NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lenvatinib for untreated advanced hepatocellular carcinoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lenvatinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using lenvatinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 30 August 2018

Second appraisal committee meeting: 27 September 2018

Details of membership of the appraisal committee are given in section 5.

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1 Recommendations

1.1 Lenvatinib is not recommended within its anticipated marketing authorisation for untreated, advanced, unresectable hepatocellular carcinoma in adults.

1.2 This recommendation is not intended to affect treatment with lenvatinib 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 considers it appropriate to stop.

Why the committee made these recommendations

Advanced unresectable hepatocellular carcinoma is treated with sorafenib. But sorafenib is not always effective and many people cannot tolerate it because of side effects.

Clinical trial evidence shows that lenvatinib slows disease progression and causes more tumours to shrink than sorafenib. The evidence also shows that people having lenvatinib live for around as long as those having sorafenib. Lenvatinib has different side effects to sorafenib and this would benefit some people.

However, the cost-effectiveness estimates for lenvatinib compared with sorafenib are uncertain and there is no estimate that can be considered to be the most plausible. Most estimates that contained plausible assumptions are higher than the range normally considered to be an acceptable use of NHS resources. Also, lenvatinib does not meet NICE's criteria to be considered a life-extending treatment at the end of life. Because of this, lenvatinib is not recommended.

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2 Information about lenvatinib

Anticipated marketing authorisation indication	On 28 June 2018 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product lenvatinib. The CHMP adopted a new indication as follows: 'the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy'.
Dosage in the marketing authorisation	The recommended daily dose of lenvatinib is 8 mg (2x4 mg capsules) given orally for patients who weigh less than 60 kg and 12 mg (3x4 mg capsules) orally for patients who weigh 60 kg or over (based on company submission).
Price	£1,437 for 30x4mg capsules (excluding VAT; British national formulary [BNF] online [accessed May 2018]). The company has a commercial agreement (patient access scheme) which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Eisai and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Unmet need

People with advanced hepatocellular carcinoma would welcome an alternative treatment option

3.1 Advanced unresectable hepatocellular carcinoma is often diagnosed late in life and has a poor prognosis. It is a debilitating condition with many distressing symptoms, including pain, digestive problems and weight loss. The patient experts noted that people with advanced unresectable hepatocellular carcinoma consider improving their quality of life to be particularly important. Sorafenib is currently the only licensed option for people who have had not already had systemic treatment. The committee understood that an alternative first-line treatment option would be valuable to patients with the condition.

Treatment pathway

Lenvatinib may offer benefits over current treatment options

3.2 The clinical experts explained that there is a low response rate with sorafenib and around 25% of patients stop treatment because they cannot tolerate it. They added that hand-foot syndrome is more common with sorafenib, which can be very unpleasant for patients. Common side effects of lenvatinib, such as hypertension, may be more acceptable to some patients. A patient expert also noted that lenvatinib offers a longer time to disease progression compared with sorafenib, although there is no evidence showing a difference in overall survival. The clinical experts indicated that they may use lenvatinib instead of sorafenib based on individual patient characteristics, but also because of the improvements it offers in side-effect profile, time to disease progression and response rates. The committee agreed that lenvatinib would offer improved benefits for people with advanced unresectable hepatocellular carcinoma who have not had systemic treatment.

Population

The company positioned lenvatinib in line with the REFLECT trial

3.3 The company positioned lenvatinib in line with the REFLECT trial (that is, for adults with advanced unresectable hepatocellular carcinoma who have not already had systemic treatment and who have Child–Pugh class A liver impairment). This was narrower than both the anticipated marketing authorisation and the final scope issued by NICE, but was in line with the REFLECT trial population and previous NICE technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma. The clinical experts explained that treatment may not be clinically effective in people with more impaired liver function (for example, people with Child–Pugh class B liver impairment). The committee accepted the company's positioning of lenvatinib and agreed that adults with advanced

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unresectable hepatocellular carcinoma who have not already had systemic treatment and who have Child–Pugh class A liver impairment.

