NICE National Institute for Health and Care Excellence

NICE guidance

Cabozantinib for previously treated advanced hepatocellular carcinoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance replaces TA582.

1 Recommendations

1.1 Cabozantinib is recommended as an option for treating advanced hepatocellular carcinoma (HCC) in adults who have had sorafenib, only if:

- they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with cabozantinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for advanced HCC in adults who have had sorafenib is regorafenib. Cabozantinib is an alternative for these people.

Clinical trial evidence shows that cabozantinib is effective for treating advanced HCC compared with placebo. But cabozantinib has not been compared directly with regorafenib. The results of indirect comparisons suggest that cabozantinib is likely to be similarly effective to regorafenib, although this is not certain.

The most plausible cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. Because of this, and because there are few treatment options for people with advanced HCC who have tried sorafenib, cabozantinib is recommended.

2 Information about cabozantinib

Marketing authorisation indication

2.1 Cabozantinib (Cabometyx, Ipsen) is indicated for 'the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cabozantinib.

Price

2.3 The list price of cabozantinib is £5,143 for a 30-tablet pack of 20 mg, 40 mg or 60 mg tablets (excluding VAT; BNF online accessed October 2022). The company has a commercial arrangement. This makes cabozantinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Ipsen, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

HCC has a substantial impact on the quality of life of patients and carers

3.1 Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage. Symptoms of HCC include weakness, deep fatigue, nausea, abdominal pain, ascites, and hepatic encephalopathy. Patient experts described how the physical symptoms of HCC can affect everyday life, making basic functions like eating, speaking, writing and even staying awake difficult. Aside from physical symptoms, people with HCC often experience depression from the poor prognosis. The patient experts explained that people with advanced HCC live with uncertainty, hopelessness and often stigma and isolation because of the perception of liver cancer. They described how the physical symptoms and the psychological impact of HCC can also have a considerable impact on the quality of life of families and carers. The committee concluded that HCC has a substantial impact on the quality of life of people with the condition, and their families and carers.

Regorafenib is the relevant comparator for people with Child–Pugh grade A liver impairment and an ECOG status of 0 to 1

3.2 The company proposed that cabozantinib would be used in the same position as regorafenib in the treatment pathway. That is, as a second-line or third-line systemic therapy after progression on or intolerance to sorafenib. The NICE technology appraisal guidance on regorafenib for previously treated advanced HCC recommends it only for people who have Child–Pugh grade A liver impairment and an Eastern Cooperative

Oncology Group (ECOG) performance status of 0 or 1. The company positioned cabozantinib at the same position and in the same population as regorafenib. This is because the clinical trial evidence is relatively limited for cabozantinib in people with advanced HCC with more severe liver disease or a poorer performance status. The clinical experts agreed with the company's proposed positioning of cabozantinib and explained that in clinical practice atezolizumab plus bevacizumab, lenvatinib and sorafenib are used as first-line systemic therapies. After first-line atezolizumab plus bevacizumab, lenvatinib and sorafenib can be used second line, with regorafenib available as a third-line option if someone has previously had sorafenib. For those treated with sorafenib first line, regorafenib can be used second line. So, the committee concluded that the company's proposed positioning in the treatment pathway was appropriate, and regorafenib was the relevant comparator.

People with HCC whose disease has progressed on, or who are intolerant to, sorafenib would welcome a new treatment option

3.3 The patient and clinical experts said that if people's disease has progressed on sorafenib, or if they cannot tolerate it, there are limited treatment options. Only regorafenib is available. They said a new treatment option would be welcomed. Clinical experts also said that cabozantinib may be an option for a broader group of people than regorafenib, which was only evaluated in a sorafenib-tolerant population. They explained that regorafenib is generally only used if sorafenib was tolerated, whereas cabozantinib could be used for people who could not tolerate sorafenib. The committee concluded that cabozantinib would offer a new treatment for people with limited options.

Clinical evidence

Cabozantinib is clinically effective compared with placebo

3.4 The clinical effectiveness evidence was based on CELESTIAL, a randomised, double-blind trial that compared cabozantinib plus best supportive care with placebo plus best supportive care. CELESTIAL included people with HCC who had had 1 or 2 treatments already, and

who had had sorafenib (whether they tolerated it or not). People also had to have an ECOG performance status of 0 or 1 and Child–Pugh grade A. The primary outcome was overall survival. Secondary outcomes included progression-free survival and objective response rate. At a median follow up of 22.9 months, the median overall survival in the cabozantinib arm was 10.2 months, compared with 8.0 months in the placebo arm (hazard ratio 0.76, 95% confidence interval [CI] 0.63 to 0.92). The median progression-free survival was 5.2 months, compared with 1.9 months in the placebo arm (hazard ratio 0.44, 95% CI 0.36 to 0.52). The committee concluded that cabozantinib was clinically effective compared with placebo.

