BRACCO

IMPORTANT SAFETY INFORMATION

SONOVUE® (sulphur hexafluoride)
Restriction of the indication to non-cardiac imaging

Dear Healthcare Professional,

In agreement with the European Agency for the Evaluation of Medicinal Products (EMEA) and the Irish Medicines Board (IMB) , we would like to inform you of important new safety information regarding SonoVue® ® (sulphur hexafluoride) and its use in patients with underlying cardiac disease.

There have been rare post-marketing reports of serious allergy-like and cardiac adverse events, with the use of SonoVue®. These events include severe hypotension, bradycardia, cardiac arrest and acute myocardial infarction. Most events occurred in the context of idiosyncratic hypersensitivity in patients undergoing echocardiography.

In three cases, fatalities have been reported in temporal association with the use of SonoVue®. In all three cases, the patients were at high underlying risk for major cardiac complications, which could have led to the fatal outcome.

In view of these serious reactions the following changes have been introduced urgently in the Summary of Product Characteristics of SonoVue® as a precautionary measure pending further evaluation of this issue:

- **Restriction of the indication to non-cardiac imaging (echo-Doppler of macro- and microvasculature) ;**
- **Contra-indication in patients with known coronary artery disease, myocardial infarction, unstable angina, acute cardiac failure, class III/IV cardiac failure, severe rhythm disorders, acute endocarditis and prosthetic valves ;**
- **Recommendations to keep patients under close medical supervision during and for at least 30 minutes following the administration of SonoVue® and to have emergency equipment and personnel trained in its use readily available.**

SonoVue® contains sulphur hexafluoride in microbubbles, which is used as a diagnostic agent for enhancing the echogenicity of blood, specifically for Doppler investigations of macrovasculature (cerebral, extra-cranial carotid or peripheral arteries) and microvasculature (vascularity of liver and breast lesions) where study without contrast enhancement has been inconclusive. It was originally authorised in the EU on 26 March 2001.

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Please see the revised SPC enclosed with this letter.

Any suspected adverse drug reactions (ADRs) associated with use of Sonovue should be notified to the company and/or the IMB in the usual way.

Should you have any questions or require additional information concerning the use of SonoVue® , please contact Maurizio Denaro, MD Group Vice-President Head of Research & Development. Medical Affairs Department at +390221772606 and/or Fabio Pitzoi, Bracco UK +44 16 28 85 1500

Sincerely,

Maurizio Denaro, MD
Group Vice-President
Head of Research & Development

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ANNEX I
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.

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 is:

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 known coronary artery disease, myocardial infarction, unstable angina, acute cardiac failure and class III/IV cardiac failure and severe arrhythmic disorders or those** known to have right-to-left shunts, **acute endocarditis, prosthetic valves**, 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 is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue.
Emergency equipment and personnel trained in its use should be readily available.
Caution is advised when SonoVue is administered to patients to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease.

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 systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent **non cardiac** thromboembolism, and end-stage renal or hepatic disease.

SonoVue is not suitable for use in ventilated patients, and those with unstable neurological diseases.

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 VO8DA.
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.

