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27 October 2014

Direct Healthcare Professional Communication

Revised Contraindications and Warnings and Precautions for the use of SonoVue® (sulphur hexafluoride)

Dear Healthcare Professional,

Bracco International BV, in agreement with the European Health authorities and the Health Products Regulatory Authority (formerly Irish Medicines Board), would like to inform you of important new safety information for SonoVue®.

Summary

- **Rare but severe arrhythmias, sometimes fatal, have been reported in patients with cardiovascular instability during stress echocardiography procedure with SonoVue used in combination with dobutamine.**
- **Therefore, in patients with conditions suggesting cardiovascular instability (e.g. recent acute coronary syndrome or clinically unstable ischaemia), SonoVue should not be used in combination with dobutamine.**
- **When administered alone in patients with cardiovascular instability, SonoVue should be used with extreme caution and only be administered after careful risk/benefit assessment; a close monitoring of vital signs should be performed during and after administration, because in these patients allergy-like and/or vasodilatory reactions may lead to life-threatening conditions.**

Additional information

In the European Union, SonoVue is approved for use in:

- **echocardiography**, as a transpulmonary echocardiographic contrast agent, in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation;
- **doppler of macrovasculature**, to increase the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries;
- **doppler of microvasculature**, to improve display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.

Bracco International BV

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Rare but severe arrhythmias, sometimes fatal, have been reported in patients with cardiovascular instability who underwent stress echocardiography using SonoVue in combination with dobutamine (*i.e.* ventricular arrhythmia, cardiorespiratory arrest and severe bradycardia).

In view of the frequent use of the direct-acting inotropic agent dobutamine for stress echocardiographic procedures and the risk of serious adverse cardiac reactions when used in combination with SonoVue in patients with cardiovascular instability, the European Health Authorities have decided to add a contraindication for the use of this combination in patients with conditions suggesting cardiovascular instability.

In addition, based on the results of literature and clinical experience the existing contraindication in patients with recent acute coronary syndrome or clinically unstable ischemic cardiac disease was removed and replaced by a warning. This included a retrospective non-interventional safety study (BR1-132) investigating the in-hospital mortality rate (within the same day as or the calendar day following performance of the echocardiography procedure) and major adverse events in 757 critically ill patients undergoing echocardiography with the administration of SonoVue in comparison with 3,087 patients undergoing echocardiography without the use of a contrast agent showing no significant difference between the two groups.

However, when Sonovue is administered alone in this context, **Sonovue should be used with extreme caution and only be administered after careful risk/benefit assessment; a close monitoring of vital signs should be performed during and after administration** (see annex).

An updated educational brochure will be provided reflecting these changes and will contain a checklist on cardiac disease and co-morbidities for good reporting.

Call for reporting

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 HPRAs Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Company contact points

Suspected adverse reactions should also be reported to Bracco International BV:

braccodsu@bracco.com

Fax: +390221772766

Phone: +390221772327

For further inquiries concerning the information contained in this communication please contact Professional Services: Services.ProfessionalEurope@bracco.com

Yours faithfully,

A handwritten signature in black ink, appearing to read "Alberto Spinazzi".

Alberto Spinazzi MD

Senior Vice President,

Global Medical and Regulatory Affairs



Annex

Summary of Product Characteristics revised sections 4.3 and 4.4:

(new text added and text moved from Contraindications to Special Warnings and precautions for use in bold,)

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

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 precautions for use

ECG monitoring should be performed in high-risk patients as clinically indicated.

It should be emphasized 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 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.

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.



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Numbers of patients with the following conditions who were exposed to SonoVue in 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.