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

Each mL of the dispersion contains 8 µL sulphur hexafluoride microbubbles, equivalent to 45 micrograms.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for dispersion for injection.
White powder
Clear, colourless solvent

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, or of fluids in the urinary tract 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 adult 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 in adult patients 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 in adult patients.

Doppler of microvasculature
SonoVue improves display of the vascularity of liver and breast lesions during Doppler sonography in adult patients leading to more specific lesion characterisation.

Ultrasonography of excretory urinary tract
SonoVue is indicated for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux. For the limitation in the interpretation of a negative urosonography, see section 4.4. and 5.1.

4.2 Posology and method of administration

This product should only be used by physicians experienced in diagnostic ultrasound imaging. Emergency equipment and personnel trained in its use must be readily available.

Posology

Intravenous use
The recommended doses of SonoVue in adults 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 dose recommendations for intravenous administration also apply to elderly patients.

Paediatric Patients
The safety and efficacy of SonoVue in patients under 18 years of age has not been established for intravenous administration and use in echocardiography and vascular Doppler imaging.

Intravesical use
- In paediatric patients the recommended dose of SonoVue is 1 mL

Method of administration
For instructions on reconstitution of the medicinal product before administration see section 6.6.

Intravenous use
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.

Intravesical use
After introduction of a sterile 6F-8F urinary catheter into the bladder under sterile conditions, the bladder is emptied of urine and then filled with saline (normal sterile 0.9% sodium chloride solution) to approximately one third or half of its predicted total volume [(age in years + 2) x 30] mL. SonoVue is then administered through the urinary catheter. Administration of SonoVue is followed by completion of bladder filling with saline until patient has the urge to micturate or there is the first slight sign of back pressure to the infusion. Ultrasound imaging of the bladder and kidneys is performed during filling and voiding of the bladder. Immediately following the first voiding, the bladder may be refilled with saline for a second cycle of voiding and imaging, without the need of a second SonoVue administration. A low mechanical index (≤ 0.4) is recommended for imaging the bladder, ureters, and kidney during ultrasonography of the urinary tract with contrast.

4.3 Contraindications

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

Intravenous use of SonoVue is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome.
SonoVue must 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

Hypersensitivity reactions
Serious hypersensitivity reactions have been observed during or shortly following SonoVue administration in patients with no prior exposure to sulphur hexafluoride microbubbles products, including patients with prior hypersensitivity reaction(s) to macrogol, also known as polyethylene glycol (PEG) (see section 4.8).

SonoVue contains PEG (see section 6.1). There may be increased risk of serious reactions in patients with prior hypersensitivity reaction(s) to PEG.
It is recommended to keep all patients under close medical supervision during and for at least 30 minutes following the administration of SonoVue to monitor the risk of serious hypersensitivity reactions (see section 4.2).

Use caution when treating anaphylaxis with epinephrine in patients on beta blockers since response may be poor or promote undesired alpha-adrenergic and vagotonic effects (hypertension, bradycardia).

Intravenous use

Patients with unstable cardiopulmonary status
ECG monitoring should be performed in high-risk patients as clinically indicated and a close medical supervision is recommended.

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.

It should be emphasised that stress echocardiography not only can induce an ischaemic episode but also the stressors may induce predictable, dose-dependent effects on the cardiovascular system (e.g., increase in heart rate, blood pressure and ventricular ectopic activity for dobutamine, or decrease in blood pressure for adenosine and dipyridamole) as well as unpredictable, hypersensitivity reactions. 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).

Other concomitant diseases
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, as the numbers of patients with those conditions who were exposed to SonoVue in the clinical trials were limited.

Interpretation of voiding urosonography with SonoVue and limitations of use
False negative cases can occur with voiding ultrasonography with SonoVue and have not been clarified (see section 5.1).

Technical recommendation
In animal studies, the application of echo-contrast agents revealed biological adverse reactions (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.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy, lactation, and fertility

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.

Fertility

No clinical data are available. Animal studies do not indicate harmful effects on fertility.

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

Adult population-Intravenous use

The safety of SonoVue after intravenous administration was evaluated in 4653 adult patients who participated in 58 clinical trials. The undesirable effects reported with SonoVue after intravenous administration were, in general, non-serious, transient and resolved spontaneously without residual effects. In clinical trials, the most commonly reported adverse reactions after intravenous administration are: headache, injection site reaction, and nausea.

The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < /100), Rare (≥ 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 (≥ 1/1,000 to < 1/100)	**Rare (≥ 1/10,000 to < 1/1000)**	**Not known Cannot be estimated from available data**
Immune system disorders		Hypersensitivity*	
Nervous system disorders	Headache, paraesthesia, dizziness, dysgeusia		Vasovagal reaction
Eye disorders		Vision blurred,	
Cardiac disorders			Myocardial infarction** Myocardial ischemia** Kounis syndrome***
Vascular disorders	Flushing	Hypotension	
Gastrointestinal disorders	Nausea, Abdominal pain		Vomiting
Skin and subcutaneous tissue disorders	Rash	Pruritus	
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	

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

***Allergic acute coronary syndrome

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.