Comparator

Sorafenib is the most relevant comparator

3.4 The company did not consider best supportive care to be an appropriate comparator because it is only used in clinical practice if systemic treatment is not appropriate. The company's clinical expert estimated that less than 5% of patients have best supportive care; most people instead have sorafenib. The clinical experts stated that most people would be eligible for systemic therapy and would have sorafenib. Having noted that it had not seen comparative evidence for best supportive care, the committee concluded that sorafenib was the most relevant comparator.

Clinical evidence

REFLECT included a clinically appropriate population with Child–Pugh class A liver impairment and ECOG performance status of 0 or 1

3.5 The clinical evidence came from a phase III, open-label randomised controlled trial (REFLECT) comparing lenvatinib with sorafenib for untreated, advanced hepatocellular carcinoma in 954 adults with Child–Pugh class A liver impairment and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial excluded people with Child–Pugh class B liver impairment or worse and people with an ECOG performance status of 2 or more, and the committee understood the results may not be generalisable to these groups. The clinical experts explained that lenvatinib may not be clinically effective in these groups, and that these criteria are also used in clinical practice to decide the most appropriate treatment options. The committee concluded that people with both Child–Pugh class A liver impairment and ECOG performance status 0 to 1 was the most clinically appropriate population, and agreed to consider the trial inclusion criteria when making its recommendations.

Baseline characteristics were imbalanced but the clinical-effectiveness results are relevant to NHS practice

3.6 The company highlighted that in REFLECT, more people in the lenvatinib group had alpha-fetoprotein levels of 200 ng/ml or above compared with the sorafenib group, and there were differences in the pre-existing liver conditions associated with hepatocellular carcinoma (hepatitis C, hepatitis B or alcohol) across the 2 groups. The company explained that these variables were not included as randomisation stratification factors. It considered that these imbalances in baseline characteristics may affect the treatment benefit seen with lenvatinib because they were potentially important prognostic factors. However, the clinical experts explained that a similar treatment benefit was likely regardless of pre-existing liver conditions. The ERG's clinical expert agreed that although alpha-fetoprotein level was a prognostic factor, they did not consider the cut-off value of 200 ng/ml to be clinically relevant. The committee understood that the company had made adjustments to account for the imbalances in baseline characteristics (see section 3.12) and that the difference in alpha-fetoprotein levels may not be clinically meaningful. The committee concluded that although there may be some imbalances in the baseline characteristics, the REFLECT trial was relevant to clinical practice in the NHS.

It is appropriate to use clinical data from the full trial population

3.7 Around two thirds of the trial population were from the Asia-Pacific region and the rest were from Western countries including the UK. The ERG noted important differences between the Western subgroup and the full trial population (the Western subgroup was heavier, had more heart disease, less underlying cirrhosis, less hepatitis B and more pre-existing hepatitis C or alcohol related conditions), but explained that these differences may not have changed the relative treatment effect. The ERG also noted that baseline characteristics in the full population were more balanced than those in the Western subgroup, and the clinical experts

agreed that the overall population reflected clinical practice in England. The committee was aware that the imbalance in post-progression treatment was larger in the Western subgroup compared with the full trial population. It understood that after adjusting for post-progression treatment (see section 3.13), the overall survival results were similar for both the Western subgroup and the full trial population. The committee agreed that there was no sufficient justification for using results from the Western subgroup instead of the full trial population because it was not more clinically relevant and had a relatively small sample size. It agreed that the baseline characteristics for the full trial population were generally in line with clinical practice in England, and it preferred to use these results.

The company's approach to censoring is likely to overestimate the gain in progression-free survival for lenvatinib

3.8 In the company's submission, progression-free survival results were censored (because not all patients will be followed up until the end of the trial) if there was no disease progression when treatment is stopped. The ERG explained that this could be considered to be informative censoring (that is, reasons for drop-out may potentially be related to disease progression or survival time) and that it may lead to inaccurate conclusions about the size of the treatment difference between lenvatinib and sorafenib. Based on the clinical evidence presented, the ERG explained that the company's method of censoring would likely favour lenvatinib because more people stopped lenvatinib either through choice or because of adverse effects. More events may therefore be missed because of censoring in the lenvatinib group. At clarification, the company provided results that included all events in the analysis and only censored if there were missing assessments or no disease progression at the patients' last assessment. Progression-free survival was lower after applying the censoring rules at clarification stage, but the results still showed a statistically significant improvement for lenvatinib compared with sorafenib. The committee noted the consistency in the direction of the

results and concluded that the company's approach to censoring was likely to overestimate the gain in progression-free survival for lenvatinib.