The anchored MAIC analyses are likely to be more robust than the unanchored MAIC but all analyses have limitations

3.5 Because there was no direct head-to-head evidence for cabozantinib compared with regorafenib, the company provided a series of indirect treatment comparisons. The indirect treatment comparisons used the Bucher approach and matching-adjusted indirect comparison (MAIC). Data for cabozantinib was from the CELESTIAL trial. Data for regorafenib was from the RESORCE trial, a randomised, double-blind trial of regorafenib plus best supportive care compared with placebo plus best supportive care. The relative treatment effect of cabozantinib compared with regorafenib was estimated for overall survival and progression-free survival. The company acknowledged that population differences between the CELESTIAL and RESORCE trials introduced bias into the Bucher analysis, so it had to do the MAICs. The ERG agreed and said that the Bucher approach does not provide robust results because of the observed cross-trial differences. So, the committee discussion focused on the 3 MAIC approaches presented by the company:

- anchored MAIC with constant hazard ratio
- anchored MAIC with time-varying hazard ratio
- unanchored MAIC.

The MAICs used a second-line population from CELESTIAL. Indirect treatment comparisons in the third-line population were not possible because the

RESORCE trial was restricted to second line. The ERG noted that each of the MAICs had limitations, but from a methodological perspective, the preferred option was the anchored MAIC analyses. This was because the unanchored MAIC relies on the strongest assumptions and is likely the least robust. Specifically, the unanchored MAIC relies on the assumption that all prognostic factors and treatment effect modifiers are accounted for, an assumption that is rarely met. Also, the unanchored MAIC is limited because trial randomisation is not preserved.

The ERG also said that the proportional hazards assumption in the MAIC with a constant hazard ratio was not met. This meant that the MAIC with time-varying hazard ratios may be preferred from a purely methodological point of view. But it added that from a clinical point of view the MAIC with constant hazard ratios may be the better option because the extrapolation for overall survival based on that MAIC was the one most consistent with the 4-year overall survival prediction from its clinical advisers. Before the committee meeting, the company said that the anchored MAIC with constant hazard ratios was its preferred option because the underlying assumptions were more likely to be met compared with the unanchored MAIC. But during the meeting the company noted the limitations of the anchored MAICs, including concerns about the comparability of the placebo arms across both trials. The company clarified the limitations with all of the options and said that all 3 options should be considered because of the uncertainty associated with all of the methods. The committee acknowledged the limitations with all 3 MAICs but it agreed that the anchored MAICs are likely to be more robust because the underlying assumptions are more likely to be met.

The MAICs suggest no clear difference in efficacy between cabozantinib and regorafenib, but the results should be interpreted with caution

3.6 The committee noted that the anchored MAICs showed a non-statistically significant progression-free survival benefit for cabozantinib and a non-statistically significant overall survival benefit for regorafenib. The anchored MAIC analysis with constant hazard ratios produced hazard ratios of 1.09 (95% CI 0.73 to 1.62) for overall survival and 0.80 (95% CI 0.55 to 1.15) for progression-free survival. The anchored MAIC analysis with time-varying hazard ratios produced time-varying hazard

ratios of:

- more than 1.0 for overall survival (95% CI includes a time-varying hazard ratio of 1.0)
- less than 1.0 for progression-free survival (95% CI includes a time-varying hazard ratio of 1.0).

The non-statistically significant results from the anchored MAICs were supported by clinical experts, who said that they believed that cabozantinib and regorafenib had broadly similar efficacy. The committee concluded that the MAIC analyses show no clear evidence of any difference in efficacy between cabozantinib and regorafenib but that the results should be interpreted with caution because of the limitations outlined in section 3.5.

Economic model

It is uncertain whether cabozantinib would result in higher healthcare management costs than regorafenib

3.7 The company's model assumed equivalent healthcare management costs in the progression-free health state for cabozantinib and regorafenib. This was based on the company's clinical expert opinion, which was that clinicians are experienced in handling generic tyrosine kinase inhibitor toxicities, and that cabozantinib's tolerability issues can be managed. The ERG preferred to include additional monitoring costs, based on the views of its clinical advisers that cabozantinib has a comparatively worse toxicity profile than regorafenib. This was supported by the comparison of safety outcomes from the MAICs. Only the odds ratio for diarrhoea was statistically significant in favour of regorafenib but the point estimate odds ratios for hypertension, elevated aspartate transaminase, fatigue and palmar-plantar erythrodysaesthesia syndrome were also above 1 (in favour of regorafenib). The odds ratio for elevated bilirubin was in favour of cabozantinib but was not statistically significant. The ERG provided an alternative scenario that included the cost of 0.5 additional oncologist visits per month (0.46 visits per 28-day model cycle).

