergy. J Allergy Clin Immunol Pract. 2020;8:1416-9.e3.

93 Oyarzabal NA, Areso NL, Belar NB, Popolizio IG, Arregui AV, Balza De Vallejo OV. Anaphylactic shock due to allergy to macrogol 4000 contained in SonoVue. Case Reports Clin Med. 2017;6:143-147.

94 Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M, et al. Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography guidelines update. J Am Soc Echocardiogr. 2018;31:241-274.

95 Morcos SK. Review article: Acute serious and fatal reactions to contrast media: our current understanding. Br J Radiol. 2005;78:686-693.

96 Idée JM, Pinès E, Prigent P, Corot C. Allergy-like reactions to iodinated contrast agents. A critical analysis. Fundam Clin Pharmacol. 2005;19:263-281.

97 Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. CMAJ. 1987;136:929-933.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

Preventability (cont'd)	As for all contrast media, the possibility of a reaction, including serious, life-threatening, or fatal anaphylactic or other idiosyncratic reactions, should always be considered, especially in those patients with history of asthma or other allergic disorders. In such patients, a premedication with corticosteroids (prednisolone or methylprednisolone) should be considered, even if clinical evidence of the effectiveness of premedication is limited and premedication may not prevent anaphylaxis.[98] **Section 4.2** (Posology and method of administration) of the SonoVue CDS states that appropriate facilities should be available for coping with any complications of the procedures, as well as for emergency treatment of severe reactions to the contrast itself. **Section 4.3** (Contraindications) of the SonoVue CDS indicates that SonoVue should not be administered to patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue such as PEG. SonoVue is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome. **Section 4.4** (Special warnings and precautions for use) of the SonoVue CDS indicates that serious hypersensitivity reactions have been observed during or shortly following SonoVue administration in patients with no prior exposure to sulphur hexafluoride microbubble products, including patients with prior hypersensitivity reaction(s) to macrogol, also known as PEG. SonoVue contains PEG. There may be increased risk of serious reactions in patients with prior hypersensitivity reaction(s) to PEG. It is recommended to keep the patient under close medical supervision during and for at least 15 minutes following the administration of the SonoVue to monitor the risk of serious hypersensitivity reactions. 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 (hypertension, bradycardia).
Impact on the risk-benefit balance of the product:	Reported anaphylactic/anaphylactoid reactions are mostly transient and reversible with/without prompt and appropriate medical intervention. Cumulatively in the integrated clinical trial database (comprising 7,341 subjects) as of the DLP of this RMP, there was only 1 confirmed case (same case as referenced in first paragraph in tabular section above) of serious anaphylactic/anaphylactoid reaction related to SonoVue (a serious life-threatening anaphylactic shock), which corresponds to an incidence rate of 0.0136% (95% CI: 0.0003%-0.0759%), equivalent to about 1:10,000 exposures. No fatal anaphylactic/anaphylactoid reactions were reported in completed studies in the integrated clinical trial database. No serious anaphylactic/anaphylactoid reactions have been reported in the prospective post-marketing observational studies. The incidence of serious anaphylactic/anaphylactoid reactions reported in the post-marketing retrospective epidemiological non-interventional study BR1-132 is 1/757 (0.1321%) (95% CI: 0.0233%-0.7444%). In post-marketing surveillance over the cumulative period 01 April 2001 to 30 June 2025, a total of 1,376 spontaneous reports of anaphylactic/ anaphylactoid reactions, including 1,115 serious and 261 non-serious, were retrieved from the drug safety pharmacovigilance database using the SMQ Anaphylactic reaction, while 2,315 (1,419 serious and 896 non-serious) spontaneous reports were retrieved with the MedDRA SMQ Hypersensitivity. With the SMQ Anaphylactic reaction, the estimated RR for serious cases of anaphylactic/anaphylactoid reactions was 0.0078% (95% CI: 0.0074%, 0.0082%), corresponding to approximately 8 in 100,000 exposed patients.

98 ESUR Guidelines on Contrast Media. Version 10.0.

Part II Module SVII Table 2: Important identified risks: Anaphylactic/ anaphylactoid reactions

Impact on the risk-benefit balance of the product: (cont'd)	With the SMQ Hypersensitivity, the estimated RR for serious cases of hypersensitivity reactions was 0.0131% (95% CI: 0.0125%, 0.0136%), corresponding to approximately 1 in 10,000 exposed patients. With SMQ Anaphylactic reaction, 45 cases with fatal outcome were retrieved, whereas with SMQ Hypersensitivity, 47 cases with fatal outcome were retrieved. Only for 20 cases with fatal outcome, death could be considered as an outcome of the anaphylactic reaction. In the other cases, there were confounding/predisposing/contributing factors to which the fatal outcome should be most likely attributed.
Potential public health impact of safety concern	Serious anaphylactic/anaphylactoid reactions associated with the use of SonoVue are rare, occurring in approximately 6:100,000 patients from data retrieved with the SMQ Anaphylactic reaction and approximately 8:100,000 patients from data retrieved with the SMQ Hypersensitivity. In extremely rare cases of confirmed and/or suggestive serious anaphylactic/ anaphylactoid reactions (i.e., about 1 in 1 million exposed patients for data extracted with the SMQ Hypersensitivity and less than 1 in 1 million exposed patients for data extracted with the SMQ Anaphylactic reaction), these reactions lead to fatal outcomes in patients with high underlying risk of major cardiac complications or fatalities.

