SonoVue(r) (sulphur hexafluoride microbubbles)

Diagnostics Assessment Report (DAR) - Comments

Responder reference no.	Comment no.	Page no.	Section no.	Comment	Response
1	1.	19	1.4	In general, diagnostic imaging tests are considered safe and side effects comparably low. Thus, publications on clinical studies (covering comparably low patient numbers) are not well suited to provide information on side effects and the risks associated with different diagnostic modalities. Instead, product information (SPCs) containing market surveillance data on safety could be used to assess safety of different imaging modalities (e.g. cancer risk due to radiation, contrast-induced nephropathy, nephrogenic systemic fibrosis, etc.)	Whilst it is certainly true that safety data are generally poorly reported in clinical studies of diagnostics tests, a full systematic review of post-marketing surveillance data was outside the scope and resources of this project. We have provided a summary/discussion of a large safety study of SonoVue, which was incidentally identified during the course of the review (see page 158 of the report).
1	2.	35	4.1	For characterisation of incidental liver lesions the radiation exposure may be relevant, since this patient group does not predominantely include older patients. In two large multicenter studies the mean age was 59.8 years with a range 12-91 years (Strobel et al, Ultraschall in Med 29, 2008, 499-505) and mean 55.7 +/– 17.9 years (Tranquart et al, Eur J cancer 2008, Suppl 6, 9-15), respectively. This includes a representative age distribution of the population.	The decision not to include radiation exposure as an outcome measure was made at the scoping meeting and agreed at the protocol stage. Previous DAR (new generation cardiac CT) experience of modelling radiation exposure has suggested that it is unlikely to significantly affect cost-effectiveness particularly in older populations and, as such, modelling the effects of radiation exposure does not represent an effective

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					use of the limited resources available. It should be noted that, whilst the age range may extend to younger patients, the mean age is in the 'older patients' range.
1	3.	158	6.3.1	Although there is not enough clinical data, SonoVue safety profile is likely to be better than other modalities in terms of: – No radiation exposure – No nephro-toxicity – Mortality and SAE rates	No response required – this observation is speculative (no supporting data).
1	4.	161	7.1	We agree that the experience with CEUS can have an important impact on diagnostic accuracy. As a new modality, CEUS is biased in clinical studies by lower experience compared to reference modalities being available for many years. We would suggest including a recommendation for educational training for CEUS users into the conclusions, to encourage medical societies and hospitals to establish adequate training programs as suggested by the EFSUMB guidelines.	No response required – possible recommendations for training are a matter for consideration by the appraisal committee, conditional upon the guidance issued.
1	5.	161	7	Higher mortality rates and SAEs have also a direct economical impact because they result in lowering life years.The increased treatment costs to rescue and monitor patients after a SAE are probably significant.	CEUS may have less SAE than other imaging modalities, which may in turn lead to more QALYs and less costs. However, as with point 3, this observation is speculative

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					(no supporting data).
1	6.	162	7.2	There is a long-lasting debate on the optimal design of DTA studies. Although we agree that a common reference standard would be the optimal situation for such a trial, this is almost impossible for ethical reasons. The only accepted gold standard is histology, which can not be justified in lesions of some types suggested by the previous non-invasive imaging tests, due to unacceptable risks (e.g. bleeding in adenomas and hemangiomas). Parallel use of all three imaging modalities in consecutive patients of large population multicenter studies is currently not feasible due to the resources available. Therefore mostly patients of higher pre-test probability and lack of contraindications (e.g. renal insufficiency) are included in such studies, which creates a potential inclusion bias. Furthermore, CT imaging (being the most common alternative diagnostic test) performed in parallel as comparator without clear clinical necessity is barely acceptable due to the radiation burden and usually not approved by radiation protection authorities. Nephro-toxicity works as an exclusion criteria for CECT and CEMRI and, in the absence of CEUS, determines reduced accessibility and reduce QALYs gained by other modalities. In other words, being an important	We recognise the ethical problems associated with biopsy as the reference standard and our inclusion criteria therefore allowed studies which used follow-up in test negative patients or confirmation with multiple imaging tests as the reference standard (see page 34-35 of the report 'reference standard inclusion criteria'). 'Parallel' studies provide the most reliable comparative accuracy data and, as these were available, were the study design of choice for this assessment (as specified in the protocol). The exclusion of patients with contra-indications for CT and MRI from comparative accuracy studies generally involves very small numbers of patients, and is unlikely to have any effect on accuracy estimates; were imaging possible in these patients, there is no reason to presume that it would perform systematically less well in this group.

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				exclusion criteria for CECT and CEMRI, the accuracy of both modalities resulting from the published studies should be considered as biased upward.	