

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

One ml contains 8 µl 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 the 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.

Posology

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.

Method of administration

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 of the medicinal product before administration see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

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.

Sonovue should not be used in combination with dobutamine in patients with conditions suggesting cardiovascular instability where dobutamine is contraindicated.

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).

Use extreme caution when considering the administration of Sonvue 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 because in these patients allergy like and/or vasodilatory reactions may lead to life threatening conditions. SonoVue should only be administered to such patients after careful risk/benefit assessment and a closely monitoring of vital signs should be performed during and after administration.

Emergency equipment and personnel trained in its use must be readily available.

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.

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 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

Pregnancy

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). As a precautionary measure, it is preferable to avoid the use of SonoVue during pregnancy.

Breastfeeding

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.

4.7 Effects on ability to drive and use machines

SonoVue has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of SonoVue was evaluated in 4653 adult patients who participated in 58 clinical trials.

The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

System Organ Class	Adverse Drug Reactions		
	Frequency Category		
	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1000$)	Not known Cannot be estimated from available data
Immune system disorders		Hypersensitivity*	
Psychiatric disorders		Insomnia	
Nervous system disorders	Headache, paraesthesia, dizziness, dysgeusia	Sinus headache	Vasovagal reaction
Eye disorders		Vision blurred,	
Vascular disorders	Flushing	Hypotension	
Cardiac disorders			Myocardial infarction** Myocardial ischemia**
Respiratory, thoracic and mediastinal disorders	Pharyngitis		
Gastrointestinal disorders	Nausea, Abdominal pain		
Skin and subcutaneous tissue disorders	Pruritus, rash		
Musculoskeletal, connective tissue and bone disorders	Back pain		
General disorders and administration site conditions	Chest discomfort, injection site reaction, feeling hot	Chest pain, pain, fatigue	
Investigations	Blood glucose increased		

* Cases suggestive of hypersensitivity may include: skin erythema, bradycardia, hypotension, dyspnoea, loss of consciousness, cardiac/cardio-respiratory arrest, anaphylactic reaction, anaphylactoid reaction or anaphylactic shock.

** In some of the cases of hypersensitivity, in patients with underlying coronary artery disease, myocardial ischemia and/or myocardial infarctions were also reported.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

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: VO8DA.

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 2.5 µm, with 90% having a diameter less than 6 µm and 99% having a diameter less than 11 µm. Each millilitre of SonoVue contains 8 µl 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 retinopathy.

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

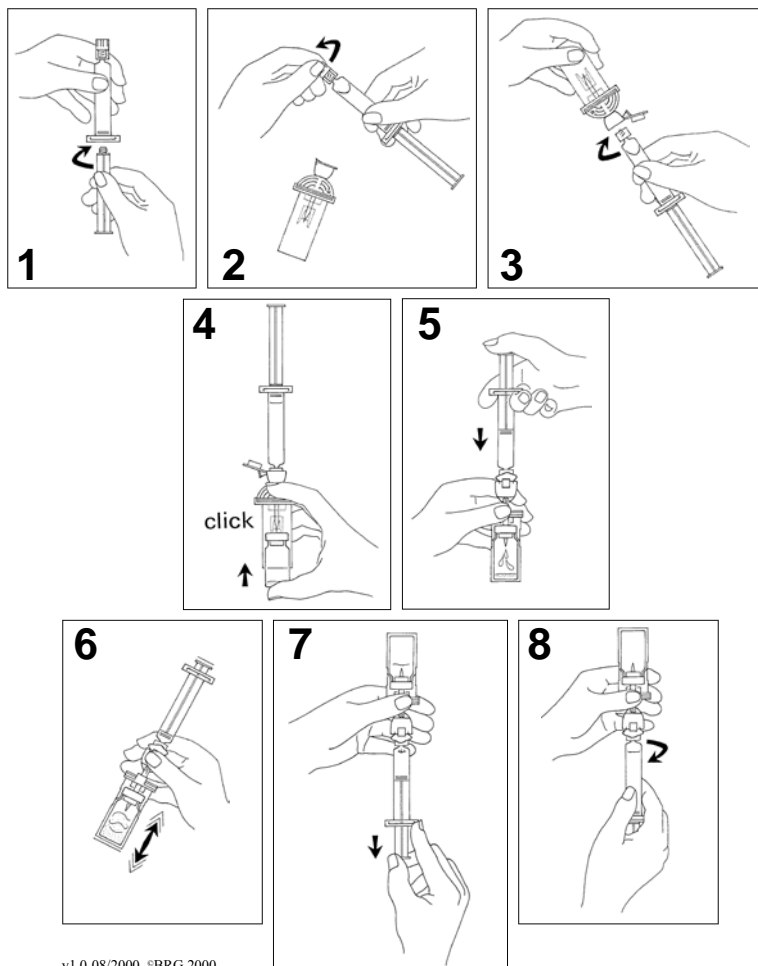
Presentation 02 (with separate MiniSpike transfer system):
25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride in a colourless Type I glass vial, with elastomeric closure.
Separate transfer system.
Type I glass pre-filled syringe containing 5 ml sodium chloride 9 mg/ml (0.9%) solution 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:

Presentation 02 (with separate MiniSpike transfer system)



v1.0-08/2000 ©BRG 2000

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 the 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 to obtain a white milky homogeneous liquid.
7. Invert the system and carefully withdraw SonoVue into the syringe.
8. Unscrew the syringe from the transfer system.

Do not use if the liquid obtained is clear and/or if solid parts of the lyophilisate are seen in the suspension.

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 medicinal product or waste material must be discarded in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/177/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 March 2001 / 24 April 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bracco Imaging S.p.A.
Via Ribes 5, Biondustry Park
Colleretto Giacosa - 10010 (TO)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer label, presentation 02

1. NAME OF THE MEDICINAL PRODUCT

SonoVue sulphur hexafluoride microbubbles 8 microlitres/ml
Powder and solvent for dispersion for injection

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 8 µl of sulphur hexafluoride microbubbles

3. LIST OF EXCIPIENTS

Macrogol 4000, distearoylphosphatidylcholine, dipalmitoylphosphatidylglycerol sodium, palmitic acid.
Solvent: sodium chloride 9 mg/ml (0.9%) solution for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial containing 25 mg lyophilized powder to be reconstituted with 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection
1 pre-filled syringe containing sodium chloride 9 mg/ml (0.9%) solution for injection
1 Mini-Spike Plus 6/8 (CE 0123) transfer system.
1 ml of the reconstituted dispersion contains 8 microlitres sulphur hexafluoride microbubbles.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read carefully the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only, discard any unused portion

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/177/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SonoVue 8 microlitres/ml powder for dispersion for injection

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg lyophilised powder to be reconstituted with 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection before administration.

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sodium chloride 9 mg/ml solution for injection

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

Exp:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

For use with SonoVue

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What SonoVue is and what it is used for
2. What you need to know before you use SonoVue
3. How to use SonoVue
4. Possible side effects
5. How to store SonoVue
6. Contents of the pack and other information

1. What SonoVue is and what it is used for

SonoVue is a contrast agent for ultrasound scans of blood vessels and tissues of the body.

SonoVue is a dispersion containing millions of tiny bubbles (microbubbles). Each of these bubbles is smaller than a red blood cell. The bubbles act as a reflector of the ultrasound beam and provide a better echo than the tissues of the body.

SonoVue is a contrast agent that reflects ultrasound waves differently from the tissues of the body and improves the picture from the scan. This helps your doctor to identify the part of your body or blood vessel and to see any abnormalities. SonoVue can be used for scans of the chambers of the heart, scans of large blood vessels and scans to assess lesions in the breast and the liver.

This medicine is for diagnostic use only.

2. What you need to know before you use SonoVue

Do not use SonoVue:

If you are allergic to sulphur hexafluoride or any of the other ingredients of this medicine (listed in section 6) or if you have:

- right-to-left shunts of the heart,
- severe increase in pulmonary artery blood pressure,
- uncontrolled hypertension,
- adult respiratory distress syndrome.
- you should not be given this medicine together with dobutamine, if dobutamine has been contraindicated to you due to your severe cardiac disease.

If you have had an allergic reaction in the past to SonoVue or any other ultrasound contrast agent tell your doctor.

Warnings and precautions

If you have to undergo echocardiography during stress, tell your doctor if in the past 2 days you have:

- had frequent and/or repeated angina or chest pain, especially if you have history of heart disease,
- recent electrocardiography changes.

During SonoVue-enhanced echocardiography examination with a pharmacological stress, ECG and blood pressure will be carefully monitored.

