NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

Sorafenib for treating advanced hepatocellular carcinoma (Cancer Drugs Fund reconsideration of TA189)

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sorafenib 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 base (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?

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 determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using sorafenib 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: 23 January 2017

Third appraisal committee meeting: 1 February 2017

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Sorafenib is recommended for use within the Cancer Drugs Fund as an option for treating advanced hepatocellular carcinoma in adults only if:

- surgical or locoregional therapies have failed or are not suitable and
- the company submits a proposal for sorafenib to be included in the Cancer Drugs Fund.

1.2 The Cancer Drugs Fund proposal should:

- detail any commercial access arrangements
- detail how data collection will address the key clinical uncertainties described in section 4
- state the likelihood that additional research will reduce uncertainty enough to support positive guidance in the future
- state the proposed data collection approach and current status
- state the timeframe for availability of the results
- summarise the study protocol or proposed study protocol, specifying:
  - methodology
  - study governance details (information governance, patient consent, ethical approval)
  - analysis plans
  - data access and accountability for disseminating results
  - accountability for monitoring and validation
  - any funding arrangements.

2 The technology

Description of the technology	Sorafenib (Nexavar, Bayer) is a multikinase inhibitor that inhibits tumour blood vessel development and tumour cell proliferation. It does this by inhibiting the Raf cascade, and vascular endothelial growth factor /platelet-derived growth factor receptors of tumour cells, vascular endothelial cells and pericytes.
Marketing authorisation	Sorafenib has a marketing authorisation in the UK for treating hepatocellular carcinoma.
Adverse reactions	The summary of product characteristics includes the following conditions that may be associated with sorafenib treatment: dermatological toxicities, hypertension, haemorrhage, cardiac ischaemia and/or infarction, gastrointestinal perforation, hepatic impairment and wound healing complications. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Sorafenib is administered orally as 200-mg film-coated tablets. The recommended dosage is 400 mg twice daily (a total daily dose of 800 mg). The dosage may be adjusted to 2×200-mg tablets once daily if adverse drug reactions are suspected. The summary of product characteristics recommends that treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.
Price	The price for a pack of 200-mg tablets (112 tablets per pack) is £3,575.56. The company has agreed a nationally available price reduction for sorafenib with the Commercial Medicines Unit. The contract prices agreed through the framework are commercial in confidence. The Commercial Medicine Unit price replaces the patient access scheme that was agreed during the development of NICE technology appraisal guidance 189.

3 Evidence

3.1 The appraisal committee (section 6) considered evidence submitted by Bayer and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma.

3.2 The company's original submission presented clinical effectiveness data from the SHARP study. SHARP was a multicentre, double-blind, placebo-controlled, randomised trial in patients with advanced hepatocellular carcinoma who had not received previous systemic treatment. The study included 602 patients and assessed the effect of sorafenib plus best supportive care (n=299) compared with placebo plus best supportive care (n=303). The primary outcomes in SHARP were overall survival and time to symptomatic progression.

3.3 Sections 4.1 to 4.17 reflect the committee's consideration of the evidence submitted in the original appraisal. Section 4.18 onwards reflects the committee's consideration of the additional evidence submitted for the Cancer Drugs Fund reconsideration. It focused on:

- data from the key source of evidence, SHARP
- observational data from Palmer et al. (2013) and the GIDEON study to validate survival extrapolations from the company's original submission
- estimates of treatment duration using individual patient data for time on treatment from SHARP
- updated resource use data
- cost-effectiveness analyses using a new Commercial Medicines Unit price, providing sorafenib at a reduced cost (commercial in confidence)
- estimates of how much sorafenib is wasted.

3.4 See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE's original technology appraisal guidance on sorafenib for treating advanced hepatocellular carcinoma.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of sorafenib, having considered evidence on the nature of hepatocellular carcinoma and the value placed on the benefits of sorafenib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 The committee considered the UK treatment pathway for patients with hepatocellular carcinoma. The clinical experts described that in UK clinical practice one third of patients with hepatocellular carcinoma would be eligible for procedures such as local resection, radiofrequency ablation or chemoembolisation. They noted that these procedures are not considered clinically effective for approximately 50% of patients, who would progress to further locoregional therapy or systemic treatment. The committee accepted that the scope of this technology appraisal was restricted to these patients. The committee further reviewed the treatment pathway consistent with the Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule as presented by Llovet et al. (2008). The clinical experts agreed that the BCLC staging system is used in UK clinical practice.

