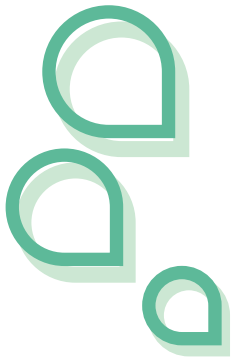

SONOVue®
Sulphur Hexafluoride



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SonoVue® is:

Patient-friendly

- Well tolerated
- No human plasma-derived components

User-friendly

- Storage at room temperature
- Two years' shelf life
- Six hours' stability after reconstitution

Technology-friendly

- Real-time imaging (low MI)
- Intermittent imaging (high MI)

SonoVue®: an ultrasound contrast agent enabling real-time imaging

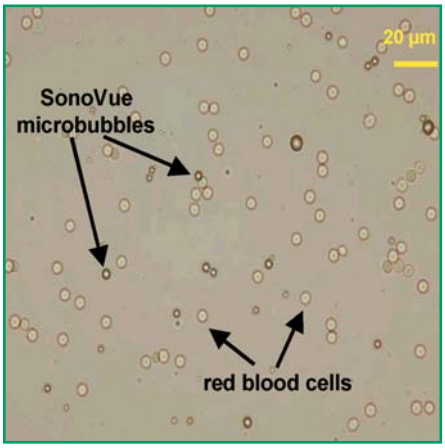
The result of many years of research and development conducted within Bracco, SonoVue® is a flexible shell ultrasound contrast agent designed and optimized with regard to the resistance to pressure. This has led to the selection of SF_6, a gas with a low solubility in blood for the gaseous phase of the microbubbles, and to a phospholipidic monolayer[1,2,3] for the shell.

The development of equipment technology yielded some new contrast-specific imaging techniques, dedicated to a better differentiation between the signal from microbubbles and the signal from tissues.

SonoVue® microbubbles, thanks to the high flexibility and resistance to pressure of their shell, are strongly echogenic in a wide range of frequencies and acoustic pressure. They exhibit significant harmonic response even at very low MI. Therefore SonoVue® can be used with both destructive and conservative contrast-specific imaging methods[1].

SonoVue® can be used with both high and low MI contrast-specific imaging methods

SonoVue® microbubbles are very flexible and resistant to pressure. They exhibit significant harmonic response even at very low MI



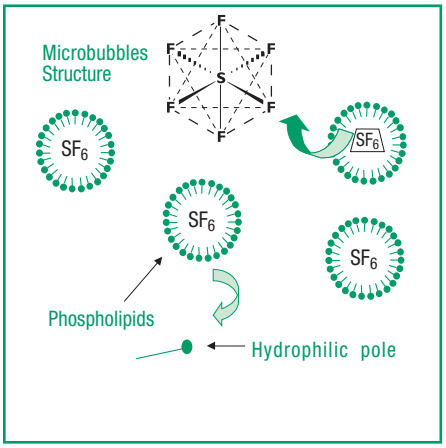


Fig.1. SonoVue® microbubbles microscopic image.

Fig.2. Schematic representation of SonoVue® microbubbles structure.

Cardiac Doppler: enhancement of transvalvular flow signals

The assessment of cardiac valve insufficiencies and stenoses is dependent on an adequate representation of the transvalvular flow signals. In patients with valvular insufficiency, the regurgitant valvular flow volume is often quite small and the flow jet has unusual directions. The adequate assessment of valvular regurgitation requires an excellent signal-to-noise ratio to identify the regurgitation jet in color-coded Duplex echocardiography and to record an optimal flow spectrum in the peak flow region of the jet. The same problem exists in patients with valvular stenoses, where the peak flow velocity is very high and the direction of the jet is also often unusual.

SonoVue® improves significantly the signal-to-noise ratio of the Doppler signal. Depending on the dose administered, a peak enhancement of 20 dB (0.05 ml) up to 34 dB (2.0 ml) can be obtained[4]. This results in a more adequate representation of the color-coded flow jets and a better envelop profile in the Doppler spectrum[5].

Endocardial border delineation and assessment of EF and cardiac volumes

The reliable delineation of the endocardial border is essential for the assessment and quantitative measurement of ventricular volumes and the resulting ejection fraction (EF). In conventional echocardiography, the delineation of the endocardial wall is often impaired by 'drop outs' (i.e. regions without proper reflection of the ultrasound wave) or by noise signals located in the cavum. Due to this inadequate delineation of the endocardial border, there are large intraobserver variabilities in left ventricular volume measurements[6,7].

Two multicenter studies have demonstrated that SonoVue® improves the endocardial border delineation in patients with suboptimal view in comparison with conventional ultrasound, saline and Albunex® [8].

The left ventricle opacification and left ventricle endocardial border detection scores are significantly higher for all doses of SonoVue® compared with saline and Albunex® [6].