SVII.3.2 Presentation of the missing information

Missing information which may be considered among the safety concerns for SonoVue is characterised below.

Missing information: Pregnant or lactating women

Evidence source(s) and strength of evidence:	There are no or limited amount of data from the use of SonoVue in pregnant women. As precautionary measure, it is preferable to avoid the use of SonoVue during pregnancy, unless the clinical condition of the woman requires its use.
Population in need of further characterisation	It is unknown whether sulphur hexafluoride/metabolites are excreted in human milk. However, based on its rapid elimination from the body via the expired air, it is considered that breastfeeding can be resumed two to three hours after administration of SonoVue.

Missing information: Paediatric patients

Paediatric population	
Evidence source(s) and strength of evidence: Population in need of further characterisation	SonoVue is authorised in paediatric patients for voiding ultrasonography (VUS) in the EU and for VUS, ultrasonography of the liver and echocardiography in the United States. The age group of infants/toddlers (less than 2 years) is a population at particular risk, especially if they are premature neonates, due to the presence of conditions which are contraindication to the use of SonoVue, like congenital cardiovascular malformations which cause severe pulmonary hypertension or right-to-left shunts (except in the United States). Moreover, babies below 2 years of age have incomplete pulmonary development and maturation which might impact the elimination of the SF_6 from the lungs. The cumulative reviewed data indicate that adverse reactions reported in paediatric patients are similar to those reported in adults. There is no evidence to suggest that paediatric patients are a special at-risk group. On the contrary, CEUS is well suited to paediatric use because the contrast agents are safe for children, the equipment is portable and the technique does not require pre-screening laboratory testing or sedation. Most importantly, it does not expose patients to the harmful effects of ionising radiation. This is particularly relevant for paediatric oncology patients, who undergo numerous radiological examinations during diagnosis and staging, throughout treatment, and during surveillance after completing therapy. There is no difference in risk or safety profile when comparing the paediatric and adult populations. Furthermore, the data demonstrate that the risk-benefit ratio of SonoVue is unaffected when used in an off-label indication in the paediatric population.

Part II: Module SVIII - Summary of the safety concerns

The safety concerns identified in previous Module SVII of Part II, are summarized in **Part II Module SVIII Table 1** below.

Part II Module SVIII Table 1: Summary of the safety concerns

Important identified risks	• Anaphylactic/anaphylactoid reactions
Important potential risks	• None
Missing information	• Pregnant or lactating women • Paediatric patients

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection is outlined below.

Part III Table 1: Identified Safety Concerns

Anaphylactic/Anaphylactoid Reaction		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
Risk of anaphylactic/anaphylactoid reactions following exposure to SonoVue	**1) Routine Pharmacovigilance Activities** a) collection, review and submission of individual reports of hypersensitivity reactions from all sources; b) ongoing monitoring of hypersensitivity reactions reports with regular and *ad hoc* aggregate reports; c) regular and ad hoc signal detection and evaluation **2) Additional Pharmacovigilance Activities** None necessary.	a) Continue to improve the quality and completeness of the data collected for the reactions; b) Continue to identify any changes in the frequency and severity of reports or cases of hypersensitivity; c) Identify any additional signal related to hypersensitivity.

Part III Table 2: Missing Information

Pregnant or Lactating Women		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
There are no risk-specific areas to be confirmed or investigated. Section 4.6 of the current SmPC states the following: "No clinical data on exposed pregnancies are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of SonoVue during pregnancy. It is not known if sulphur hexafluoride is excreted in human milk. However, based on its rapid elimination from the body via the expired air, it is considered that the breastfeeding can be resumed two to three hours after administration of SonoVue".	**1) Routine pharmacovigilance activities** a) collection, review and submission of spontaneous reports of off-label use from all sources b) regular and *ad-hoc* signal detection and evaluation activities **2) Additional pharmacovigilance activities** None necessary	To monitor off-label use in pregnant or lactating women and detect any specific safety concerns.

Part III Table 2: Missing Information

Paediatric Patients		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
There are no risk-specific areas to be confirmed or investigated. The current SmPC Section 4.2 states that "The safety and efficacy of SonoVue in patients under 18 years of age has not been established for intravenous administration and use in echocardiography and vascular Doppler imaging." The risks associated with off-label uses in the paediatric population seem to be limited and not substantially different from those experienced by the adult population. There have been no data from the published literature and from spontaneous reporting suggesting paediatric patients above 2 years of age being a special at-risk group. Moreover, the number of ADR reports in paediatric population is sporadic and generally consistent with the known safety profile of the product administered in adults.	**1) Routine pharmacovigilance activities** a) collection, review and submission of spontaneous reports of off-label use from all sources b) regular and *ad-hoc* signal detection and evaluation activities **2) Additional pharmacovigilance activities** None necessary	To monitor off-label intravenous use in paediatric patients and detect any specific safety concerns.