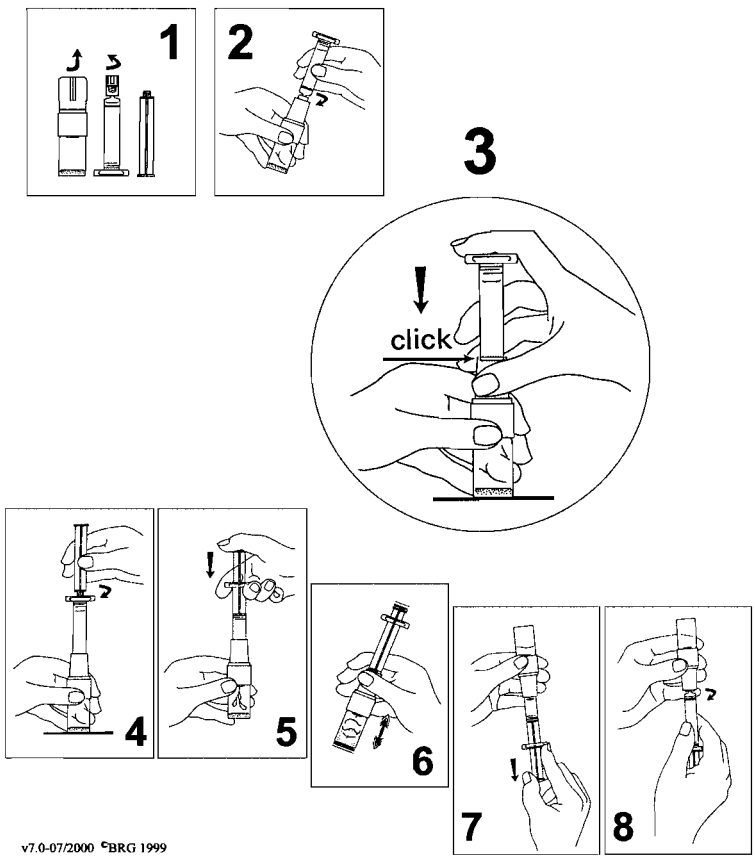
Presentation 02 (with separate MiniSpike transfer system):-
25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride in a colourless Type I glass vial, with elastomeric closure.
Separate transfer system.
Type I glass pre-filled syringe containing 5 ml sodium chloride 0.9%w/v solution for injection.

6.6 Instructions for use/handling

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

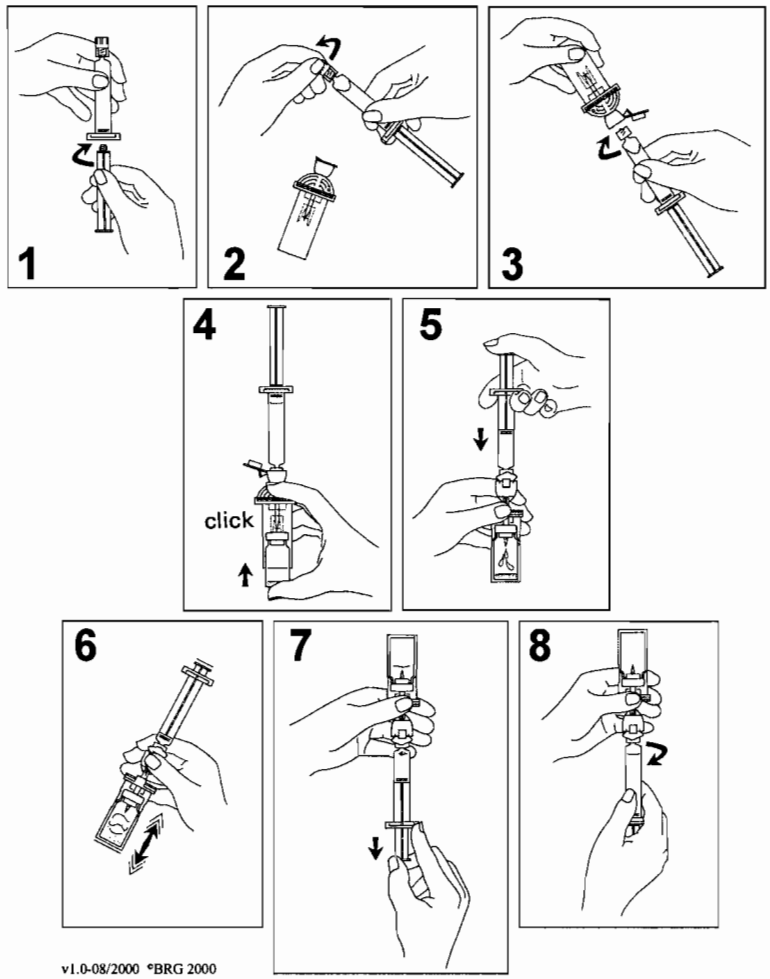
SonoVue must be prepared before use by injecting through the septum 5 ml of sodium chloride 0.9%w/v solution for injection to the contents of the vial. The vial is then shaken vigorously for twenty seconds after which the desired volume of the dispersion can be drawn into a syringe as follows, depending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

