Review decision

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Published: 8 December 2023

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NICE's technology appraisal guidance on selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma (TA688) was published in 2021.

Decision

QuiremSpheres for treating hepatocellular carcinoma (HCC) should be reevaluated, likely as a cost-comparison evaluation with other SIRT technologies for the population they were recommended for in TA688.

Rationale

The clinical evidence submitted by the company would be unlikely to have an impact on decision making, considering it is observational data and the committee preferred randomised controlled trial (RCT) data for decision making in TA688.

QuiremSpheres were considered to have equivalent quality-adjusted life year (QALY) loses than other SIRT technologies in TA688 compared to (what was) current care. The other evaluated SIRT technologies were recommended for a subgroup of people with unresectable advanced HCC with Child–Pugh grade A liver impairment when conventional transarterial therapies (CTT) are inappropriate. [redacted content]. Therefore, QuiremSpheres would likely be a cost-effective use of NHS resources, if the same assumptions in TA688 were used (for example, sorafenib was the appropriate comparator). Given this, it is likely to be appropriate to evaluate QuiremSpheres using the cost-comparison technology appraisal process.

Since consideration of QuiremSpheres in TA688, atezolizumab plus bevacizumab has been recommended for treating advanced or unresectable HCC with Child–Pugh grade A liver impairment and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 in people who have not had previous treatment (TA666). This is likely to be a relevant comparator for a subgroup of people considered in TA688. Therefore, if evaluated as a cost-utility analysis, it would be appropriate that QuiremSpheres were reevaluated with atezolizumab plus bevacizumab included in the decision problem. It is unknown what impact on cost-effectiveness estimates this would have.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

A patient access scheme (PAS) offer conditional on a positive recommendation for QuiremSpheres was made at the time of the evaluation. Email communication from Terumo states [redacted content]. Further company correspondence indicates [redacted content].

QuiremSpheres list price is greater than the list price for the other technologies in TA688 (SIR-Spheres and TheraSpheres). Given that PAS offers are conditional on positive NICE guidance, the PAS offered by the company for QuiremSpheres during the evaluation of TA688 is not operational. The below shows the difference in the current operational prices for a single treatment of the SIRT technologies evaluated in TA688:

- QuiremSpheres: £9,896 (list price)
- SIR-Spheres: £8,000 (list price); £[redacted content] (PAS price)
- TheraSpheres: £8,000 (list price); £[redacted content] (PAS price)

Depending on the level of PAS discount, QuiremSpheres could potentially be considered cost-effective.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

The details of the CE mark for QuiremSpheres at the time of TA688 publication were:

'QuiremSpheres received its CE mark in April 2015. It is classified as an Active Implantable Medical Device by Council Directive 90/385/EEC. It is indicated for treating unresectable liver tumours'.

There has since been an update to the details of the CE mark:

'QuiremSpheres received CE Mark on 4 April 2023 under the Medical Device Regulation (MDR) 2017/745. QuiremSpheres™ is intended for implantation into hepatic tumours by delivery via the hepatic artery for the treatment of patients with unresectable liver tumours'.

The update is unlikely to have an impact on the evaluation of this technology.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The committee concluded that there are 3 subgroups relevant for this appraisal (see section 3.7 of TA688):

- People for whom liver transplant is appropriate, including people with Barcelona Clinic Liver Cancer (BCLC) A and Child–Pugh A or B.
- People for whom CTT is appropriate, including people with BCLC B and Child–Pugh A or B.
- People for whom CTT is inappropriate, including people with BCLC C and Child–Pugh A or B.

Evidence for the first 2 subgroups was not sufficient for decision making (section 3.13 to 3.17, section 3.21, section 3.28 and section 3.29 of TA688).

Only the third subgroup (people for whom CTT is inappropriate), in combination with Child–Pugh grade A liver impairment, were included for the recommended SIRTs.

The clinical evidence for QuiremSpheres came from 1 retrospective case series including 9 people that showed a 56% response rate (section 3.12 of TA688). The committee concluded that there was not enough evidence for QuiremSpheres to allow an assessment of its clinical effectiveness in any of the subgroups relevant to the evaluation. Therefore, the committee considered evidence from SIR-Spheres to estimate the clinical effectiveness of QuiremSpheres (see section 9 of TA688).

