NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

Sorafenib for the treatment of advanced hepatocellular carcinoma

The Department of Health has asked the National Institute for Health and Clinical Excellence (NICE) to produce guidance on using sorafenib for the treatment of advanced hepatocellular carcinoma in the NHS in England and Wales. The Appraisal Committee has had its third meeting to consider the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists 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 draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from www.nice.org.uk

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 for the treatment of hepatocellular carcinoma in the NHS in England and Wales.

For further details, see the 'Guide to the technology appraisal process' (available at www.nice.org.uk).

The key dates for this appraisal are:

Closing date for comments: 30th September 2009

Next Appraisal Committee meeting: 14th October 2009

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

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

1 Appraisal Committee's preliminary recommendations

1.1 Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma (HCC) in patients for whom surgical or locoregional therapies have failed or are not suitable.

1.2 People currently receiving sorafenib for the treatment of advanced HCC should have the option to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Sorafenib (Nexavar, Bayer HealthCare) 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 (VEGF)/platelet-derived growth factor (PDGF) receptors of tumour cells, vascular endothelial cells and pericytes. Sorafenib has a UK marketing authorisation for the treatment of hepatocellular carcinoma.

2.2 The summary of product characteristics (SPC) lists 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 side effects and contraindications, see the SPC.

2.3 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 two 200-mg tablets once

daily if adverse drug reactions are suspected. The SPC recommends that treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs. The manufacturer has agreed a new price under the Pharmaceutical Price Regulation Scheme (PPRS) from 1 February 2009. The price for a pack of 200-mg tablets (112 tablets per pack) is £2980.47 (excluding VAT). The manufacturer has agreed a patient access scheme (PAS) with the Department of Health for sorafenib for advanced HCC (see 3.16). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

3.1 The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of sorafenib and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.2 The manufacturer's decision problem compared sorafenib with best supportive care (BSC), and defined the population as being patients with advanced HCC for whom surgical or locoregional therapies have failed or are not suitable. Outcomes were defined as being overall survival, progression-free survival, time to symptomatic progression, tumour response, health-related quality of life and adverse effects of treatment. In the economic evaluation both the incremental cost per quality-adjusted life year (QALY) gained and the incremental cost per life year gained were presented. A lifetime horizon was used, and costs were considered from the NHS perspective.

3.3 In the submission the manufacturer identified three studies providing evidence on the clinical effectiveness of sorafenib for the treatment of hepatocellular carcinoma. The manufacturer's submission presented clinical-effectiveness data from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol

(SHARP) study, a registration randomised controlled trial (RCT). The remaining two studies identified (a multicentre RCT and an uncontrolled open-label study) provided supporting data.

3.4 The SHARP study was a multicentre, double-blind, placebo-controlled randomised trial in patients with advanced HCC who had not received previous systemic treatment. The study included 602 patients and assessed the effect of sorafenib plus BSC (n = 299) versus placebo plus BSC (n = 303). The study was conducted in patients who were predicted to have a life expectancy of at least 12 weeks and who had the following characteristics: an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; histologically or cytologically documented HCC; and at least one measurable tumour not previously treated with local therapy. The majority of patients had a Child–Pugh liver function status of grade A or B (96.5% and 3.3% respectively). The Child-Pugh score can be used to predict the prognosis and strength of required treatment. The score classifies liver disease into Child-Pugh A, B and C class; people with Child-Pugh class A have the best prognosis. The majority of patients had BCLC stage B (intermediate) or C (advanced) disease (17.4 and 82.4% respectively) and one patient had BCLC stage D (end stage) disease (0.2%).

3.5 Randomised patients received 400 mg sorafenib twice daily plus BSC, or matching placebo plus BSC. If there were adverse events related to sorafenib, dosages could be reduced to 400 mg once daily, and then to 400 mg every 2 days. The mean dose of sorafenib administered in the SHARP study was 710.5 mg per day. Treatment was continued until there was radiological progression according to response evaluation criteria in solid tumours (RECIST) and symptomatic progression; death; adverse events that required study treatment to be stopped; withdrawal from the study; or until

another criterion for stopping therapy was met (such as deterioration to an ECOG performance status of 4).