4.3 The committee was aware that the licensed indication for sorafenib is hepatocellular carcinoma without specific restrictions. However, the clinical effectiveness evidence from the SHARP study was for patients with advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable. This population was consistent with UK clinical practice and clinical guidelines as outlined in the company's decision problem. The committee noted that the company presented evidence from SHARP in which patients had predominantly BCLC stage C (that is, advanced stage) disease (82.4%). They also had predominantly

good liver function (that is, Child-Pugh grade A liver function; 96.5%), and good Eastern Cooperative Oncology Group (ECOG) performance status (0 to 2). The committee considered how the clinical effectiveness evidence from SHARP related to the total UK population with advanced hepatocellular carcinoma, particularly for patients with Child-Pugh grade B liver function. The committee heard from the clinical experts that systemic therapy with sorafenib would be considered for patients with Child-Pugh grade B liver function although this type of therapy may be less clinically effective than for patients with Child-Pugh grade A liver function. The committee accepted that patients with advanced hepatocellular carcinoma with either Child-Pugh grade A or B liver function may benefit from systemic therapy, although not necessarily to the same degree. The committee accepted that the company's decision problem focused on advanced hepatocellular carcinoma and was in accordance with the scope.

4.4 The committee then discussed possible comparators used in the UK for advanced hepatocellular carcinoma in clinical practice. The committee accepted that in UK clinical practice, treatment with conventional chemotherapy (such as doxorubicin) would be recommended only for a minority of patients who are able to tolerate it. The committee noted that usual treatment for patients with intermediate hepatocellular carcinoma (defined as asymptomatic tumours without vascular invasion or hepatic spread) is transarterial chemoembolisation, in line with current clinical guidelines. The committee was aware that this subgroup was outside the decision problem presented by the company. Therefore best supportive care was accepted as an appropriate comparator for most patients with advanced hepatocellular carcinoma.

Clinical effectiveness (NICE technology appraisal guidance 189)

4.5 The committee considered the clinical effectiveness data presented by the company. It noted that evidence from the clinical studies of sorafenib plus best supportive care suggested that it increased median survival by more than 2.8 months compared with placebo plus best supportive care. The committee also noted that there was a statistically significant difference in median time to radiological disease progression for patients in the sorafenib group compared with the placebo group. The committee was aware that there was an extension in time to disease progression of 11.7 weeks according to independent assessment or 5.1 weeks according to investigator assessment, compared with placebo. The committee accepted the evidence from SHARP, but was aware that the study was stopped early, potentially underestimating the survival benefit attributable to sorafenib. The committee heard from clinical experts and patient experts that the observed benefits in overall survival and time to radiological disease progression were clinically meaningful. It noted that a statistically significant difference was not seen for time to symptomatic disease progression for sorafenib compared with placebo. However, the committee accepted the company's and evidence review group's (ERG's) view that the questionnaire used to measure time to symptomatic disease progression (FHSI-8) may not have been able to distinguish between the toxicity of sorafenib, symptoms of the underlying liver disease, and the symptoms of advanced hepatocellular carcinoma.

4.6 The committee heard from a patient expert that severe adverse events (such as diarrhoea and hand-foot skin reaction) had been experienced during 15 months of treatment with sorafenib, and occasionally it was necessary to stop treatment temporarily. The clinical experts confirmed that similar adverse events have been seen in clinical practice, but no patients in their experience had

completely stopped treatment with sorafenib for this reason. The patient experts agreed that although the adverse events experienced were unpredictable and affected health-related quality of life, they could be tolerated because of the benefits in terms of extension to life.

4.7 Based on the clinical effectiveness evidence and the testimony from clinical experts and patient experts, the committee concluded that sorafenib is a clinically effective treatment for advanced hepatocellular carcinoma when surgical or locoregional therapy had failed or was not suitable.