SIR-Spheres was the only technology of the 3 SIRTs included in TA688 which the committee agreed had usable evidence available for decision making. Comparative effectiveness estimates for SIR-Spheres for people for whom CTT is inappropriate came from a mixed treatment comparison including 3 RCTs. To include TheraSpheres into the network meta-analysis, 2 retrospective studies comparing TheraSpheres with SIR-Spheres were included in sensitivity analysis. The committee concluded that this sensitivity analysis was not appropriate for decision making as the non-RCT evidence was at high risk of bias and had uncertain results.

The company has submitted evidence for QuiremSpheres from:

- A retrospective feasibility and safety assessment (Radosa 2018; included in TA688 evidence review).
- An early phase single arm study including 9 people with unresectable HCC which would be inappropriate for treatment with CTT (BCLC stage C). Results are presented for the intention to treat (ITT) population and not the subgroups of interest. The primary objective was toxicity; secondary objectives included efficacy outcomes (Reinders 2022).
- A prospective observational study including 14 patients with HCC, reported by BCLC status. Only people with BCLC stage A or B were included (Drescher 2023).
- A single arm study including 3 people with large HCC which would be inappropriate for treatment with CTT (BCLC stage C). Results are presented for the ITT population and not the subgroups of interest. Primary objectives were feasibility, safety and toxicity; secondary objectives included overall response rate and time to progression (Baclau; RETOUCH).
- A retrospective real world evidence study including 11 people with HCC BCLC stage C) Schulze-Zachau; RECORD).

In TA688, the committee showed a preference for RCT evidence, even when adding observational evidence to the network meta-analysis increased the number of SIRT technologies included in the network (see the section on SIR-Spheres). Given the committee's conclusion in TA688, it is unlikely that the evidence presented by the company, which is all observational, would add meaningful additional evidence to a mixed treatment comparison.

Cost effectiveness of QuiremSpheres and TheraSpheres was estimated by assuming equal efficacy with SIR-Spheres. This was an uncertain assumption as the 3 technologies use different beads to give treatment and QuiremSpheres use a different isotope to the other SIRTs. The committee agreed that these differences might result in different effectiveness and adverse event profiles. Therefore, cost-effectiveness estimates were most uncertain for QuiremSpheres out of the SIRTs evaluated.

It is reasonable to assume that the committee may still conclude that it is appropriate to consider all 3 SIRT technologies as having equal efficacy. The uncertainty around the cost-effectiveness estimates for QuiremSpheres may be reduced given the additional observational evidence presented by the company.

The committee concluded that the appropriate comparator for all 3 SIRTs in the subgroup of interest was sorafenib. All 3 SIRTs (equal effectiveness had been assumed) resulted in fewer QALYs than sorafenib. QuiremSpheres were more costly than sorafenib. Therefore, the committee concluded that QuiremSpheres were not a cost-effective use of NHS resources.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

Since TA688 was considered by the appraisal committee, 3 related pieces of NICE guidance have been published or scheduled:

- Cabozantinib is recommended for treating advanced HCC with Child–Pugh grade A liver impairment and ECOG performance status of 0 or 1 use after sorefinib [TA849, December 2022].
- Atezolizumab plus bevacizumab is recommended for treating advanced or unresectable HCC with Child–Pugh grade A liver impairment and ECOG performance status of 0 or 1 in people who have not had previous treatment [TA666, December 2020].
- The evaluation for tislelizumab for untreated unresectable HCC [ID6129] is currently scheduled with invitation to participate expected in March 2024.

Section 3.10 of TA688 suggests that another NICE recommended technology (regorafenib) is not an appropriate comparator because it is recommended for use after sorefinib. Therefore, it is unlikely that cabozantinib (TA849) would be an appropriate comparator.

It is anticipated that atezolizumab plus bevacizumab would be an appropriate comparator (TA666). Clinical effectiveness estimates from TA666 indicate that atezolizumab plus bevacizumab is more effective than sorafenib. Whether tislelizumab (ID6129) would be an appropriate comparator depends on evaluation timings and the recommendations made.

It is unclear what impact the additional comparators would have on decision making if included in a cost-utility analysis.

Equality issues

No equality issues have been discussed in the FAD or equality impact assessment for TA688.

Decision paper sign off

Jasdeep Hayre
Associate Director, Technology Appraisals and Highly Specialised Technologies

30 November 2023

Contributors to this paper

Albany Chandler
Technical analyst

Jasdeep Hayre
Associate Director, Technology Appraisals and Highly Specialised Technologies