Paediatric population-Intravesical use

The safety of SonoVue after intravesical administration was based on evaluation of published literature involving use of SonoVue in over 6000 paediatric patients (age range 2 days to 18 years). No adverse reactions were reported.

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 52 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: VO8DA05.
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**.** 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 intensity of the reflected signal is dependent on concentration of the microbubbles and frequency of the ultrasound beam. 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.

Intravenous use
At the proposed clinical doses for intravenous administration, 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.

Intravesical use
For ultrasonography of the excretory urinary tract in paediatric patients, after intravesical administration, SonoVue increases the signal intensity of fluids within the urethra, bladder, ureters, and renal pelvis, and facilitates the detection of reflux of fluid from the bladder into the ureters.
The efficacy of SonoVue for detection/exclusion of vesicoureteral reflux was studied in two published open label single centre studies. The presence or absence of vesicoureteral reflux with SonoVue ultrasound was compared to the radiographic reference standard. In one study including 183 patients (366 kidney-ureter units), SonoVue ultrasound was correctly positive in 89 out 103 units with reflux and correctly negative in 226 out of 263 units without reflux. In the second study including 228 patients (463 kidney-ureter units), SonoVue ultrasound was correctly positive in 57 out of 71 units with reflux and correctly negative in 302 out of 392 units without reflux.

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.

Intravesical local tolerance for SonoVue was also assessed. A single-dose study and a repeat-dose study, both followed by a treatment-free period, were performed in female rats with local toxicity

evaluated through macroscopic and histopathological examination of both kidneys, ureters, the urinary bladder and urethra. It did not reveal any test item-related lesions in any of the examined organs, in particular in the urinary bladder, in both the single-dose and the repeat-dose studies. It was therefore concluded that SonoVue is well tolerated in the urinary tract in the rat.

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 medicinal 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

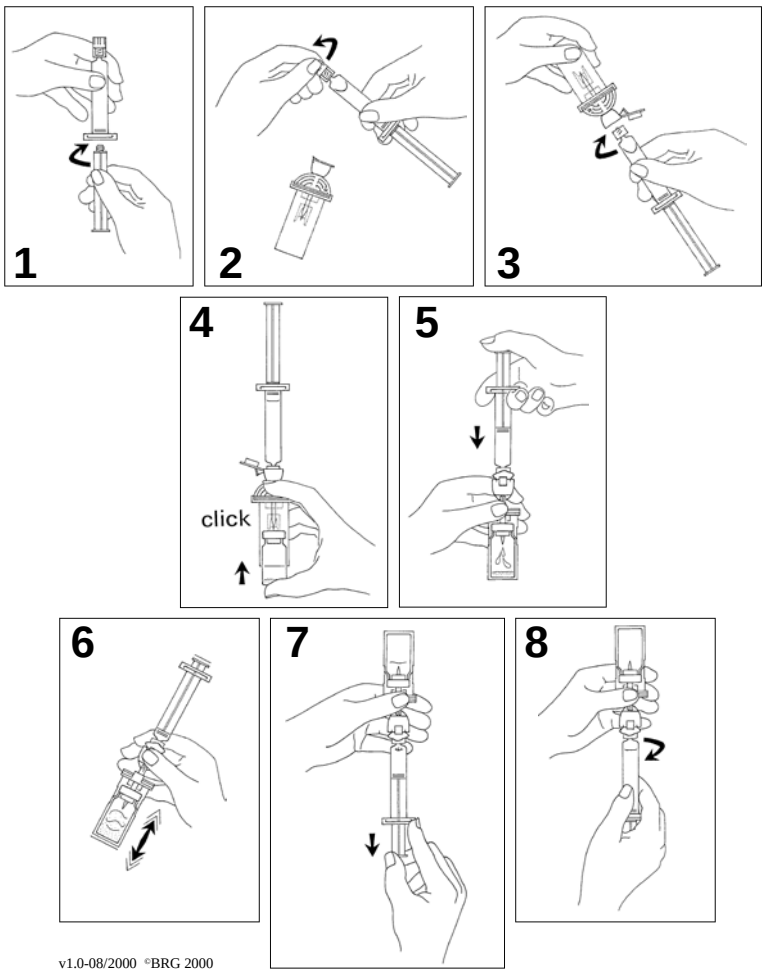
Type I colourless glass vial containing 25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride closed with a grey butyl rubber stopper and sealed with an aluminium crimp seal with a flip-off disc. A transfer system (MiniSpike).