Talk to your doctor or pharmacist before using SonoVue, tell your doctor if you have any of the following conditions:

- if you had a myocardial infarction or coronary artery intervention,
- if you suffer from angina or chest pain, or heart failure or severe heart rhythm disorders,
- if you had recent electrocardiography changes
- in case you have severe lung disease and shortage of breath,
- in case you have a neurological illness which is unstable, respiratory ventilation, acute endocarditis, artificial heart valves, acute systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent thromboembolism, advanced kidney or liver diseases.

Other medicines and SonoVue

There are no reports of reactions between SonoVue and other medicines.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

SonoVue has not been studied in pregnant women. Danger to a developing baby is not expected. If you are pregnant, think you may be pregnant, or planning to have a baby, ask your doctor for advice before taking this medicine.

If you are breast feeding tell your doctor. It is not known if SonoVue passes into breast milk.. Usually, you should stop feeding for two to three hours after your ultrasound examination.

3. How to use SonoVue

After reconstitution, SonoVue is a homogeneous white milky dispersion. If solid parts are seen or the dispersion is not homogeneous, the product will be discarded.

If SonoVue is not used immediately after reconstitution the dispersion will be shaken again before being drawn up into a syringe.

SonoVue is injected into a vein, usually in your arm. The amount that you will be given depends on which part of your body is being scanned. The usual dose is 2 or 2.4 ml of the dispersion. This dose might be repeated. The medical staff supervising your scan will administer the injection of SonoVue to you. The dose is the same in adult and elderly patients, however SonoVue should not be given to patients under 18 years old.

You will be monitored for 30 minutes after your examination.

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

If you have any further questions on the use of this product, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most of the side effects are mild to moderate. However, some patients may experience serious side effects and may require treatment.

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- Signs of a severe allergic reaction such as swelling of the face, lips, mouth or throat which may make it difficult to swallow or breathe; skin rash; hives; swelling of the hands, feet or ankles.

Side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

The following side effects have been observed with SonoVue:

Uncommon:

- Headache
- Numbness
- Dizziness
- Strange taste in the mouth
- Flushing
- Irritation in the throat
- Feeling sick (nausea),
- Abdominal pain
- Itching; skin rash
- Back pain
- Feeling hot
- Local reactions where the injection was given such as: pain or an unusual sensation at the injection site
- Increase in blood sugar levels

Rare:

- Difficulty in sleeping
- Pain or pressure in the forehead, cheeks, nose and between the eyes
- Blurred vision
- Decrease in blood pressure
- Pain in general,
- Chest pain
- Fatigue
- Severe and less severe allergic reaction (including redness of the skin, decrease in heart rate, decrease in blood pressure, breathlessness, loss of consciousness, cardiac/cardio-respiratory arrest, anaphylactic reaction, anaphylactoid reaction or anaphylactic shock)

Not known:

- Faintness
- In some of the cases of allergic reactions, cardiac ischemia and/or heart attack were also reported in patients with underlying coronary artery disease

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system**

listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SonoVue

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of the month.

This medicinal product does not require any special storage conditions.

SonoVue dispersion should be administered to you within six hours of its preparation.

6. Content of the pack and further information

What SonoVue contains

The active substance is sulphur hexafluoride in the form of microbubbles.

The other ingredients are: macrogol 4000, distearoylphosphatidylcholine, dipalmitoylphosphatidylglycerol sodium, palmitic acid.

The glass syringe contains sodium chloride 9 mg/ml (0.9%) solution for injection.

What SonoVue looks like and content of the pack

SonoVue is a kit which includes a glass vial containing white powder, a glass syringe containing the solvent and a transfer system.

Marketing Authorisation Holder and Manufacturer:

Marketing authorisation holder

Bracco International B.V.

Strawinskylaan 3051

NL - 1077 ZX Amsterdam

The Netherlands

Manufacturer:

Bracco Imaging S.p.A.

Via Ribes 5, Biondustry Park

Colleretto Giacosa - 10010 (TO)

