The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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PUBLIC STATEMENT ON

SONOVUE[1] (SULPHUR HEXAFLUORIDE)
New contraindication in patients with heart disease. Restriction of use to non-cardiac imaging

Severe allergy and heart problems have been reported as rare side effects occurring within minutes of SonoVue being given. SonoVue is a diagnostic contrast medium for use with ultrasound imaging where study without contrast enhancement is inconclusive. As such it is only used in the hospital or clinic setting. On the basis of the reported adverse events and as a precautionary measure the EMEA has restricted the use of SonoVue by an urgent procedure. This amounts to a temporary suspension of its use in heart imaging (echocardiography), pending further evaluation of the balance of benefits and risks. The EMEA has consulted its scientific committee, the CPMP before taking this action.

EMEA wishes to inform health care professionals and the public as follows:

- **SonoVue should no longer be used in echocardiography**
- **SonoVue is now contra-indicated in patients with known coronary artery disease, myocardial infarction, unstable angina, acute cardiac failure, class III/IV cardiac failure, severe rhythm disorders, acute endocarditis and prosthetic valves**
- **SonoVue is still indicated for use in non-cardiac imaging (echo-Doppler of macro- and microvasculature): imaging of blood vessels, breast and liver**
- **Patients should be kept under close medical supervision during and for at least 30 minutes following the administration of SonoVue.**

The adverse events that led to the above regulatory action included severe hypotension (lowering of blood pressure), bradycardia (slow heart rate), cardiac arrest and acute myocardial infarction (heart attack). Most occurred in patients undergoing echocardiography, in the context of an idiosyncratic hypersensitivity reaction: this is a severe allergy where sensitivity of the individual patient is difficult to predict. Three fatalities occurred in patients with pre-existing, severe coronary artery disease.

The EMEA will continue to review all information relating to the safety of SonoVue and will take further regulatory action, as appropriate. Details of the main changes to the product information for prescribers and users of SonoVue are provided in Annex 1. Details of the marketing authorisation holder and their local representatives are provided in Annex 2. For further information please also refer to the SonoVue Question and Answer Document.

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or the national health authority in your country

[1] SonoVue was authorised (licensed) in the EU on 26 March 2001. The Marketing Authorisation Holder is Bracco International B.V. SonoVue is currently marketed in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxemburg, Netherlands, Portugal, Spain, Sweden and United Kingdom and also in Norway.

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Details of the changes[2] to relevant parts of the Summary of Product Characteristics for SonoVue

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

The recommended doses of SonoVue is~~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.

4.3 Contraindications

SonoVue should not be administered to patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue.

SonoVue is contraindicated for use in patients with ***known coronary artery disease***, ***myocardial infarction, unstable angina, acute cardiac failure and class III/IV cardiac failure and severe arrhythmic disorders*** or those known to have right-to-left shunts, ***acute endocarditis***, ***prosthetic valves***, severe pulmonary hypertension (Pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome.

The safety and efficacy of SonoVue have not been established in pregnant and lactating women therefore, SonoVue should not be administered during pregnancy and lactation (see Section 4.6).

[2] Highlighted by strikethrough and bold italic

4.4 Special warnings and special precautions for use

It is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue.
Emergency equipment and personnel trained in its use should be readily available. Caution is advised when SonoVue is administered to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease.

Numbers of patients with the following conditions who were exposed to SonoVue in the clinical trials were limited, and therefore, caution is advisable when administering the product to patients with: acute systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent ***non cardiac*** thromboembolism, and end-stage renal or hepatic disease.

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

4.8 Undesirable effects

Post marketing
Rare cases suggestive of hypersensitivity, which could include: skin erythema, bradycardia, hypotension or anaphylactic shock have been reported following the injection of SonoVue. In some of these cases, in patients with underlying coronary artery disease, bradycardia and hypotension were accompanied by myocardial ischemia and/or myocardial infarctions.

In very rare cases, fatal outcomes have been reported in temporal association with the use of SonoVue. In all these patients there was a high underlying risk for major cardiac complications, which could have led to the fatal outcome.

Annex 2

Details of the marketing authorisation holder of SonoVue and their local representatives

Marketing Authorisation Holder

Bracco International B.V.
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List of local representatives

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