Type I clear 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:



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 for use in echocardiography and in vascular Doppler imaging in adults or by intravesical administration for use in ultrasonography of the excretory urinary tract in paediatric patients.

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 use only.
Any unused medicinal product or waste material should be disposed of 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

Date of first authorisation: 26 March 2001
Date of latest renewal: 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, Bioindustry 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): in order to assess subject management among children undergoing SonoVue-enhanced VUS in comparison with children undergoing VCUG for assessment of VUR, the MAH should conduct and submit the results of the observational cohort study (according to the agreed protocol).	Final study report to be submitted by 1Q 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer packaging

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of the dispersion contains 8 µLsulphur hexafluoride microbubbles, equivalent to 45 micrograms.

3. LIST OF EXCIPIENTS

Macrogol 4000, distearoylphosphatidylcholine, dipalmitoylphosphatidylglycerol sodium, palmitic acid, Solvent: sodium chloride 9 mg/mL

4. PHARMACEUTICAL FORM AND CONTENTS

1 powder vial, 1 pre-filled syringe of solvent, 1 transfer system

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous or intravesical use
Read the package leaflet before use.
For single use only

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

Keep out of the sight and reach 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

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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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
sulphur hexafluoride

2. METHOD OF ADMINISTRATION

Intravenous or intravesical use

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg powder

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
Solvent for SonoVue

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

Read all of this leaflet carefully before you are given 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

SonoVue is for diagnostic use only.

SonoVue is an ultrasound contrast agent that contains tiny bubbles filled with a gas called sulphur hexafluoride.

If you are an adult, SonoVue helps to obtain clearer ultrasound pictures of your heart, your blood vessels and/or tissues of the liver and breast.

SonoVue helps to obtain clearer pictures of the urinary tract in children.

2. What you need to know before you are given 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).
- If you have been told you have a right-to-left heart shunt.
- If you have severe pulmonary hypertension (pulmonary artery pressure > 90mmHg).
- If you have uncontrolled hypertension.
- If you have adult respiratory distress syndrome (a severe, medical condition characterized by widespread inflammation in the lungs).
- If you have been told not to take dobutamine (medicine that stimulates the heart) due to your severe heart disease.

Warnings and precautions

Please 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,
- had recent electrocardiography changes.

Talk to your doctor before you are given SonoVue if:
- you had a recent myocardial infarction or a recent surgery on your coronary arteries,
- you suffer from angina or chest pain or severe cardiac disease,
- you suffer from severe heart rhythm disorders,
- your cardiac disease has worsened recently,
- you have an acute inflammation of the cardiac envelope (endocarditis),
- you have artificial heart valves,
- you have an acute general inflammation or infection,
- you have known blood clotting problem,
- you have severe kidney or liver diseases,

If you are given SonoVue together with a medicine, exercise or a device that stimulates the heart in order to visualise your heart under stress work, your heart activity, your blood pressure and rhythm will be monitored.
SonoVue contains macrogol, an ingredient also known as polyethylene glycol (PEG). Cases of serious allergic reactions have been reported. There may be increased risk of serious reactions in patients with prior allergic reaction(s) to PEG. Inform your doctor if you had prior allergic reactions to PEG containing products.
A close medical supervision during at least 30 minutes is necessary following the administration of SonoVue to monitor the risk of serious allergic reactions.

Children and adolescents
For patients under 18 years of age SonoVue can be used only for ultrasound of the urinary tract**.**

Other medicines and SonoVue

Tell your doctor if you are taking, have recently taken or might take any other medicines.
In particular, please tell your doctor if you are taking beta-blockers (medicines for heart disease and hypertension or for glaucoma in eye drops).

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

It is not known if SonoVue passes into breast milk. However, you must stop breastfeeding for two to three hours after your ultrasound examination.

Driving and using machines

SonoVue does not affect the ability to drive and use machines.

SonoVue contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

3. How SonoVue is given

SonoVue is given to you by medical or healthcare professionals who are experienced in this type of examination.

For ultrasound scan of heart or your blood vessels and/or tissues of the liver and breast in adults, the dose to be administered into a vein will be calculated for you depending on which part of your body is being examined. The recommended dose is 2 or 2.4 mL per patient. This dose might be repeated if

needed up to 4.8 mL.

For ultrasound scan of urinary tract in children the recommended dose is 1 mL per patient to be administered into the bladder as follows:
After emptying the bladder, a saline solution will be introduced into the bladder via a thin tube. SonoVue will then be administered through the thin tube and will be followed by administration of saline to continue filling the bladder. The filling and emptying of the bladder with saline solution may be repeated if needed.

If you have a serious pulmonary or cardiac condition, you will be under close medical supervision during and for at least 30 minutes after the injection of SonoVue.