EU/1/01/177/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/03/01

10. DATE OF REVISION OF THE TEXT

04/12/02

First Name	Surname	Hospital
Niall	Colwell	Mercy Hospital
Omar	Hyat	Mercy Hospital
Ramon	Martos	Mercy Hospital
Ali	Samraj	Mercy Hospital
Adrian	Brady	Mercy Hospital
Edward	Fitzgerald	Mercy Hospital
Ray	Lovertt	Mercy Hospital
Neil	O Donovan	Mercy Hospital
Ahamed	Gamal	Monaghan General Hospital
Brenden	Mcmahon	Monaghan General Hospital
Abdalla Salah	Mohamed	Monaghan General Hospital
S	O Neill	Monaghan General Hospital
Gamel	Ahamed	Monaghan General Hospital
Pauline	Diamond	Mater Private Hospital
Micheal	Behan	Mater Private Hospital
Eammon	Breathnach	Mater Private Hospital
Joseph	Ennis	Mater Private Hospital
Stephen	Eustace	Mater Private Hospital
Helen	Fenelon	Mater Private Hospital
David	Legge	Mater Private Hospital
John	Stack	Mater Private Hospital
Angie	Brown	Beaumont Hopital
Tom	Gumbrielle	Beaumont Hopital
Paul	Brennon	Beaumont Hopital
Fiona	Butler	Beaumont Hopital
Patricia	Fitzpatrick	Beaumont Hopital
John	O Callaghan	Beaumont Hopital
Anthony	o Dwyer	Beaumont Hopital
John	Thornton	Beaumont Hopital
Micheal	O Reilly	Waterford Regional Hospital
Chris	Farrelly	Waterford Regional Hospital
Joan	Hennahan	Waterford Regional Hospital
Ian	Kelly	Waterford Regional Hospital
Donal	Ormonde	Waterford Regional Hospital
Daniel	Walshe	Waterford Regional Hospital
Paul	Kelly	South Infirmary Hospital
Simon	Blake	South Infirmary Hospital
Gerry	Fahy	South Infirmary Hospital
Anne Marie	Galligan	South Infirmary Hospital
Neil	O Donovan	South Infirmary Hospital
Pauline	Smiddy	South Infirmary Hospital
Jim	Crowley	University College Hospital
Kieron	Daly	University College Hospital
Eoin	Bresnihan	University College Hospital
Ian	Davison	University College Hospital
Peter	McCarthy	University College Hospital
Ray	McLoughlin	University College Hospital
Joe	Murphy	University College Hospital
Niall	Murphy	University College Hospital
David	O Keefe	University College Hospital
Gerry	O Sullivan	University College Hospital
Mohamed	Albasheer	James Connolly Memorial

Ali	Alhindawi	James Connolly Memorial
Niall	Hickey	James Connolly Memorial
Paul	Nicell	James Connolly Memorial
David	Stafford Johnson	James Connolly Memorial
Louise	Coffee	St Vincents Hospital
Conor	Collins	St Vincents Hospital
Robin	Gibney	St Vincents Hospital
James	Griffin	St Vincents Hospital
Gerrad	Lonergen	St Vincents Hospital
Dermot	Malone	St Vincents Hospital
James	Materson	St Vincents Hospital
Donal	McErleane	St Vincents Hospital
Anne	O Doherty	St Vincents Hospital
Risteard	o Laoide	St Vincents Hospital
Stephen	Skehan	St Vincents Hospital
Anthony	Owens	St Vincents Hospital
Eamonn	Bannon	Tralee General Hospital
Thomas	Geaney	Tralee General Hospital
Hilary	Kelly	Tralee General Hospital
Mary	Caffrey	Tralee General Hospital
Patrick	Kiely	Limerock Regional Hospital
Cathetrine	Mc Daid	Waterford Regional Hospital
Joanne	Fielding	Waterford Regional Hospital
Micheal	O Reilly	Waterford Regional Hospital
Karl	Ryan	Mater Private Hospital
Clare	Mchugh	Mater Private Hospital
Anne	Dolan	Mater Private Hospital
Denis	O Connell	Mater Private Hospital