More patients had post-progression treatment in the sorafenib arm than in the lenvatinib arm and the overall survival results may favour sorafenib

3.9 In REFLECT, treatment after disease progression was allowed in both the lenvatinib and sorafenib arms. In the lenvatinib arm, patients could switch to sorafenib but were not eligible for trials using second-line treatment. In the sorafenib arm, patients could continue sorafenib and were eligible for trials using second-line treatments such as regorafenib. Regorafenib is not used in England because it is not currently recommended by NICE (see NICE technology appraisal guidance on regorafenib for previously treated advanced hepatocellular carcinoma). The committee understood that 51% of patients in the sorafenib group had post-progression treatment compared with only 43% in the lenvatinib group. It noted that longer overall survival may be expected for people having post-progression treatment, so the overall survival results may favour patients randomised to sorafenib. The committee concluded that more patients having post-progression treatment in the sorafenib arm may affect the estimates of treatment effect for overall survival.

Overall survival with lenvatinib is non-inferior compared with sorafenib

3.10 The primary end point of REFLECT was overall survival and the study was powered to demonstrate non-inferiority. There was no statistically significant difference in overall survival (see table 1). However, the results for overall survival met the pre-specified criteria for non-inferiority (that is, the upper limit of the 95% confidence interval was less than 1.08). There was also a statistically significant improvement in median investigator-assessed progression-free survival with lenvatinib (7.4 months) compared with sorafenib (3.7 months; see table 1). Similar results were reported for independently assessed progression-free survival using standard response evaluation criteria in solid tumours (RECIST) to measure disease progression, and a modified version of RECIST that evaluates

change more accurately in hepatocellular carcinoma. The committee understood that the proportional hazards assumption (that is, there is a constant treatment effect over time) was not met for the overall and progression-free survival results, so these should be interpreted with caution. The committee noted the consistency in the progression-free survival results using the 2 different censoring rules (see section 3.8), and agreed there was robust evidence of a progression-free survival benefit, although there is some uncertainty around the size of this benefit (see section 3.15). Lenvatinib also improved response rates compared with sorafenib. The committee concluded that overall survival with lenvatinib was non-inferior compared with sorafenib.

Table 1 Clinical-effectiveness results from REFLECT

Outcome	Lenvatinib – median (range)	Sorafenib – median (range)	Result – (95% CI)
Overall survival			
Unadjusted	13.6 (12.1 to 14.9)	12.3 (10.4 to 13.9)	HR 0.92 (0.79 to 1.06)
Adjusted for post-progression treatment	–	–	confidential and cannot be reported
Investigator-assessed progression-free survival			
Using modified RECIST	7.4 (6.9 to 8.8)	3.7 (3.6 to 4.6)	HR 0.66 (0.57 to 0.77)
Using modified RECIST and committee's preferred censoring rules	–	–	confidential and cannot be reported
Independently assessed progression-free survival			
Using modified RECIST	7.3 (5.6 to 7.5)	3.6 (3.6 to 3.7)	HR 0.64 (0.55 to 0.75)
Using standard RECIST (1.1)	7.3 (5.6 to 7.5)	3.6 (3.6 to 3.9)	HR 0.65 (0.56 to 0.77)
Response rate			
Objective response rate	24.1%	9.2%	OR 3.13 (2.15 to 4.56)
Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RECIST, response evaluation criteria in solid tumours.			

