

TRANSPARENCY COMMITTEE OPINION SUMMARY

SONOVUE (sulphur hexafluoride), contrast agent



High clinical benefit in urinary tract ultrasonography in children (0-18 years) for detecting vesicoureteral reflux and minor clinical added value in the current diagnostic strategy, which includes retrograde urethrocytography techniques, with administration of contrast agents.

Main points

- ▶ SONOVUE has been granted marketing authorisation for urinary tract ultrasonography in children from birth to 18 years, with a view to detecting vesicoureteral reflux.
- ▶ The efficacy data are based upon 4 clinical studies and one pooled analysis of these 4 studies, comparing urinary tract ultrasonography (UTU) with SONOVUE with retrograde mictional urethrocytography (RMU) to detect vesicoureteral reflux in children. In total, in the 4 studies, approximately 60% additional vesicoureteral reflux diagnoses were made with UTU (329 diagnoses) compared to RMU (195 diagnoses) and 28 cases of vesicoureteral reflux diagnosed with RMU were not observed with UTU.
- ▶ The safety profile of SONOVUE is consistent with that already known in its other indications, and is favourable compared to RMU due to the lack of exposure to ionising radiation.

Pre-existing indications*

SONOVUE has already been granted marketing authorisation for echocardiography, Doppler examination of major vessels and micro-vessels (see MA for further details)

Diagnostic strategy

- The diagnosis of vesicoureteral reflux (VUR) is the basis for the management of children with urinary tract infections. The reference imaging technique is retrograde mictional urethrocytography (RMU). This technique is accompanied by the administration of an iodinated contrast agent which enhances the visualisation of the tissue of interest. The main limitation of this examination is the risk of cancer induced by exposure to ionising radiation of the gonads in development in children. Mictional isotope cystography is an imaging alternative, requiring less exposure to ionising radiation than RMU and offering similar sensitivity and specificity. This technique, however, has lower anatomical resolution and is less precise for grading VUR.
- Urinary tract ultrasonography without contrast agent offers low sensitivity for VUR detection and is thus not recommended for this use. Urinary tract ultrasonography with contrast agent for VUR detection is a recognized technique. The urethra can be evaluated and VUR can be graded with a high degree of sensitivity and specificity compared to RMU.
- **Role of the medicinal product in the diagnostic strategy**
Ultrasonography with SONOVUE is a second-line examination in the detection of vesicoureteral reflux in children; it can be performed instead of RMU after urinary tract ultrasonography.

Clinical data

* This summary does not cover these indications.

- The efficacy data are based upon 4 clinical studies and one pooled analysis of these 4 studies, comparing urinary tract ultrasonography (UTU) with SONOVUE 1 ml to retrograde mictional urethrocystography (RMU) to detect vesicoureteral reflux (VUR) in children. RMU is the reference comparator, though it is not an accurate standard; care should thus be taken when interpreting the results. In all those studies, the authors considered that the VUR diagnoses by UTU, that had not been detected by RMU, were false positives relative to the RMU technique.
- Approximately 60% of additional VUR diagnoses were made with UTU (329 diagnoses) compared to RMU (195 diagnoses): this infers reduced specificity for SONOVUE as these cases were considered to be false positives. The results of the pooled analysis of these 4 controlled studies revealed a sensitivity of between 80 and 100%, along with a specificity of between 77 and 86% for UTU with SONOVUE compared to RMU.
- In total, 28 cases of VUR diagnoses by RMU were not observed with UTU. The indication of UTU with SONOVUE was thus established in VUR detection, not in VUR exclusion.
- There is no safety signal specific to the use of SONOVUE in urinary tract ultrasonography in children.

Special prescription requirements

- Medicinal product subject to special monitoring during treatment.
- Prescription reserved for the following specialists: angiologists, cardiologists, neurologists, radiologists, medical resuscitation specialists and anaesthesiologists.

Benefit of the medicinal product

- The actual clinical benefit* of SONOVUE is high.
- SONOVUE provides minor clinical added value** (CAV IV) in the current diagnostic strategy, which includes RMU techniques with administration of contrast agents.
- Approved for non-hospital pharmacy reimbursement or for hospital use.



HAUTE AUTORITÉ DE SANTÉ

This document was drafted on the basis of the Transparency Committee opinion dated 13 June 2018 (CT-16665) available at www.has-sante.fr

* The actual clinical benefit of a medicinal product (ACB) is its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"