patients with suspected or established cardiovascular disease to provide echocardiographic information.

4.4 Special warnings and special precautions for use

Echocardiography

SonoVue® is a transcutaneous echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide echocardiographic information.

Elders

The dosage recommendations also apply to elderly patients.

Pneumococcal 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 recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest or at rest in last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery revascularization or other factors suggesting clinical instability (e.g., recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class IIb heart failure, and severe rhythm disorders.

SonoVue® is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >30 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 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). ECG monitoring should be performed in high-risk patients as clinically indicated.

Care should be taken in patients with ischaemic cardiac disease because in these patients allergy-like and/or vasodilatory reactions may lead to life-threatening conditions.

Emergency equipment and personnel trained in its use should be readily available. Caution is advised when SonoVue® is administered to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease.

It is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue®.

Numbers of patients with the following conditions who were exposed to SonoVue® in the clinical trials were limited, and therefore, caution is advised when administering the product to patients with:

- acute endocarditis, prosthetic valves, acute systemic inflammation and/or sepsis, hypervascular coagulation states and/or recent thrombomembolism, and end-stage renal or hepatic disease.

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

In animal studies, the application of echo-contrast agents revealed biological side effects (e.g., endocardial cell injury, capillary rupture) by interaction with the ultrasound beam.

Although the biological side effects have not been reported in humans, the use of a low mechanical index is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed. There was no apparent relationship with respect to occurrence of adverse events in the clinical studies for patients receiving various categories of the most common concomitant medications.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 Preclinical safety data). Caution should be exercised when prescribing to pregnant women. It is not known if sulphur hexafluoride is excreted in human milk. Therefore, caution should be exercised when SonoVue® is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacokinetic and pharmacodynamic profiles, no or negligible influence is expected with the use of SonoVue® on the ability to drive or use machines.

4.8 Undesirable effects

Like all medicines, SonoVue® 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
- Flush
- Irritation in the throat
- Feeling sick (nausea)
- Itching, skin rash
- Black skin
- Feeling hot
- Chest pain or discomfort
- Fatigue
- Local reactions where the injection was given such as: pain or an unusual sensation at the injection site
- Pain in general
- Increase in blood sugar levels
- Rare:
  - Difficulty in sleeping
  - Pain or pressure in the forehead, cheeks, nose and between the eyes
  - Blurred vision
  - Abdominal pain
The intensity of the reflected signal is dependent on concentration of the sulphur hexafluoride bubble and the aqueous medium acts as a microbubble. Each millilitre of SonoVue® contains 8µl of the microbubbles.

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 6µl 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 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. 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® it is 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 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.

6.4 Special precautions for storage

No special precautions for storage.

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 U 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:

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 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.

Not known:

- Loss of consciousness
- Severe and less severe allergic reaction

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.

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.

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