The company's model

The model structure is appropriate for decision-making

3.11 The company used a partitioned survival model with 3 health states (progression free, progressed disease and death). The committee noted that although progression-free and overall survival data were relatively mature in the REFLECT trial, extrapolations were needed for both to model effects over a lifetime horizon. The ERG considered the model structure to be appropriate but identified an inconsistency in the half-cycle correction because it was not fully applied to all costs and quality-adjusted life years (QALYs). The ERG corrected this in its own preferred base case. At clarification, the company did not consider this to be an error and so did not correct it. Ultimately these corrections had little effect on the cost-effectiveness estimates, and the committee concluded that the model structure was appropriate for decision-making.

Survival estimates in the model

The company's adjustment for baseline characteristics introduces uncertainty but the corrected group prognosis method is preferred

3.12 The company adjusted the treatment estimates used in the model to account for imbalances in baseline characteristics of patients in REFLECT. Multivariable parametric survival models were fitted to the progression-free and overall survival data and a covariate adjustment was applied using the mean of covariates approach. The committee was aware that:

- The company's adjusted model for progression-free survival was potentially more unreliable than the model for overall survival, because only overall survival data were used to select potential covariates for adjustment and this is based on a different underlying model.

- Each variable was assumed to have a relative effect on the hazard ratio but proportional hazards were not tested for all potential covariates, so the results should be interpreted with caution.
- The corrected group prognosis method is more appropriate for categorical variables.

The ERG noted that it could not assess how a different adjustment method would affect the cost-effectiveness estimate. The committee agreed that the company's covariate adjustment introduced uncertainty, and that using the corrected group prognosis method was more appropriate because the model contained categorical variables (such as Child–Pugh class) and interpreting these variables using the mean of covariates approach is problematic. The committee had not seen these analyses with its preferred assumptions (see section 3.21). It concluded that the company's adjusted analyses introduced uncertainty, and that it preferred the corrected group prognosis method to adjust for baseline characteristics.

It is appropriate to include post-progression benefit in line with REFLECT

3.13 The company's base case included the clinical benefit of post-progression treatment. The committee recalled that in REFLECT, fewer people in the lenvatinib arm had post-progression treatment compared with the sorafenib arm (see section 3.9). The ERG explained that this may bias overall survival estimates in favour of sorafenib, because people who have post-progression treatment may have longer overall survival. The committee understood that the company used a crude binary adjustment for post-progression treatment (patients either had or did not have post-progression treatment) that did not produce reliable results; moreover, the company confirmed that there were some missing data about the types of post-progression treatments people had. The committee had not seen scenario analyses using alternative statistical adjustments for post-progression treatment (for example, by including post-progression treatment as a time-varying covariate), or analyses with post-progression

treatment that included its preferred assumptions (see section 3.19). Nevertheless, the committee concluded that it could accept the inclusion of post-progression treatment benefit in line with REFLECT.

A log-logistic distribution is appropriate for extrapolating overall survival

3.14 The company used a log-logistic model in its base case to extrapolate overall survival for both lenvatinib and sorafenib, in line with a previous technology appraisal (sorafenib for treating advanced hepatocellular carcinoma). It understood that this model provided a good fit to data from both treatment groups. The committee concluded that a log-logistic distribution was appropriate for extrapolating overall survival for both lenvatinib and sorafenib.

A gamma distribution is most appropriate for extrapolating progression-free survival

3.15 In its base case, the company used a lognormal distribution to extrapolate progression-free survival for both lenvatinib and sorafenib. The ERG noted that although the lognormal distribution provided a good fit to the lenvatinib data, it did not fit the sorafenib data well. Instead the ERG preferred the gamma distribution with an adjustment to prevent the curves from crossing, because it provided a reasonable fit to both treatment groups. The committee compared the visual fit of the models that were not adjusted for baseline characteristics to the Kaplan–Meier data from REFLECT (that was also unadjusted) and considered that the gamma distribution fit the data better than the lognormal distribution. However, if possible, it would have also liked to compare the adjusted survival curve with the adjusted Kaplan–Meier curve to fully assess model fit. The committee concluded that the gamma distribution was most appropriate for extrapolating progression-free survival for both lenvatinib and sorafenib.