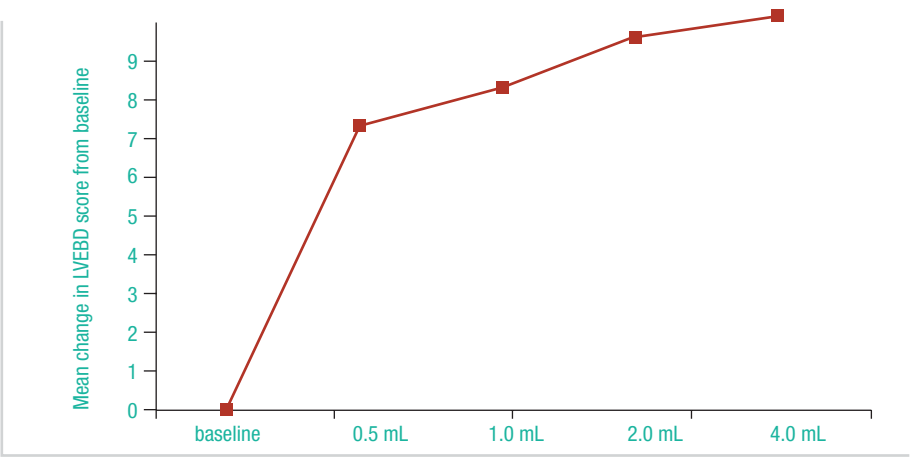


Fig. 3. Within controlled multicenter trials[7,8] including a total of 264 patients, significant improvement in the delineation of the endocardial border compared to unenhanced images was demonstrated for SonoVue versus active control groups. Four different doses of SonoVue (0.5 mL, 1 mL, 2 mL and 4 mL) were evaluated and the images were reviewed by four independent, blinded offsite readers. The endocardial border delineation score was established according to the following scale: 0: inadequate (border not visible), 1: sufficient (border barely visible), 2: good (border clearly visible). A total delineation score (0-24) was obtained by adding the scores from the 12 individual segments in two views (Apical four-chamber view and apical two-chamber view). The mean change value of the score is expressed according to the different doses and indicates that in most patients a dose of 2 mL is sufficient to obtain an optimal result. By definition the baseline score corresponds to zero.

The delineation of the endocardial border clearly improved with recent technical developments in ultrasound machines, especially with the introduction of 'tissue harmonic imaging'. Nevertheless, even with these most advanced ultrasound machines a significant number of patients has an inadequate image quality with poor endocardial border delineation.

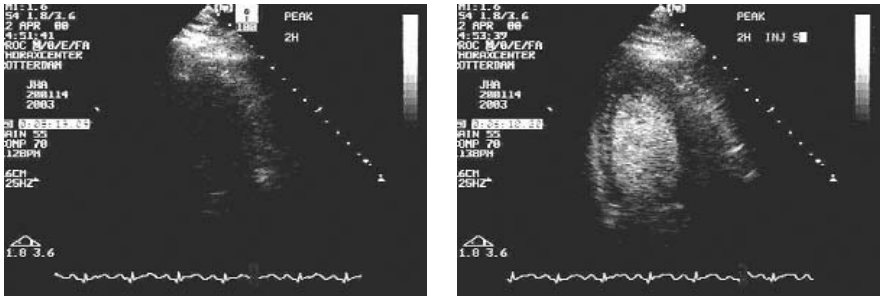


Fig. 4. Improvement of the endocardial border delineation in a patient with poor image quality. Even with harmonic imaging there is insufficient delineation of the endocardial border during the native examination (left side). After the administration of SonoVue® a clear and complete endocardial border delineation is obtained in this patient with very poor acoustic window (right side), allowing an adequate assessment of the left ventricular volume.

An even better endocardial border delineation is obtained with machines able to perform contrast-specific imaging with low insonation power ('low MI imaging'). In this imaging modality, signals from tissue and contrast agent (representing the blood volume) are separated by the software of the machine and the contrast agent in the cavity can be displayed without overlap of tissue signals.