Cost effectiveness (NICE technology appraisal guidance 189)

4.8 The committee discussed the cost effectiveness of sorafenib for patients with advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable. The committee noted that the base-case incremental cost-effectiveness ratio (ICER) presented by the company was originally £64,800 per quality-adjusted life year (QALY) gained. When the patient access scheme was included this went down to £51,900 per QALY gained. Both ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources.

4.9 The committee noted that the ICER presented in the company's base case depended on the extrapolation of overall survival beyond the SHARP study timeframe by fitting a log normal probability distribution. Several alternative probability distributions were considered and fitted the data well, and the committee was aware that although the log normal curve provided a slightly better fit, particularly for the early trial data, alternatives also fitted the data well. The main differences were in the shape of the curves at the tail of the distribution where, for example, a Weibull curve with a heavier tail was a good fit. The committee concluded that, although

the log normal curve provided a slightly better fit to the observed data, it could not be accepted as the definitive function to extrapolate beyond the study data. The Weibull distribution, which also provided an acceptable fit, should also be considered in any consideration of uncertainty. The base-case log normal extrapolation produced an ICER for sorafenib of £51,900 per QALY gained, which was at the lowest end of the range. The Weibull extrapolation of survival data produced an ICER that was substantially higher (commercial in confidence) than the log normal base case.

4.10 The committee then discussed the ERG's critique of the company's patient access scheme submission. The committee noted concerns about the discrepancies in the dosage of sorafenib and the length of time a pack would last between the patient access scheme as modelled and as described in the summary of product characteristics. It agreed that the description in the summary of product characteristics did not account for dose reductions or stopping treatment temporarily, and that the treatment intensity modelled in the company's submission (based on SHARP) was more appropriate. The committee considered that the cost of post-progression sorafenib treatment was removed from the model but that the benefits were not adjusted. It agreed that, because in clinical practice the benefit from post-progression treatment is likely to be small, retaining the benefits in the model would have a minimal effect on the ICER.

4.11 The committee also noted the inconsistencies in costs associated with treatment duration and agreed that the treatment costs should be based on the actual length of the model cycle. This increased the ICER derived using the log normal extrapolation from £51,900 to £52,600 per QALY gained. It also increased the corresponding (commercial in confidence) ICER using the Weibull extrapolation of survival data. The committee also noted that the company's model

did not take into account the administration costs to the NHS of the patient access scheme but concluded that this would only increase the ICERs marginally.

4.12 The committee was aware of the concerns raised by the ERG about inconsistencies in the utilities used in the company's model. However, it noted that when alternative utility values from a previous renal cell carcinoma assessment report (used to develop NICE's technology appraisal guidance on sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma and bevacizumab [first-line], sorafenib [first- and second-line], sunitinib [second-line] and temsirolimus [first-line] for the treatment of advanced and/or metastatic renal cell carcinoma) were used in a sensitivity analysis, the log normal base-case ICER was not significantly affected.

4.13 The committee considered the additional work by the ERG on the independent and investigator assessments of time to radiological disease progression. It noted that the ICER presented in the company's base case depended on investigator assessment (rather than independent assessment, which was the primary analysis in SHARP). The committee noted that the ERG's analyses demonstrated that the original log normal base case increased to £76,000 per QALY gained (not including the patient access scheme) when using the independent assessment of time to radiological disease progression. The corresponding (commercial in confidence) ICER derived using the Weibull extrapolation of survival data would also be substantially higher. Therefore it concluded that sorafenib, as a treatment for advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable, would not be a cost-effective use of NHS resources.

4.14 The committee then considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.15 The committee discussed whether the benefit provided by sorafenib in hepatocellular carcinoma fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It noted from the clinical studies that life expectancy without sorafenib was unlikely to be greater than 24 months and was potentially as low as 7.9 months, although the latter was based on SHARP, which was stopped early. The committee considered that evidence from the clinical studies of sorafenib plus best supportive care suggested that it increased median survival by more than 2.8 months compared with placebo plus best supportive care, and the company's economic model predicted a mean gain in overall survival of 6.1 months, although this depended on the method of extrapolation. Although the committee noted that sorafenib is licensed for indications other than hepatocellular carcinoma, the committee considered sorafenib to fulfil the small population

criterion for an end-of life treatment. In summary, the committee was satisfied that sorafenib for advanced hepatocellular carcinoma met the criteria for an appraisal of a life-extending, end-of-life treatment, and that the evidence presented was supported by robust data.