If you are given more SonoVue than you should

Overdose is not likely to happen since SonoVue is given by a doctor. In the case of overdose, the doctor will take appropriate action.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Most of the side effects to SonoVue are rare and usually not serious. However, some patients may experience serious side effects and may require treatment.

Tell your doctor straight away if you notice any of the following side effects, you may need medical treatment: 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.

The following side effects have been reported with SonoVue:

Uncommon side effects (may affect up to 1 in 100 people):
- Headache
- Numbness
- Dizziness
- Strange taste in the mouth
- Redness
- Chest discomfort
- Feeling sick (nausea)
- Abdominal pain
- skin rash
- Feeling hot
- Local reactions where the injection was given such as: pain or an unusual sensation at the injection site

Rare (may affect up 1 in 1,000 people):
- Blurred vision
- Decrease in blood pressure
- Itching
- Back pain
- 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 or more severe reaction with difficulties in breathing and dizziness)

Not known (frequency cannot be estimated from the available data):

- Chest pain, radiating to the neck or the left arm, which can be a sign of a potentially serious allergic reaction called Kounis syndrome
- Faintness
- In some of the cases of allergic reactions, in patients with cardiac blood vessel disease, lack of oxygen supply of the heart or cardiac arrest were reported
- Vomiting

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 that 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. Contents of the pack and other 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 contents 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, Bioindustry Park
Colleretto Giacosa - 10010 (TO)
Italy

This leaflet was last revised on

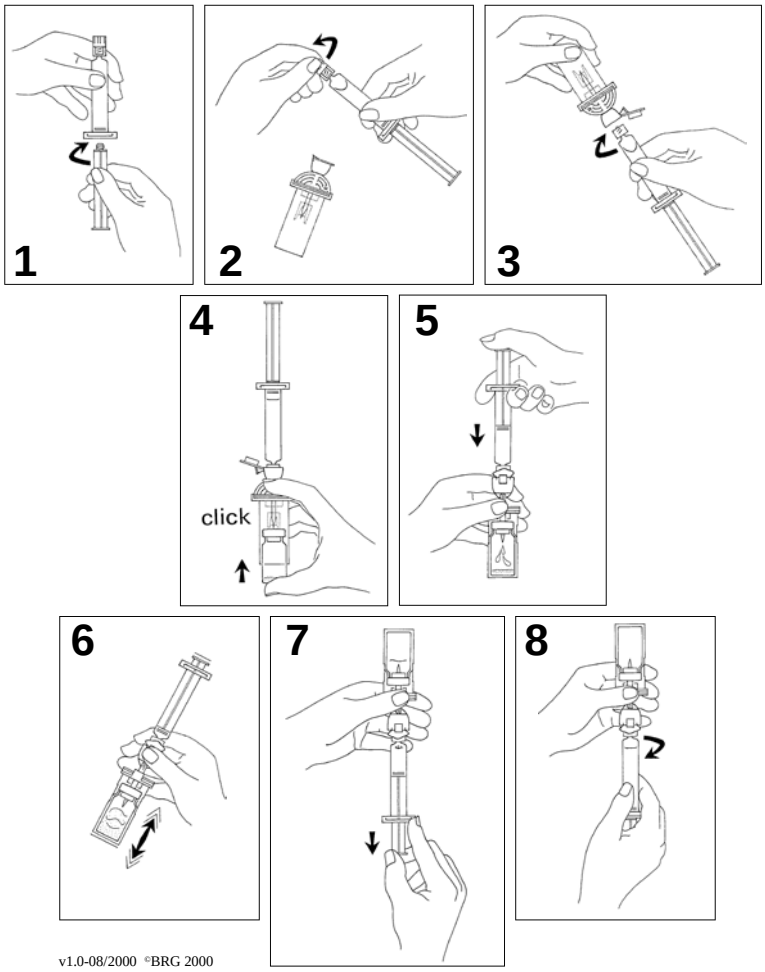
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

If SonoVue is not used immediately after reconstitution the dispersion will be shaken again before being drawn up into a syringe.
The product is for a single examination only. Any unused liquid remaining at the end of an examination must be discarded.

Reconstitution instructions:



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.

After reconstitution, SonoVue is a homogeneous white milky dispersion.

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

SonoVue dispersion should be administered within six hours of its preparation.
Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

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

In view of available data on PEG allergy from the literature, spontaneous reports including in some cases a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers that the warning section should be amended to highlight the role of PEG in the occurrence of rare but serious hypersensitivity reactions and to strengthen the existing wording about hypersensitivity reactions.

The PRAC concluded that the product information of products containing sulfur hexafluoride should be amended accordingly.

Grounds for the variation to the terms of the marketing authorisation(s)

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

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.