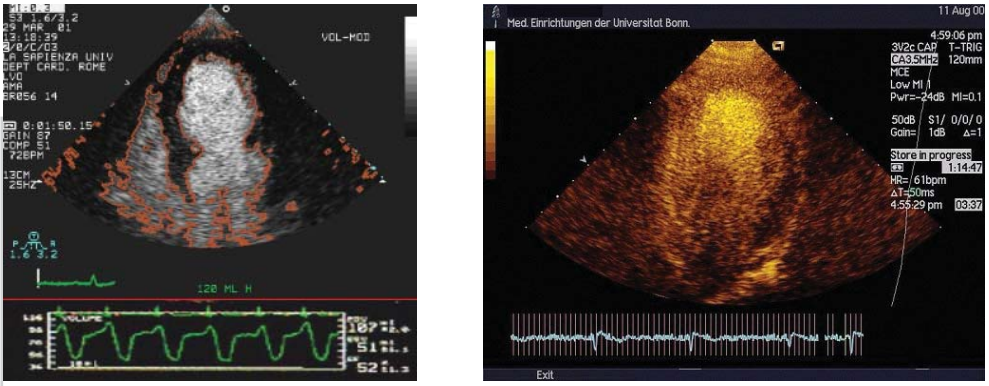


Fig. 5. Endocardial border delineation with 'low MI imaging' and automatic border tracing.

The two images in fig. 5 illustrate the benefit of using an ultrasound system with low MI contrast-specific software. The left image shows a clear difference between the left ventricle full of contrast and the myocardial tissue that appears anechoic due to the absence of microbubbles. In the right image, after several heartbeats at very low MI, the arrival of the contrast agent in the myocardial vessels induces a myocardial enhancement surrounding the stronger enhancement in the ventricular cavity. In that case a high MI flash sequence or the use of a higher MI will make the cavity/wall discrimination more evident, thus for endocardial border delineation a slightly higher MI value may be preferable.

In a clinical study with 64 patients, the endocardial border delineation was investigated during rest and dobutamine stress echocardiography, using a high-end ultrasound machine with harmonic imaging mode[9]. With contrast enhancement, the number of non-interpretable segments significantly decreased, during both rest and stress echocardiography.

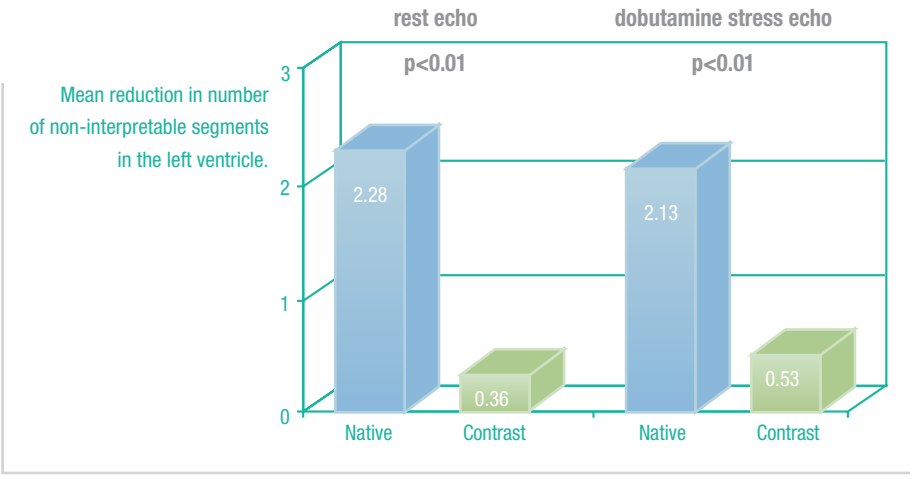


Fig. 6. Reduction of the number of non-interpretable segments after the use of a contrast agent. Even with the use of a high-end ultrasound machine with tissue harmonic mode, a significant number of cardiac wall segments (mean of 2.28 segments at rest and 2.13 segments at stress out of 16 segments in total) remains non-interpretable. The number of non-interpretable segments decreased significantly after the use of a contrast agent.

SonoVue® improves the assessment of cardiac volumes and ejection fraction

The assessment of cardiac volumes is strongly dependent on a reliable delineation of the endocardial border, either by manual or by automatic tracing. As a result of the improved endocardial border delineation after the use of SonoVue, the reproducibility of the quantitative assessment of cardiac volumes and ejection fraction is also significantly improved. Since the EF is one of the most valuable independent predictors for survival in patients with cardiac disease, a reliable determination of the EF is of high clinical importance.

In a multicenter clinical study with 115 patients, native and SonoVue®-enhanced echocardiography was compared to cine-ventriculography and cardiac MRI. The images were assessed by the examining physician (on-site reader) as well as by independent off-site readers. The results of this clinical study showed a clearly improved correlation of the measured EF values with the reference methods (cine-ventriculography and cardiac MRI). The inter-observer variability in determination of EF was estimated using an intra-class correlation coefficient. The best ICC was found for contrast-enhanced ultrasound with 0.91 followed by cardiac MRI (0.86), cine-ventriculography (0.80) and unenhanced tissue harmonic ultrasound (0.79). The inter-observer variability on contrast-enhanced ultrasound was comparable to that obtained for MRI.[10]

