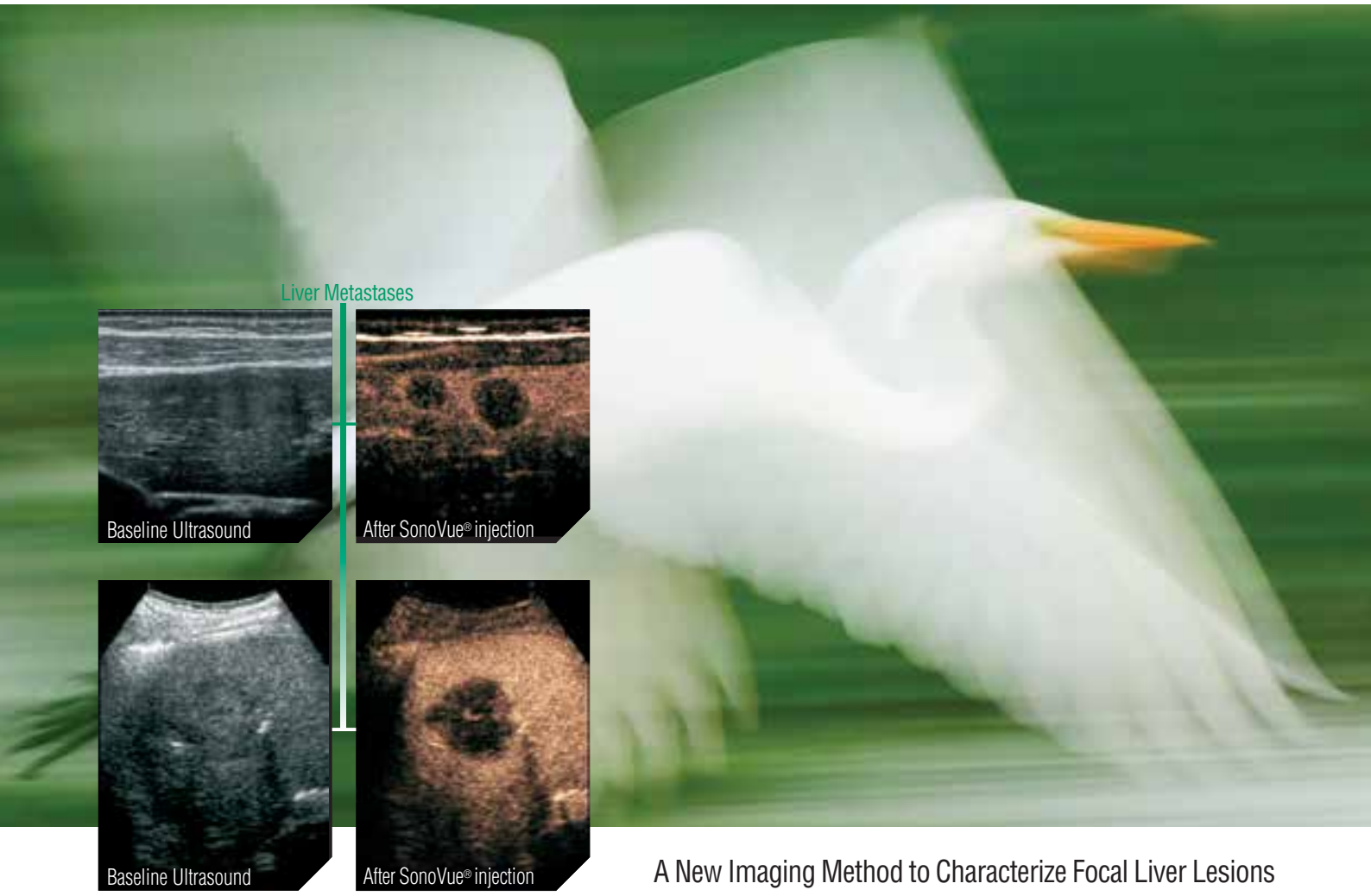
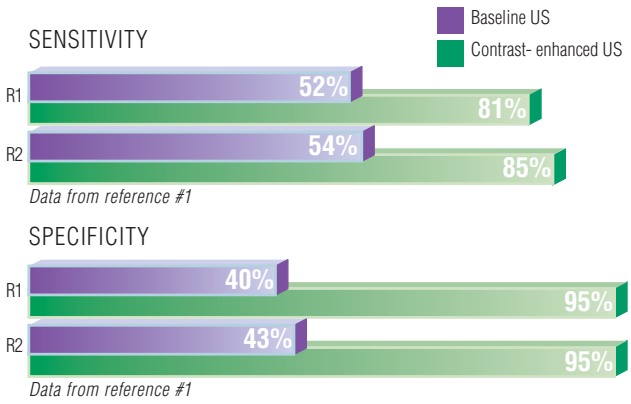
SONOVue®
Sulphur Hexafluoride