A censoring approach that categorises all disease progression and deaths as events would be appropriate

3.16 The company censored survival data from REFLECT if there was no disease progression when treatment was stopped. The committee recalled that this approach may overestimate progression-free survival compared with its preferred approach that categorised all disease progression and deaths as events (see section 3.8). The ERG presented 3 scenario analyses, reducing the scale of the lenvatinib progression-free survival curve by 5%, 10% and 15%, so that the difference between the progression-free survival for lenvatinib and sorafenib was reduced. The committee considered these scenarios to be arbitrary but noted that the incremental cost-effectiveness ratios (ICERs) increased as the post-progression benefit with lenvatinib was reduced. The committee would have preferred analyses that categorised all progressions and deaths as events and noted that it had not seen progression-free survival curves that applied this preferred censoring approach. It would have also preferred to see scenario analyses with progression-free survival curves using standard RECIST criteria to measure disease progression. The committee concluded that a censoring approach that categorises all disease progression and deaths as events would be more appropriate.

Costs in the model

Including drug wastage does not have a large effect on total costs

3.17 The company did not include drug wastage costs in its base-case analysis. The committee understood that in a previous NICE appraisal for treating advanced hepatocellular carcinoma (sorafenib for treating advanced hepatocellular carcinoma), it was considered appropriate to include drug wastage for up to 7 days. However, in a more recent NICE technology appraisal (regorafenib for previously treated advanced hepatocellular carcinoma), the committee considered 7 days to be arbitrary and associated with some uncertainty. The ERG did a scenario analysis using drug costs based on the planned number of capsules and

tablets needed each day. This led to only a modest reduction in total costs. The committee concluded that drug wastage did not have a large effect on the total costs.

It is appropriate to include the costs of post-progression treatment

3.18 The company's base case only included the costs of sorafenib and regorafenib after disease progression because these are the only licensed treatments for advanced hepatocellular carcinoma. The committee was aware that other treatments and procedures were also used after disease progression in REFLECT, but these costs had not been included in the company's base case. However, scenario analyses showed that including the cost of other post-progression treatments and procedures did not have a large effect on the cost-effectiveness estimates. The committee preferred to include the benefit of post-progression treatments and so concluded it was also appropriate to include the costs.

Utility values in the economic model

Utility values in the progressed state may be overestimated

3.19 In its base case the company used utility values from the full population in REFLECT for both lenvatinib and sorafenib because there was only a small difference in mean utility values. The company used a value of 0.745 in the progression-free state and 0.678 in the progressed state, although the company's clinical experts noted that the utility value in the progressed state was higher than would be expected given that advanced hepatocellular carcinoma can severely affect functioning and wellbeing. The committee noted that the final measurement in the post-progression stage was 30 days after the final dose of lenvatinib or sorafenib so these measurements may not include the full impact of disease progression on health-related quality of life. The committee agreed that using lower utility values in the progressed state may affect the cost-effectiveness estimate for lenvatinib and the ERG confirmed that this was not a major driver in the model. The committee accepted that utility values in the progressed

state may be overestimated and concluded that the impact on the overall cost-effectiveness estimate was uncertain.

Cost-effectiveness estimate

The company's base-case ICER does not include the committee's preferred assumptions

3.20 In its base case, the company reported ICERs showing that lenvatinib dominated sorafenib (that is, it was both more effective and less costly). These ICERs did not include the confidential commercial access agreement for sorafenib. The committee considered that the company's base case was not appropriate because it:

- used the mean of covariates approach to adjust baseline characteristics (see section 3.12)
- used a lognormal distribution to extrapolate progression-free survival but this did not fit the sorafenib data well (see section 3.15)
- used censoring rules that overestimated the progression-free survival benefit for lenvatinib (see section 3.16)

There was no most plausible ICER that included the committee's preferred assumptions

3.21 The committee noted that it had not seen analyses that included its preferred assumptions, specifically:

- results from the full trial population (see section 3.7)
- a gamma distribution to extrapolate progression-free survival for lenvatinib and sorafenib (see section 3.15)
- the corrected group prognosis method used to adjust for imbalances in baseline characteristics (see section 3.12),
- post-progression treatments in line with REFLECT (see section 3.13)
- the costs of all post-progression treatments and procedures (see section 3.18)

- a censoring approach that categorises all disease progression and deaths as events (see section 3.16).