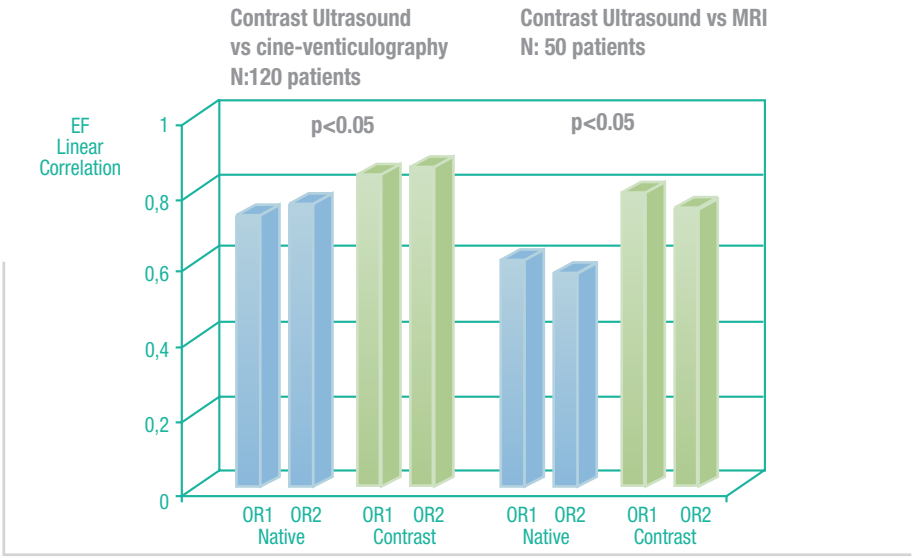


Fig. 7. Correlation of the EF values from native and SonoVue®-enhanced echo with reference methods The correlation between the measured EF values from echo with those from cine-ventriculography (left side) and cardiac MRI (right side) was clearly higher for SonoVue®-enhanced examinations (green bars) compared to native examinations (blue bars), for both off-site readers (OR1 and OR2). The difference between unenhanced and contrast-enhanced was statistically significant (p<0.05).

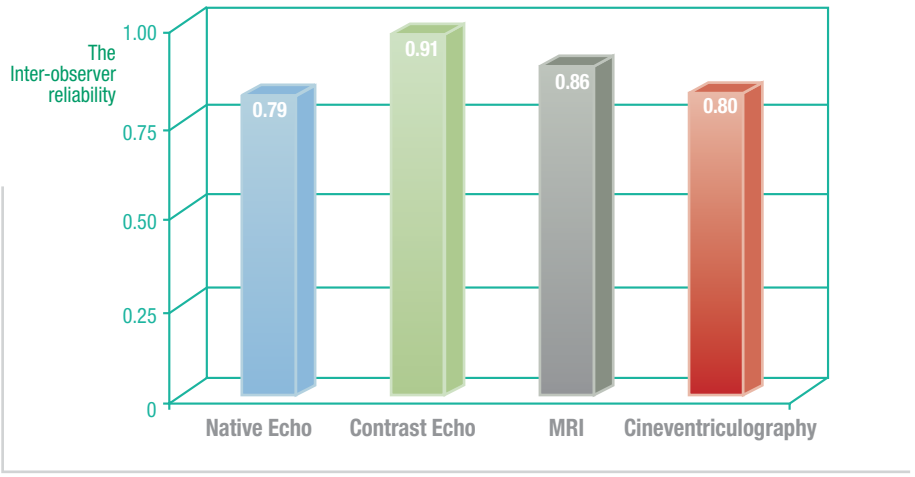


Fig. 8. ***Correlation on EF between native echocardiography, contrast echo, MRI and cine-ventriculography.*** *The inter-observer variability of EF among the three readers within each imaging modality was estimated using an intra-class correlation coefficient. With SonoVue®, the interrater variability in general is better compared to cine-ventriculography and similar to that of cardiac MRI.*

SonoVue® improves the assessment of cardiac wall motion during rest and stress echocardiography

Accurate assessment of global and regional LV systolic performance is essential to the evaluation of coronary artery disease. Because the criteria for ischemia are based on the detection of contractile dysfunction in any myocardial segment, complete visualization of all left ventricular walls is necessary to document or exclude abnormalities confidently. This is particularly important during stress echocardiography, which has shown high sensitivity and specificity for the detection of regional wall motion abnormalities. However, interpretation of stress echocardiograms is qualitative, and multiple factors may produce suboptimal image quality and decreased endocardial border delineation, leading to diminished diagnostic accuracy[11].