4.16 The committee then discussed the range of cost-effectiveness estimates for sorafenib (with the lowest being the ICER of £52,600 per QALY gained and the highest being substantially greater), in light of the end-of-life considerations. It considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great. Therefore the committee concluded that sorafenib as a treatment for advanced hepatocellular carcinoma when surgical or locoregional therapies had failed or were not suitable would not be a cost-effective use of NHS resources.

4.17 The committee considered whether there were any subgroups of people for whom sorafenib would be considered a cost-effective use of NHS resources. The committee noted that the subgroups presented by the company were based on a small number of patients, and because the clinical study was not powered to assess differential patient response to treatment, the subgroups were intended to be descriptive only. Also, no adjustments were made for multiple comparisons. The committee was aware that there was limited evidence of clinical effectiveness in these subgroups and that the ICERs would be based on a weak evidence base. Therefore the committee was not satisfied that the estimates of extension to life were robust or that the resulting subgroup ICERs were plausible. It concluded that it would not be appropriate to recommend sorafenib for specific subgroups of patients with advanced hepatocellular carcinoma.

Cancer Drugs Fund reconsideration of NICE technology appraisal guidance 189

4.18 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on sorafenib for the treatment of advanced hepatocellular carcinoma. At its first reconsideration meeting, the committee considered the company's submission that included:

- a Commercial Medicines Unit price that was lower than the price used in the original appraisal
- data from 2 observational studies:
  - GIDEON, unmatched to the characteristics of the SHARP population, and Palmer et al. (2013), also unmatched to SHARP, which the company used to validate the log normal curve it chose in the original appraisal to extrapolate overall survival beyond the end of SHARP (see section 4.9)
- an estimate of the duration of treatment using data from SHARP on time to disease progression
- the committee's preferred assumptions on costs from the original appraisal (see section 4.11)
- updated unit cost and resource use estimates.

4.19 At its second meeting, the committee considered the company's responses to the appraisal consultation document, including:

- evidence from GIDEON, now matched to the SHARP population, on the baseline characteristics of patients that might influence mortality to validate the log normal curve extrapolating overall survival beyond the end of SHARP
- further explanations of Palmer et al.
- estimating duration of treatment using individual patient data on time to stopping treatment from SHARP (the committee's preferred assumption)

- justification for using only recent data on resource use in the economic model
- a cost-effectiveness analysis calculated using a lower Commercial Medicines Unit price of sorafenib than considered at the first meeting.

The committee also considered the ERG's critique of the company's submission in this reconsideration, the ERG's critique of the company's response to the appraisal consultation document and the ERG's exploratory analyses.

Population

4.20 The committee noted that SHARP included people with Child-Pugh grade A and grade B liver function and ECOG performance status of 0 to 2. The committee noted consultation comments from professional groups that suggested sorafenib may be more clinically and cost effective in people with Child-Pugh grade A liver function and good performance status. However, the committee highlighted that the company's evidence for Cancer Drugs Fund reconsideration meeting, and in its response to the appraisal consultation document, included people with Child-Pugh grade A and grade B liver function and ECOG performance status of 0 to 2. The committee concluded that it was not presented with any evidence to restrict its recommendations to advanced hepatocellular carcinoma with Child-Pugh grade A liver function and good performance status.

Validating the overall survival extrapolation

4.21 The committee understood that the final draft guidance issued during the original appraisal went to an appeal panel. It was aware that the appeal panel agreed with the committee's view that the Weibull distribution should be taken into account in any consideration of uncertainty, and that all appeal points were dismissed.