Italy

This leaflet was last revised on

Other sources of information

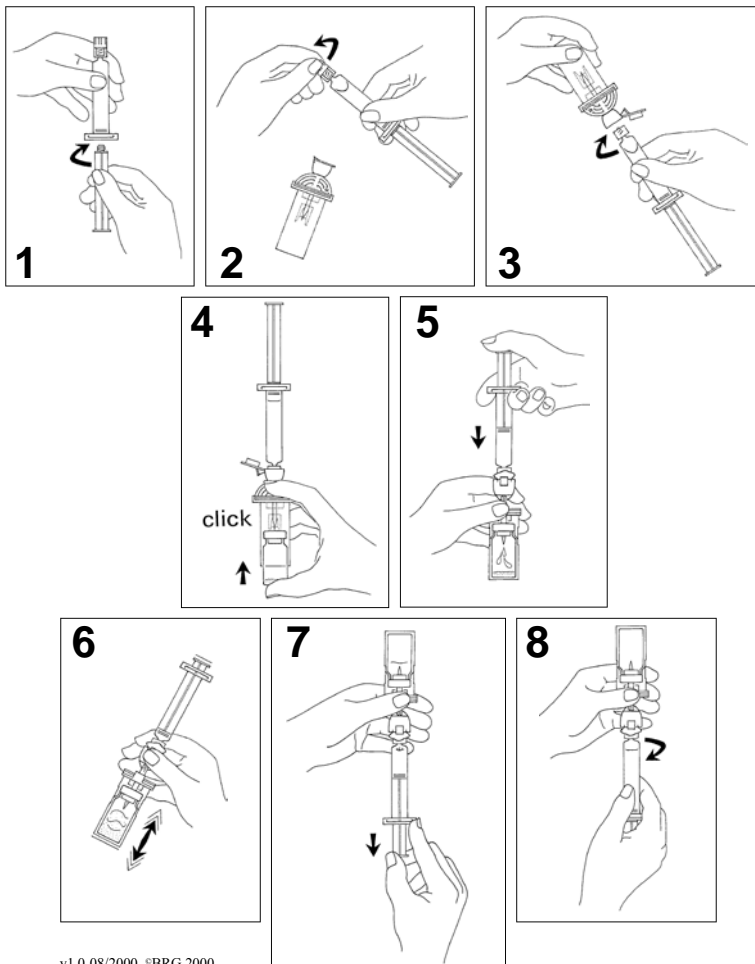
Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for medical or healthcare professionals only:

Presentation 02 (with separate MiniSpike transfer system (CE 0123))



v1.0-08/2000 ©BRG 2000

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 the 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 to obtain a white milky homogeneous liquid.
7. Invert the system and carefully withdraw SonoVue into the syringe.
8. Unscrew the syringe from the system.

Do not use if the liquid obtained is clear and/or if solid parts of the lyophilisate are seen in the suspension.

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION TO
THE TERMS OF THE MARKETING AUTHORISATION**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for sulphur hexafluoride, the scientific conclusions of CHMP are as follows:

The PRAC recommended the deletion of the contraindication to use SonoVue in pregnancy and breastfeeding.

The removal of the pregnancy contraindication is based on the following points: a) animal studies do not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. b) No clinical data on exposed pregnancies are available, and literature and PSUR data are insufficient to allow firm conclusions to be drawn. c) In the current Summary of Product Characteristics (SmPC), the wording is not consistent between sections 4.3 and 4.6. In light of this, as human data are limited, it is preferable to avoid the use of SonoVue during pregnancy as a precautionary measure. However, animal data are reassuring with the risk of malformation being unlikely in humans, consequently, the PRAC considers that the contraindication can be removed and the wording in section 4.6 updated.

The removal of the breastfeeding contraindication is based on the following points: a) SF₆ (the active component in SonoVue microbubbles) dissolves in the blood and is eliminated extremely rapidly from the body via the expired air. However, it is unknown whether SF₆/metabolites are excreted in human milk. b) No adverse events have been reported, however, literature and PSUR data are insufficient to allow firm conclusions to be drawn. c) In the current SmPC, the contraindication wording is not consistent between sections 4.3 and 4.6. As it is not known if sulphur hexafluoride is excreted in human milk but SF₆ is known to be eliminated extremely rapidly from the body the PRAC agreed that caution should be exercised when SonoVue is administered to breast-feeding women leading to the removal of the contraindication. The PRAC considers that information on the rapid elimination of the active component of SonoVue, introducing two to three hours waiting time after the administration based on 5 times the half-life of 12 min as a minimum, should be added to the product information.

Based on the new cumulative number of patients who participated in clinical trials in the approved indications the adverse drug reaction (ADR) frequencies for the following events was revised as follows:

- chest pain, fatigue and pain: from uncommon to rare;
- hypersensitivity: from unknown to rare;
- abdominal pain from rare to uncommon.

In addition to these frequency changes some minor amendments to the wording of section 4.8 of the Summary of Product Characteristics were requested to improve the readability.

Therefore, in view of available data regarding sulphur hexafluoride, the PRAC considered that changes to the product information and conditions of the marketing authorisation were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for sulphur hexafluoride the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing sulphur hexafluoride is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.