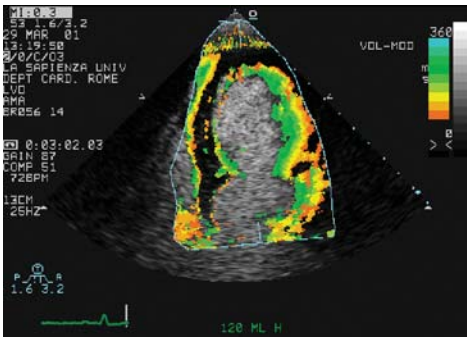


Fig. 9. Documentation of the regional systolic wall motion (contraction) with an automatic tracing function (color kinesis, Philips). The endocardial wall was clearly depicted and traced during SonoVue® enhancement. A reduced contractile function can be detected in the apical-septal wall.

The improvement of image quality and number of evaluable segments of the left ventricular walls with the use of SonoVue® allows a more adequate and reliable assessment of both global and regional wall motion during rest and stress echocardiography[12]. In a clinical study of 60 patients with 50-75% coronary stenoses, a significant improvement of the sensitivity and specificity for the detection of induced wall motion abnormalities during dobutamine stress echocardiography was found for SonoVue®-enhanced echocardiography compared to unenhanced echocardiography[9].

	native		contrast		
sensitivity:	60.0%	→	72.0%	+	12.0%
specificity:	74.4%	→	79.5%	+	5.1%
accuracy:	68.8%	→	76.6%	+	7.8%

Fig. 10. Accuracy for the detection of induced wall motion abnormalities during dobutamine stress echocardiography. SonoVue® enhanced echocardiography clearly improved sensitivity, specificity and accuracy for the detection of induced wall motion abnormalities in patients with intermediate stenosis (50-75%), compared to native echocardiography. Wall motion assessment was performed during rest and peak dobutamine stress and the results were compared to the fractional myocardial flow reserve (measured by an intracoronary flow wire) as gold standard.

SonoVue® allows a reliable assessment of myocardial wall thickness

Accurate assessment of regional wall motion and the accurate detection of regional thickening is important in patients with acute myocardial infarction to predict recovery following revascularization procedures[13].

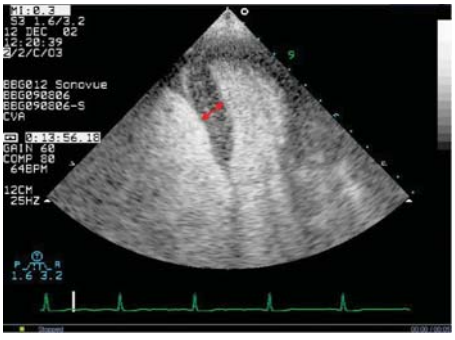


Fig. 11. Assessment of the myocardial thickness. During SonoVue® enhancement, the myocardial thickness becomes clearly visible and can be measured. Endocardial movement (wall motion) and myocardial thickening are important parameters of the regional systolic function.

SonoVue® safety

Clinical studies have been conducted in patients for left ventricular opacification and for the assessment of myocardial perfusion. Overall, a total of > 1,000 patients received one or more doses of SonoVue in these cardiac studies. No serious adverse events with fatal outcome have occurred in the completed clinical studies. No serious related cardiac or cardiovascular events were reported. No serious allergy-like events were reported in these studies [Bracco data on file].

A subset analysis of safety by degree of angiographically documented severity of coronary artery disease did not show an increased incidence or severity of cardiac adverse events in 41 patients with high grade (> 90%) coronary artery stenoses detected in one or more coronary vessels. Only two minor and self-resolving events were observed in two patients with 3-vessel severe coronary artery disease (> 90% stenoses) during or after pharmacologic stress [Bracco data on file].

An open label study of 120 patients with coronary artery disease has been recently completed. The study was aimed at comparing the agreement of unenhanced and contrast-enhanced echocardiography with calibrated biplane cine-ventriculography and cardiac MRI for determination of left ventricular volumes and ejection fraction, and at assessing myocardial perfusion at rest. Coronary angiography was performed in all 120 patients. According to the protocol, the interval between coronary angiography and study echocardiography was not to exceed 24 hours. Nine European centers participated in this study. SonoVue® was administered as a continuous infusion using an initial infusion rate of 1 mL/min and allowing individual adjustments to obtain the optimal dose for imaging. The mean infusion rate was 1.34 mL/min. The mean total dose per patient was 28.8 mL. Coronary artery stenosis of >70% luminal diameter reduction was reported in 71/120 patients (59%), while a more severe coronary artery stenosis of >90% luminal narrowing was reported in 46/120 (38%) patients. There were no serious adverse events in the study. No signs or symptoms of myocardial ischemia were ever reported. No patient study was discontinued due to an adverse event following administration of SonoVue®. A total of two non-serious adverse events (one extrasystole, one malaise) were observed. Both were minor and and rapidly self-resolving [Bracco data on file].