3.8 The ERG commented that in the CELESTIAL trial there was a potentially clinically meaningful difference in favour of placebo for health-related quality of life when measured using the EQ-5D. The company acknowledged that the EQ-5D data from RESORCE does not suggest a significant difference between regorafenib and placebo. But it said that the EQ-5D questionnaire in RESORCE was completed on the first day of each treatment cycle, when someone had not had treatment for a week. This may have affected responses. Clinical experts said that the toxicity profiles for regorafenib and cabozantinib seem broadly consistent. The committee concluded that it was uncertain if cabozantinib would result in additional monitoring costs compared with regorafenib, but it would consider both the company's and ERG's scenarios in its decision making.

Including drug wastage costs in the economic model is appropriate

3.9 The company's base case analyses assumed that packs of treatment can be split so that every tablet prescribed is taken, so they did not include wastage costs. This assumption advantages the cabozantinib group because the relative dose intensity is much lower for cabozantinib than for regorafenib (61% compared with 90%, respectively). The ERG noted that there may be some wastage because people can progress or die before completing a pack of treatment. The ERG provided an alternative scenario consistent with previous appraisals in HCC, in which the costs of 7 days' worth of treatment in both treatment groups (adjusted for relative dose intensity) was included. A clinical expert said that dose adjustments are usually made quickly; normally after 2 weeks of treatment, so wastage is likely to be minimised. The committee noted that including drug wastage costs as per the ERG's scenario was not a key driver of cost effectiveness but was likely to reflect clinical practice.

Cost-effectiveness estimates

Cabozantinib is a cost-effective use of NHS resources for advanced HCC after treatment with sorafenib

3.10 The committee agreed that its preferred approach to modelling would:

- Use scenarios that use the anchored MAIC with constant hazard ratios and scenarios that use the anchored MAIC with time-varying hazard ratios (see section 3.5).
- Include scenarios in which healthcare management costs in the progression-free health state are equivalent for cabozantinib and regorafenib, and scenarios that include the cost of 0.5 additional oncologist visits per month for cabozantinib (see section 3.7).
- Include treatment wastage costs (see section 3.9).

3.11 The committee also accepted the ERG analyses, which included corrections of minor errors, a general population mortality constraint and age-adjusted utilities. Using the committee's preferred assumptions and including the confidential discounts for cabozantinib and regorafenib, cabozantinib was associated with fewer quality-adjusted life years (QALYs) and overall lower costs than regorafenib in all scenarios. The scenario using the anchored MAIC with constant hazard ratios and equivalent healthcare management costs in the progression-free health state produced the most favourable results. The scenario using the anchored MAIC with time-varying hazard ratios and the cost of 0.5 additional oncologist visits per month for cabozantinib produced the least favourable results. The committee acknowledged that the true costs and QALYs were likely to be in between the 2 scenarios. The exact savings, net health benefits and incremental cost-effectiveness ratios (ICERs) are commercial in confidence and cannot be reported here. The committee was aware that, when an ICER is estimated for a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment is. The committee considered the limited treatment options after sorafenib, particularly for people unable to tolerate it. It took the net health benefits and the ICERs into account. It noted that the QALY losses were sufficiently small for the anchored MAICs (less than 0.1, or roughly equivalent to 1 month in perfect health) and the south-west quadrant ICERs per QALY lost were high enough to consider cabozantinib a cost-effective use of NHS resources. The exact QALYs are commercial in confidence and cannot be reported here. The committee concluded that cabozantinib can be considered cost effective for treating advanced

HCC in people who have previously had sorafenib.

Other factors

There are no equality issues relevant to the recommendations

3.12 The patient expert said that liver disease and liver cancer disproportionally affect the poorest in society, and many people with liver cancer come from disadvantaged backgrounds. Differences in prevalence and patient population cannot usually be resolved in a technology appraisal, although the committee can consider whether a specific equality issue has a significant impact on access to treatments it recommends. The committee concluded that this was not the case for its recommendations about cabozantinib.

Conclusion

Cabozantinib is recommended for people with advanced HCC who have previously had sorafenib

3.13 The committee acknowledged the need for more treatment options in advanced HCC. It took account of the commercial discounts for cabozantinib and regorafenib. In the committee's preferred analyses, cabozantinib was considered a cost-effective use of NHS resources compared with regorafenib. So, cabozantinib is recommended as a treatment option for people with advanced HCC who have had sorafenib and who have Child–Pugh grade A liver impairment and an ECOG performance status of 0 or 1.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if someone has hepatocellular carcinoma previously treated with sorafenib and the doctor responsible for their care thinks that cabozantinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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