SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SonoVue

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, 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. 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 and the product should not be used in these patients.

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.

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 SonoVue 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.

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 < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data)

	Adverse Drug Reactions

System Organ Class	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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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.

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

The expiry date of the product is indicated on the packaging materials.

Once reconstituted, the product should be used immediately, 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

Store below 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

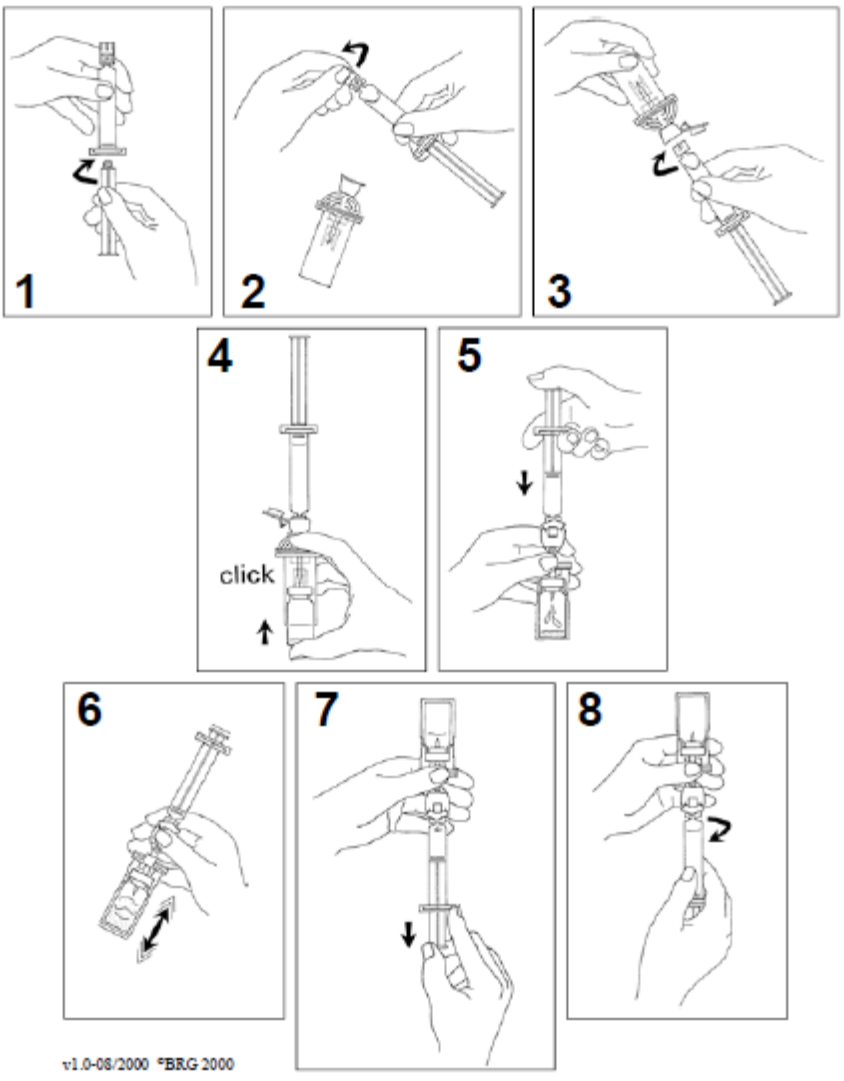
6.5 Nature and contents of container

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.

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

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

153-03-34004-00

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