A placebo-controlled, randomized, three-way crossover study was conducted to acquire and evaluate ECG data in patients with documented coronary artery disease. Each patient received SonoVue® 0.1 mL/kg (corresponding to the maximum recommended dose), and SonoVue® 0.5 mL/kg (5-fold multiple of the highest recommended dose). Even at a high dose (corresponding to 35 mL in a 70-kg b.w. person), the observed effects were not dissimilar from those occurring after similar volumes of a placebo (physiologic saline). The only cardiac adverse event (AE) was

an extrasystole observed one minute following SonoVue® administration.

A placebo-controlled, randomized study, to compare the cardiac effects of SonoVue® during insonation of the heart at low (0.4-0.5) and high (1.5-1.6) mechanical index in patients with coronary artery disease was also conducted. Again, no differences between placebo (physiologic saline) and SonoVue® were observed. Concurrent findings were derived from a retrospective analysis conducted in 675 patients with mechanical index data in three categories of mechanical index (< 0.7, 0.7 to <1.0, and > 1.0) during continuous insonation and using high mechanical index and intermittent insonation (end-systolic triggering), which did not show any significant effect of either high acoustic pressure and/or intermittent insonation on cardiac electrophysiology and, in general, on the safety profile of SonoVue® (adverse event rate, vital signs, pulse oximetry, laboratory assessments) [Bracco data on file].

In 51 completed clinical studies including 3,212 subjects, SonoVue® has been shown to be well-tolerated in all investigated patient groups, including patients with cardiovascular disease. The overall incidence of adverse events considered to be of possible, probable or unknown relationship to SonoVue® is low (7.7%) and the majority were of mild intensity and resolved without sequelae. Only one serious adverse event was considered of potential, in this case unknown, causal relationship. It described a patient with a sensory motor paresis of the right arm, which occurred approximately 20 hours after SonoVue® administration.

During post marketing surveillance hypersensitivity reactions were reported in rare instances (approximately 1:10,000) following the administration of SonoVue®, which could include skin reactions, bradycardia, hypotension or anaphylactoid shock. In patients with preexisting severe cardiovascular disease, bradycardia and hypotension were accompanied by myocardial ischemia and/or myocardial infarctions in single cases.

In very rare cases (0.0015%), fatal outcomes have been reported in temporal association with SonoVue®. In all these patients there was a high underlying risk for (spontaneous) major cardiac complications, which could have led to the fatal outcome. The contraindications for SonoVue® include patients with recent acute coronary syndrome or clinically unstable ischemic cardiac disease, including evolving or ongoing myocardial infarction, typical angina at rest within the last 7 days, significant worsening of cardiac symptoms within the last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders. When SonoVue® is administered, patients should be under medical supervision and emergency equipment and personnel trained in its use must be readily available.

For additional product and safety information and complete information on indications and contraindications please refer to the updated SonoVue® SPC.

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Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

SonoVue®, 8 microlitres / ml, powder and solvent for dispersion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulphur hexafluoride microbubbles 8µl per ml

On reconstitution as directed, 1 ml of the resulting dispersion contains 8 µl sulphur hexafluoride in the microbubbles, equivalent to 45 µg.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for dispersion for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

SonoVue® is for use with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio.

SonoVue® should only be used in patients where study without contrast enhancement is inconclusive.

Echocardiography

SonoVue® is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation.

Doppler of macrovasculature

SonoVue® increases the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal to noise ratio.

SonoVue® increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment.

Doppler of microvasculature

SonoVue® improves display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.

4.2 Posology and method of administration

This product should only be used by physicians experienced in diagnostic ultrasound imaging.

The microbubble dispersion is prepared before use by injecting through the septum 5 ml of sodium chloride 0.9%w/v solution for injection to the contents of the vial. The vial is then shaken vigorously for a few seconds until the lyophilisate is completely dissolved. The desired volume of the dispersion can be drawn into a syringe any time up to six hours after reconstitution. Just before drawing into the syringe, the vial should be agitated to re-suspend the microbubbles. SonoVue® should be administered immediately after drawing into the syringe by injection into a peripheral vein. Every injection should be followed by a flush with 5 ml of sodium chloride 0.9%w/v solution for injection.

The recommended doses of SonoVue® are:

B-mode imaging of cardiac chambers, at rest or with stress: 2 ml.

Vascular Doppler imaging: 2.4 ml.

During a single examination, a second injection of the recommended dose can be made when deemed necessary by the physician.

Elderly Patients

The dosage recommendations also apply to elderly patients.

Paediatric Patients

The safety and effectiveness of SonoVue® in patients under 18 years old has not been established and the product should not be used in these patients.

4.3 Contraindications

SonoVue® should not be administered to patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue®.

SonoVue® is contraindicated for use in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders.

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.

The safety and efficacy of SonoVue® have not been established in pregnant and lactating women therefore, SonoVue® should not be administered during pregnancy and lactation (see Section 4.6).