4.22 The committee discussed Palmer et al. and GIDEON, the 2 longitudinal observational studies. It recognised that Palmer et al. was a published retrospective cohort study comparing patients with hepatocellular carcinoma in 2 hepatobiliary oncology units in the UK who received funding for sorafenib (n=57) with those who did not receive funding (n=76) before the existence of the Cancer Drugs Fund. The committee noted that patients who did not receive funding for sorafenib did not live as long as patients who did have funding. It also considered, at its first meeting, that the association between funding and death may be confounded, that is, patients with better prognoses might be more likely to receive funding and treatment than patients with poorer prognoses. The committee was aware that there was a higher proportion of patients with metastatic disease in the unfunded group. It noted the ERG's comment that the study was not suitable for decision-making. The committee heard from the company at its second meeting that the decision to fund sorafenib was not based on clinical variables. However, the committee could not exclude the possibility of residual confounding and concluded that the data from Palmer were a less robust source of evidence than the GIDEON data, now matched to SHARP. It further noted that the Palmer data did not favour a log normal or Weibull distribution over the other. The committee concluded that the matched GIDEON data was more appropriate than Palmer for validating the extrapolation of overall survival beyond SHARP.

4.23 The committee discussed the GIDEON data, noting that the company responded to the appraisal consultation document by adjusting the data to match the characteristics of the SHARP population, particularly for risk factors for death. The company chose a propensity score, a method of statistical matching, to do this. The committee recognised that the ERG considered this approach satisfactory. The matched GIDEON sample (n=895) resulted in longer median overall survival than SHARP. The

company fitted log normal and Weibull curves to the Kaplan–Meier data for the matched GIDEON population and stated that the log normal curve provided a better statistical fit to the observed data than the Weibull curve; the committee agreed. The committee considered that beyond about 600 days, the Weibull curve fitted the data better than the log normal curve. However, the committee was aware that this meant that the uncertainty in the tail of the curve was greater. The committee understood from the ERG that the log normal function would overestimate overall survival whereas the Weibull function would underestimate it. Therefore, the ERG advised that both curves should be considered when extrapolating overall survival, and to estimate the ICER for sorafenib compared with best supportive care. The committee acknowledged that statistical goodness of fit alone should not be used to choose the most appropriate survival function. It noted that in general the log normal function used by the company to extrapolate survival beyond SHARP fitted GIDEON better than the Weibull function, but that the Weibull function was still plausible. The committee was also aware that the 3 data sets the company had presented (SHARP, GIDEON, and Palmer et al.) for informing the choice of survival distribution did not conclusively favour 1 single distribution. The committee commented that further follow-up survival data from SHARP, as used in the company's economic modelling, could clarify this uncertainty. The committee concluded that the true estimate of life expectancy with sorafenib compared with best supportive care was likely to lie between the estimates from the log normal and the Weibull distributions.

Duration of treatment

4.24 The committee discussed whether the estimates of treatment duration should come from SHARP (the source of the clinical effectiveness data) or from another source. It heard from a clinical expert that a soon-to-be-published clinical audit exists, describing

duration of treatment in the UK. However, the committee heard from the ERG and from NHS England that both the effectiveness and cost estimates should come from the same source, in this case, SHARP. The committee concluded that data from SHARP should be used to estimate duration of treatment, and the total cost of treatment.

4.25 The committee discussed which data from SHARP best reflected the duration of treatment. It understood that the company and the ERG preferred different methods; the company preferred time to disease progression as a proxy for duration of treatment, whereas the ERG and the committee preferred the actual data on duration of treatment. The committee acknowledged the debate in the original appraisal about using either investigator assessment or independent assessment of disease progression as a surrogate for time on treatment. The company continued to use time to disease progression for treatment duration in its base-case analysis despite the committee's stated preference in the appraisal consultation document. This was because the company considered that the treatment duration in SHARP was longer than seen in UK clinical practice. The committee understood that the ERG considered that the estimates of mean and median treatment duration reported from the Cancer Drugs Fund, King et al., GIDEON and Palmer et al. were inconclusive and therefore did not support the company's claim that SHARP overestimated the treatment duration of sorafenib in clinical practice. The ERG noted that time to progression based on independent assessment (the primary means of documentation in the SHARP protocol) and treatment duration were similar and also noted the committee's preference in the original appraisal for including treatment costs for patients who had treatment after progression. The committee concluded that treatment duration estimates should be based on data directly reflecting the time on treatment.