Experience Real Time Diagnosis with Contrast-Enhanced Ultrasound





For more information, please, contact: sonovue@bracco.com

A New Imaging Method to Characterize Focal Liver Lesions

- Contrast-enhanced Ultrasound with SonoVue® improves sensitivity by 55% and specificity by 120% for characterization of focal liver lesions compared with unenhanced Ultrasound[1]
- Contrast-enhanced Ultrasound findings with SonoVue® correlates well with those of MRI and CT[1,2,3]
- Low Mechanical Index Contrast-Enhanced Ultrasound better reflects high arterial perfusion of liver metastases than Arterial Phase Computed Tomography[4]

1) Quaia E et al., Radiology. 2004 Aug;232(2) :420-30.
2) Lemke AJ et al., Rofo. 2004 Nov;176(11) :1607-15.
3) Nicolau C et al., Eur Radiol. 2004 Oct;14 Suppl 8:P63-71.
4) Krix M et al., Invest Radiol. 2004 Apr;39(4) :216-22.

BRACCO
LIFE FROM INSIDE

SONOVue®

Sulphur Hexafluoride

Summary of product characteristics

For prescribing information please refer to the approved SPC in your country.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 8µl of sulphur hexafluoride microbubbles. On reconstitution as directed, 1 ml of the resulting dispersion contains 8 µl sulphur hexafluoride in the microbubbles, equivalent to 45 microgrammes. For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for dispersion for injection. SonoVue is a kit including: 1 vial containing 25 mg of lyophilised powder , 1 pre-filled syringe containing 5 ml sodium chloride , 1 Mini-Spike transfer system. Information on the appearance of the reconstituted solution is given in section 6.6.

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 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. The microbubble dispersion is prepared before use by injecting through the septum 5 ml of sodium chloride 9 mg/ml (0.9%) 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 9 mg/ml (0.9%) solution for injection. For instructions for preparation see section 6.6.

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 precautions for use

ECG monitoring should be performed in high-risk patients as clinically indicated. 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). 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 must 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, prosthetic 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 these 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 negligible 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 reaction including bruising, burning and paraesthesia at the injection site (1.7%) and injection site pain (1.4%). 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 Skin and subcutaneous tissue disorders	Nausea	Abdominal pain 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 no organ system, 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 overdose 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 overdose 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 9 mg/ml (0.9%) 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

Non-clinical 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 9 mg/ml (0.9%) solution for injection

6.2 Incompatibilities

In the absence of compatibility studies, 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

The medicinal product does not require any special storage conditions. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

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 9 mg/ml (0.9%) solution for injection.

6.6 Special precautions for disposal

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 9 mg/ml (0.9%) 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 02** (with separate MiniSpike transfer system) Connect the plunger rod by screwing it clockwise into the syringe. Open the MiniSpike transfer system blister and remove syringe tip cap. Open the transfer system cap and connect the syringe to the transfer system by screwing it in clockwise. 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. Empty the contents of the syringe into the vial by pushing on the plunger rod. Shake vigorously for 20 seconds to mix all the contents in the vial (white milky liquid). Invert the system and carefully withdraw SonoVue into the syringe. Unscrew the syringe from the transfer system. SonoVue should be administered immediately by injection into a peripheral vein. After reconstitution, a homogeneous white milky liquid is obtained. If solid parts of the lyophilisate are seen or the suspension is not homogeneous, the product should be discarded. 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 or waste material must be discarded in accordance with local requirements.

Manufactured by:
Bracco Suisse SA, 31, route de la Galaise, CH-1228 Plan-les-Ouates, Genève, Switzerland

Imported and Marketed by:
Imaging Products (I) Pvt. Ltd., R.No.1, 2nd Flr., Plot D-117, TTC Inds. Area, Village Shirwane, Nerul, Navi Mumbai, India.
Tel.: +91 22 27682703

In the event of adverse events, PQC
Tollfree no: 18002700397
Email: ipi_pharmacovigilance@imagingproductsindia.com
Updated version: 01/2016

iMAGiNG
IMAGING PRODUCTS (INDIA) PVT. LTD.
A TRIVITRON ENTERPRISE