4.4 Special warnings and special precautions for use

It should be emphasised that stress echocardiography, which can mimic an ischaemic episode, could potentially increase the risk of SonoVue® utilisation. Therefore, if SonoVue® is to be used in conjunction with stress echocardiography patients must have a stable condition verified by absence of chest pain or ECG modification during the two preceding days.

Moreover, ECG and blood pressure monitoring should be performed during SonoVue® enhanced echocardiography with a pharmacological stress (e.g.

with dobutamine). ECG monitoring should be performed in high-risk patients as clinically indicated.
Care should be taken in patients with ischaemic cardiac disease because in these patients allergy-like and/or vasodilatory reactions may lead to life-threatening conditions.
Emergency equipment and personnel trained in its use should be readily available. Caution is advised when SonoVue® is administered to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease.
It is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue®.
Numbers of patients with the following conditions who were exposed to SonoVue® in the clinical trials were limited, and therefore, caution is advisable when administering the product to patients with: acute endocarditis, prostetic valves, acute systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent thromboembolism, and end-stage renal or hepatic disease.
SonoVue® is not suitable for use in ventilated patients, and those with unstable neurological diseases.
In animal studies, the application of echo-contrast agents revealed biological side effects (e.g. endothelial cell injury, capillary rupture) by interaction with the ultrasound beam. Although the biological side effects have not been reported in humans, the use of a low mechanical index is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed. There was no apparent relationship with respect to occurrence of adverse events in the clinical studies for patients receiving various categories of the most common concomitant medications.

4.6 Pregnancy and lactation

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 (see section 5.3 Preclinical safety data). Caution should be exercised when prescribing to pregnant women. It is not known if sulphur hexafluoride is excreted in human milk. Therefore, caution should be exercised when SonoVue® is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacokinetic and pharmacodynamic profiles, no or negligibile influence is expected with the use of SonoVue® on the ability to drive or use machines.

4.8 Undesirable effects

The undesirable effects reported with SonoVue® were, in general, non-serious, transient and resolved spontaneously without residual effects. In clinical trials, the most commonly reported adverse reactions are headache (2.3%), injection site pain (1.4%), and injection site reaction including bruising, burning and paraesthesia at the injection site (1.7%).
There were changes in ECG, blood pressure and in some laboratory parameters measured, but these were not deemed to be of clinical significance.
The adverse reactions reported among 1788 adult patients in clinical studies are:

Body system	Common (>1/100, <1/10)	Uncommon (>1/1,000 - <1/100)
Metabolism and nutrition disorders		Hyperglycaemia
Nervous system disorders	Headache	Paraesthesia, dizziness, insomnia, taste perversion
Eye disorders		Vision blurred
Vascular disorder		Vasodilatation
Respiratory, thoracic and mediastinal disorders		Pharyngitis, sinus pain
Gastrointestinal disorders	Nausea	Abdominal pain
Skin and subcutaneous tissue disorders		Pruritus, rash erythematous
Musculoskeletal, connective tissue and bone disorders		Back pain
General disorders and administration site conditions	Injection site pain, injection site reaction, including bruising, burning and paraesthesia at the injection site	Chest pain, pain n.o.s., asthenia

One case of sensory-motor paresis was reported.

Post marketing

Rare cases suggestive of hypersensitivity, which could include: skin erythema, bradycardia, hypotension or anaphylactic shock have been reported following the injection of SonoVue®. In some of these cases, in patients with underlying coronary artery disease, bradycardia and hypotension were accompanied by myocardial ischemia and/or myocardial infarctions.
In very rare cases, fatal outcomes have been reported in temporal association with the use of SonoVue®. In all these patients there was a high underlying risk for major cardiac complications, which could have led to the fatal outcome.

4.9 Overdose

Since there have been no cases of overdose reported to date, neither signs nor symptoms of overdosage have been identified. In a Phase I study doses up to 56 ml of SonoVue® were administered to normal volunteers without serious adverse events being reported. In the event of overdosage occurring, the patient should be observed and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOTHERAPEUTIC GROUP: ULTRASOUND CONTRAST MEDIA

ATC CODE V08DA.

The addition of sodium chloride 0.9%w/v solution for injection to the lyophilised powder followed by vigorous shaking results in the production of the microbubbles of sulphur hexafluoride. The microbubbles have a mean diameter of about 2.5μm, with 90% having a diameter less than 6μm and 99% having a diameter less than 11μm. Each millilitre of SonoVue® contains 8μl of the microbubbles. The interface between the sulphur hexafluoride bubble and the aqueous medium acts as a reflector of the ultrasound beam thus enhancing blood echogenicity and increasing contrast between the blood and the surrounding tissues.