4.26 The committee discussed the company's methods for extrapolating time on treatment data from SHARP. The company presented a survival analysis of the time from the date of randomisation to the date of discontinuation of treatment from any cause. To extrapolate beyond the end of the trial, the company applied 5 parametric models: exponential, Gompertz, log logistic, log normal and Weibull, plus a hybrid analysis that the company considered the most robust. The committee understood that the ERG preferred the fully parametric log normal model because a hybrid approach was only appropriate when there was a strong rationale for not using all of the available data to inform the extrapolated curve. The committee stated that the log normal distribution was the best statistical fit of the 5 distributions explored by the company. The committee noted that based on criteria published by Kass et al. (1995), the Bayesian information criterion statistics strongly indicated that the Weibull distribution did not fit the data. The committee also heard from the clinical expert that based on UK audit data (in press) 10% of patients survived for 3 years, which supported using the log normal distribution. The committee concluded that the company's fully parametric method using the log normal distribution reflected the most robust estimate of treatment duration.

Cost and resource use estimates

4.27 The committee was aware that the company updated the unit cost data in its reconsideration submission. It was also aware that in clinical practice, the company charges the NHS for a full pack of sorafenib at the start of each treatment cycle. Some patients do not complete the treatment cycle. Therefore the company may have underestimated the cost of treatment in its economic modelling for the first reconsideration meeting. In its response to the appraisal consultation document, the company presented cost-effectiveness results for analyses including the wastage of up to 7 days of

treatment. The committee concluded that it was appropriate for the company to use updated unit cost data and account for 7 days of drug wastage because this reflected the price relevant to the NHS.

4.28 The committee was aware that in the original appraisal the company based its estimates of resource use, for example, number of hospitalisations, on the opinion of 4 clinicians. But in this reconsideration, the company provided recent resource use estimates based on the opinion of 3 different clinicians. At the first Cancer Drugs Fund reconsideration meeting the committee noted that the few revised resource use data estimates varied widely and therefore it was better to pool the original and revised estimates. In its response to appraisal consultation document, the company claimed that resource estimates from the original appraisal were no longer accurate because of significant changes in clinical practice. Specifically, patients now had treatment in oncology rather than hepatology clinics and had palliative care in the community. The committee noted that the company did not provide any more evidence in its response to the appraisal consultation document. The committee heard from the ERG that the parameters affecting the ICER most when using the updated resource use estimates compared with the pooled resource use estimates were in the best supportive care group, particularly those relating to admission and frequency of hospitalisation. Also, the committee understood from the ERG that the ICER was extremely sensitive to changes in these parameters. The committee concluded that the company's revised resource use data were not robust and further data would increase certainty in the ICER.

End-of-life considerations

4.29 The committee considered the advice about life-extending treatments in NICE's final Cancer Drugs Fund technology appraisal process and methods. It noted the committee's conclusion in the

original appraisal that sorafenib in hepatocellular carcinoma met the end-of-life criteria (see section 4.15). The committee agreed that sorafenib was still indicated for patients with a short life expectancy and offered an extension to life of at least 3 months compared with current NHS treatment. The committee concluded that sorafenib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment.

Conclusion

4.30 The committee discussed the most plausible ICER for sorafenib compared with best supportive care for treating advanced hepatocellular carcinoma. The committee considered that uncertainty still existed, associated with extrapolating overall survival from SHARP (see section 4.23). The committee agreed that the most plausible ICER should:

- be based on the ERG's exploratory analyses using the company's fully parametric method (log normal distribution) to estimate treatment duration (see section 4.26)
- account for drug wastage for up to 7 days and
- use the pooled resource use data in the absence of more robust updated resource use data.