Specific adverse reaction follow-up questionnaires for any safety concern:

Not applicable.

Other forms of routine pharmacovigilance activities for any safety concern:

Not applicable.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned to assess effectiveness of risk minimisation measures.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable as there are no ongoing or proposed additional pharmacovigilance and risk minimisation activities.

Part IV: Plans for post-authorisation efficacy studies (PAES)

Not applicable as there are no ongoing or proposed post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Part V Table 1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Anaphylactic/ Anaphylactoid Reaction (important identified risk)	Routine risk communication: SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Present and disseminate the specific information in the SmPC/Package Leaflet: • to contraindicate the use of SonoVue in patients with known hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1; • to contraindicate the use of SonoVue in combination with dobutamine in patients with conditions suggesting cardiovascular instability where dobutamine is contraindicated; • to recommend caution for the use of SonoVue in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease and warn about the risk that in this patient population the anaphylactic/anaphylactoid reactions and in general the vasodilatory reactions may lead to life-threatening outcomes; • to recommend caution in treating anaphylaxis with adrenaline in patients on beta-blockers since response may be poor or promote undesired alpha-adrenergic and vagotonic effects. Other routine risk minimisation measures beyond the Product Information: None necessary.
Pregnant women (missing information)	Routine risk communication: SmPC Section 4.6 Pregnancy, lactation, and fertility Routine risk minimisation activities recommending specific clinical measures to address the risk: Ensure awareness that there are gaps in knowledge about the safety profile of SonoVue during pregnancy and lactation and provide guidance use of this product. Other routine risk minimisation measures beyond the Product Information: None necessary.

Part V Table 1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Paediatric patients (missing information)	Routine risk communication: SmPC Section 4.2 Posology and method of administration Routine risk minimisation activities recommending specific clinical measures to address the risk: Ensure awareness that there are gaps in knowledge about the safety profile of intravenous use SonoVue in echocardiography and vascular Doppler imaging. Other routine risk minimisation measures beyond the Product Information: None necessary.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. No additional Risk Minimisation measures are ongoing or proposed.

V.3 Summary of risk minimisation measures

Part V Table 1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Anaphylactic/anaphylactoid reactions (important identified risk)	SmPC language (Sections 4.3, 4.4, and 4.8)	None required.
Pregnant women (missing information)	SmPC language (Section 4.6)	None required.
Paediatric patients (missing information)	SmPC language (Section 4.2)	None required.

Part VI: Summary of the risk management plan for SonoVue (sulphur hexafluoride microbubbles)

This is a summary of the RMP for SonoVue (sulphur hexafluoride microbubbles). The RMP details important risks of SonoVue, how these risks can be minimised, and how more information will be obtained about SonoVue's risks and uncertainties (missing information). Important new concerns or changes to the current ones will be included in updates of the SonoVue RMP.

SonoVue's SmPC and its package leaflet give essential information to healthcare professionals and patients on how SonoVue should be used.

This summary of the RMP for SonoVue should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be include in updates of SonoVue's RMP.

VI.I The medicine and what it is used for

SonoVue is authorised for use as a contrast agent for ultrasound imaging for the following indications (see SmPC for the full list of indications):

- Adults: echocardiography, doppler of macrovasculature, doppler of microvasculature;
- Children: Ultrasonography of excretory urinary tract

It contains sulphur hexafluoride as the active substance and it is given intravenously for echocardiography and vascular doppler or intravesically for ultrasonography of the excretory urinary tract.

This medicinal product is for diagnostic use only.

Further information about the evaluation of SonoVue's benefits can be found in SonoVue's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

VI.II Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SonoVue's together with measures to minimise such risks and the proposed studies for learning more about SonoVue's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of SonoVue is not yet available, it is listed under 'missing information' below.

VI.IIA List of important risks and missing information

Important risks of SonoVue are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SonoVue. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	• Anaphylactic/anaphylactoid reactions
Important potential risks	• None
Missing information	• Pregnant or lactating women • Paediatric patients

VI.IIB Summary of important risks and missing information

The safety information in the proposed SmPC is aligned to the reference medicinal product.

VI.IIC Post-authorisation development plan

VI.II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of SonoVue.

VI.II.C.2 Other studies in post-authorisation development plan

There are no studies required for SonoVue.

Part VII: Annexes

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable since the MAH has not been requested and does not plan to use specific questionnaires to obtain structured information on reported adverse reactions of special interest.

Annex 6 – Details of proposed additional risk minimisation activities

Not applicable as no additional risk minimisation measures have been proposed.