The intensity of the reflected signal is dependent on concentration of the microbubbles and frequency of the ultrasound beam. At the proposed clinical doses, SonoVue® has been shown to provide marked increase in signal intensity of more than 2 minutes for B-mode imaging in echocardiography and of 3 to 8 minutes for Doppler imaging of the macrovasculature and microvasculature.

Sulphur hexafluoride is an inert, innocuous gas, poorly soluble in aqueous solutions. There are literature reports of the use of the gas in the study of respiratory physiology and in pneumatic retinopexy.

5.2 Pharmacokinetic properties

The total amount of sulphur hexafluoride administered in a clinical dose is extremely small, (in a 2 ml dose the microbubbles contain 16 μl of gas). The sulphur hexafluoride dissolves in the blood and is subsequently exhaled.

After a single intravenous injection of 0.03 or 0.3 ml of SonoVue/kg (approximately 1 and 10 times the maximum clinical dose) to human volunteers, the sulphur hexafluoride was cleared rapidly. The mean terminal half-life was 12 minutes (range 2 to 33 minutes). More than 80% of the administered sulphur hexafluoride was recovered in exhaled air within 2 minutes after injection and almost 100% after 15 minutes.

In patients with diffuse interstitial pulmonary fibrosis, the percent of dose recovered in expired air averaged 100% and the terminal half-life was similar to that measured in healthy volunteers.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and toxicity to reproduction. Caecal lesions observed in some repeat- dose studies with rats, but not in monkeys, are not relevant for humans under normal conditions of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Macrogol 4000

Distearoylphosphatidylcholine

Dipalmitoylphosphatidylglycerol Sodium

Palmitic acid

Solvent:

Sodium chloride 0.9% w/v solution for injection

6.2 Incompatibilities

SonoVue should not be admixed with any other medicinal product except the solvent provided.

6.3 Shelf life

2 years.

Once reconstituted, chemical and physical stability has been demonstrated for 6 hours. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Presentation 01(with integral Bio-Set transfer system) -

25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride in a colourless Type I glass vial, with elastomeric closure and integral transfer system.

Type I glass pre-filled syringe containing 5 ml sodium chloride 0.9%w/v solution for injection.

Presentation 02 (with separate MiniSpike transfer system):-

25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride in a colourless

Type I glass vial, with elastomeric closure.

Separate transfer system.

Type I glass pre-filled syringe containing 5 ml sodium chloride 0.9%w/v solution for injection.

6.6 Instructions for use/handling

Before use examine the product to ensure that the container and closure have not been damaged.

SonoVue® must be prepared before use by injecting through the septum 5 ml of sodium chloride 0.9%w/v solution for injection to the contents of the vial. The vial is then shaken vigorously for twenty seconds after which the desired volume of the dispersion can be drawn into a syringe as follows, depending on the presentation :

Presentation 01 (with integral Bio-Set transfer system)

1. Remove vial cap and syringe tip-cap.
2. Connect the syringe (without plunger rod) to the Bio-Set transfer system by screwing it in clockwise.
3. While holding the vial vertically on a table, push firmly down on the syringe until the red line disappears into the white tube of the transfer system with a click.
4. Connect the plunger rod by screwing it in clockwise into the syringe.
5. Empty the contents of the syringe into the vial by pushing on the plunger rod.
6. Shake vigorously for 20 seconds to mix all the contents in the vial (white milky liquid).
7. Invert the system and carefully withdraw SonoVue® into the syringe.
8. Unscrew the syringe from the transfer system.

Presentation 02 (with separate MiniSpike transfer system)

1. Connect the plunger rod by screwing it clockwise into the syringe.
2. Open the MiniSpike transfer system blister and remove syringe tip cap.
3. Open the transfer system cap and connect the syringe to the transfer system by screwing it in clockwise.
4. Remove Flipcap glass protective disk from the vial. Slide the vial into the transparent sleeve of the transfer system and press firmly to lock the vial in place.
5. Empty the contents of the syringe into the vial by pushing on the plunger rod.
6. Shake vigorously for 20 seconds to mix all the contents in the vial (white milky liquid).
7. Invert the system and carefully withdraw SonoVue® into the syringe.
8. Unscrew the syringe from the transfer system.

SonoVue® should be administered immediately by injection into a peripheral vein.

If SonoVue® is not used immediately after reconstitution the microbubble dispersion should be shaken again before being drawn up into a syringe. Chemical and physical stability of the microbubble dispersion has been demonstrated for 6 hours.

The vial is for a single examination only. Any unused dispersion remaining at the end of an examination must be discarded.

7. MARKETING AUTHORISATION HOLDER

Bracco International B.V.
Strawinskylaan 3051
1077ZX Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/01/177/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 March 2001

10. DATE OF REVISION OF THE TEXT

27 September 2004