The committee also noted that it could not fully assess model fit because it had not seen adjusted progression-free survival curves that included adjusted Kaplan–Meier data, standard and modified definitions of disease progression and used its preferred censoring approach. In the absence of these analyses, the committee concluded that there was no most plausible ICER for lenvatinib compared with sorafenib that included the committee's preferred assumptions.

The most likely cost-effectiveness estimate is higher than the range normally considered to be a cost-effective use of NHS resources

3.22 Despite the uncertainty in the analyses, the committee considered all the reported ICERs (including the patient access scheme for lenvatinib and commercial access agreement for sorafenib) and noted that in a number of plausible scenarios, they were above the range normally considered to be a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). Furthermore, some estimates that reduced the progression-free survival benefit with lenvatinib (see section 3.16) were above £50,000 per QALY gained (specific ICERs are confidential and cannot be reported here). Based on the evidence presented, the committee concluded that the most likely ICER for lenvatinib compared with sorafenib would be higher than the range NICE normally considers to be an acceptable use of NHS resources.

End of life

Lenvatinib meets the criterion for short life expectancy but there is uncertainty as to whether it meets the criterion for extension to life

3.23 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. The committee discussed

whether life expectancy without lenvatinib would be less than 24 months. It noted that median overall survival in the sorafenib group in REFLECT was 12.3 months. The committee understood that without treatment, median survival for people with advanced hepatocellular carcinoma was around 4 to 8 months; this was confirmed by the clinical experts. The committee concluded that lenvatinib met the short life expectancy criterion.

3.24 The committee discussed whether a survival benefit of over 3 months could be expected for lenvatinib compared with sorafenib. It noted that median survival in the lenvatinib group in REFLECT was extended by 1.3 months. The committee understood that the company model predicted a mean overall survival benefit of 3.1 months for lenvatinib whereas the ERG model predicted a survival benefit of 4.1 months. Based on the evidence presented to it, the committee concluded it was uncertain whether lenvatinib met the extension to life criterion for treatments at the end of life.

Equality

There are no equality issues relevant to the recommendations

3.25 The committee considered whether its recommendations were associated with any potential issues related to equality. The committee noted comments from patient and clinical expert submissions that hepatocellular carcinoma is more common in men and people of some ethnicities. The committee did not consider this to be an equality issue because its recommendations apply to everyone with advanced, unresectable hepatocellular carcinoma.

Innovation

There is no evidence of any additional benefits with lenvatinib

3.26 The company considered lenvatinib to be innovative because there is an unmet need for treatment options other than sorafenib that delay disease

progression and improve survival without decreasing health-related quality of life. The clinical experts acknowledged that lenvatinib is the only alternative first-line treatment option for advanced hepatocellular carcinoma in over 10 years, and they were not aware of any benefits that were not already captured in the model. The committee concluded that lenvatinib would be beneficial for patients (see sections 3.2 and 3.10), but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

Cancer Drugs Fund

Lenvatinib does not meet the criteria to be included in the Cancer Drugs Fund

3.27 Having concluded that lenvatinib could not be recommended for routine use, the committee then considered if it could be recommended for treating hepatocellular carcinoma within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee understood that the company had not made a specific case for lenvatinib to be considered for funding through the Cancer Drugs Fund. It also considered that the clinical data presented were mostly mature, there was no most plausible ICER that included the committee's preferred assumptions and all ICERs (including the patient access agreement for lenvatinib and commercial access arrangement for sorafenib) were above the range normally considered to be cost effective (that is, £20,000 to £30,000 per QALY gained) and some were above £50,000 per QALY gained. The committee therefore concluded that lenvatinib did not meet the criteria to be included in the Cancer Drugs Fund, and that the clinical uncertainties could not be resolved through collecting data on lenvatinib's use in the Cancer Drugs Fund.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Prof Stephen G O'Brien
Chair, appraisal committee
August 2018

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.

Issue date: August 2018

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ISBN: [to be added at publication]