The committee's preferred ICER range was between £49,500 (using a log normal distribution to extrapolate overall survival) and £87,000 (using a Weibull extrapolation) per QALY gained for sorafenib compared with best supportive care, including the new Commercial Medicines Unit price. The committee agreed that the most plausible ICER was likely to be lower than the mid-point of the its preferred ICER range (that is, likely to be lower than approximately £68,250 per QALY gained), but would be higher than ICERs previously accepted for technologies that had met the end-of-life criteria. Taking into account all factors, including the end-of-

life criteria, the committee concluded that it could not recommend sorafenib for routine commissioning in the NHS.

Cancer Drugs Fund considerations

4.31 Having concluded that sorafenib could not be recommended for routine use, and recognising the unmet need for patients with advanced hepatocellular carcinoma, the committee then considered if sorafenib could be recommended for use within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee was aware that in considering this, the following criteria must be met:

- The ICERs have plausible potential for satisfying the criteria for routine use.
- It is possible that the uncertainty can be addressed through collecting outcome data from patients treated in the NHS.
- It is possible that the data could inform a subsequent update of the guidance (normally within 24 months).

4.32 The committee agreed that the ICERs for sorafenib compared with best supportive care (including the new Commercial Medicines Unit price) indicated a plausible potential to be cost effective (see section 4.30). The committee noted that in response to the appraisal consultation document, the company had presented several inconclusive sources on the length of treatment in clinical practice, and that it preferred using both the effectiveness and cost estimates from the same source, in this case SHARP (see section 4.24). The committee appreciated that people continued treatment after progression in SHARP, which may no longer reflect clinical practice. However, the committee also considered that it was reasonable to assume that prolonging treatment in SHARP would also lead to benefits in the effectiveness of sorafenib relative

to best supportive care. Therefore, the committee stated that considerable uncertainty remained about the relationship between length of sorafenib treatment and its effectiveness in clinical practice. The committee considered that collecting data from the Systemic Anti-Cancer Therapy dataset may help resolve some of this uncertainty. Also, the committee would have preferred to have seen longer follow-up survival data from SHARP. The committee noted that the company's updated resource use estimates had considerable impact on the ICERs (see section 4.28) and this had the potential to be addressed with further data collection. The committee concluded that several uncertainties remained that could be addressed through collecting outcome data from patients treated in the NHS.

4.33 The committee was reassured that, as part of the process of considering sorafenib for inclusion within the Cancer Drugs Fund, the committee would have the opportunity to consider the data collection arrangements, timeframe, and the commercial access arrangement agreed by the company and NHS England, before providing a final recommendation for use. The committee therefore invited the company to submit a proposal for including sorafenib in the Cancer Drugs Fund, and to lay out how data collection will address the main uncertainties. The committee concluded that sorafenib should be recommended for use within the Cancer Drugs Fund as an option for treating advanced hepatocellular carcinoma in adults only if surgical or locoregional therapies have failed or are not suitable and the company's proposal is agreed by NHS England.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Sorafenib for treating advanced hepatocellular carcinoma	Section

Key conclusions: Cancer Drugs Fund reconsideration of TA189		
Sorafenib is recommended for use within the Cancer Drugs Fund as an option for treating advanced hepatocellular carcinoma in adults when surgical or locoregional therapies have failed or are not suitable. The committee has invited the company to submit a proposal for inclusion in the Cancer Drugs Fund for sorafenib for use within the Cancer Drugs Fund as an option for treating advanced hepatocellular carcinoma in adults when surgical or locoregional therapies have failed or are not suitable, and to lay out how data collection in the Cancer Drugs Fund will address the main uncertainties.		1.1 4.31–33
Additional factors taken into account		
Equalities considerations and social value judgements	The committee noted that in response to the appraisal consultation document a consultee noted that the prevalence of liver cancer deaths is higher in socially deprived areas. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.	–

5 Recommendations for data collection

5.1 As a condition of the positive recommendation, the company is required to submit a proposal for sorafenib to be included in the Cancer Drugs Fund, and is agreed by NHS England before final guidance can be published. Part of this proposal includes collecting outcome data from patients in the NHS:

- efficacy (for example, overall survival)
- time on treatment and
- healthcare resource data (for example, frequency of hospitalisations).

6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

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.

NICE project team

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

TA189

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Cancer Drugs Fund reconsideration of TA189

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