3.6 At baseline, 325 patients had an ECOG performance status of 0 (161 patients receiving sorafenib and 164 patients receiving placebo), and 277 patients had an ECOG performance status of 1 or 2 (138 patients receiving sorafenib and 139 patients receiving placebo). Tumour burden, defined as the presence of macroscopic vascular invasion and/or extrahepatic spread, was present in 421 patients (209 receiving sorafenib and 212 receiving placebo). The majority of patients had Child–Pugh grade A liver function (284 patients receiving sorafenib and 297 patients receiving placebo). The remaining patients had Child–Pugh B or C liver function (Child–Pugh B: 14 patients receiving sorafenib, 6 patients receiving placebo; Child-Pugh C: 1 patient receiving sorafenib, no patients receiving placebo). Liver cirrhosis was confirmed by histological or clinical criteria in 429 patients. The most frequent aetiology of underlying liver disease was hepatitis C (169 patients) followed by alcohol (159 patients) and hepatitis B (111 patients). Patients were stratified before randomisation according to the following factors:

- tumour burden
- ECOG performance status of 0 versus 1 versus 2

geographical region (North America; South America, including Mexico; and Europe and Australasia).

3.7 The manufacturer provided information about the two studies used as supporting evidence. The Asia–Pacific study by Cheng et al. (2008) was a multicentre RCT of sorafenib plus BSC versus placebo plus BSC in 226 patients with advanced HCC (and hepatitis B) from China, Korea and Taiwan. An uncontrolled open-label study by Abou-Alfa et al. (2006) was carried out in 137 patients from Europe receiving sorafenib for advanced HCC. The manufacturer also highlighted that there were several ongoing

studies: sorafenib alone; sorafenib versus placebo, doxorubicin, and sunitinib; and sorafenib plus doxorubicin versus doxorubicin alone.

3.8 The primary outcomes in the SHARP study were overall survival and time to symptomatic progression (which was defined as a decrease of four or more points from baseline on the functional assessment of cancer therapy – hepatobiliary [FACT-hep] questionnaire, deterioration in ECOG performance status to 4, or death). There was no statistically significant difference in time to symptomatic progression between the sorafenib and placebo groups. The manufacturer suggested that the FACT-hep symptom index 8 (FHSI-8) questionnaire used to measure this may not have been able to distinguish between the toxicity of sorafenib, symptoms of the underlying liver disease, and the symptoms of advanced HCC. The FACT-hep was also used to measure health-related quality of life (HRQoL) and data from the SHARP trial report demonstrated that 11.5% of patients receiving sorafenib and 19.6% of patients receiving placebo had at least an 8-point improvement in score. The blinded phase of the SHARP study was stopped early when the second interim analysis indicated that sorafenib significantly prolonged median overall survival (46.3 weeks, 95% confidence interval [CI] 40.9 to 57.9) compared with placebo (34.4 weeks, 95% CI 29.4 to 39.4). The hazard ratio (HR) for overall survival (sorafenib over placebo) was 0.69 (95% CI 0.55 to 0.87). This represented a 30.7% reduction in hazard (risk of death) over placebo. Following stoppage, all patients in the double-blind phase (as well as those in follow-up) were entered into an unblinded extension phase of the study.

3.9 Analyses of the secondary outcome, time to radiological disease progression, were based on both independent (primary analysis) and investigator assessment. These analyses demonstrated that, in total, there were 263 and 403 progressions with independent and

investigator assessment respectively. The analyses indicated that the median time to radiologically determined disease progression (according to RECIST criteria) was statistically significantly extended by 11.7 weeks according to independent assessment, or 5.1 weeks according to investigator assessment, in the sorafenib group compared with the placebo group. The manufacturer's analyses of tumour response revealed small differences between the sorafenib and placebo groups, with patients having very low levels of complete or partial response in both groups.

3.10 The manufacturer developed a Markov model to assess the cost effectiveness of sorafenib compared with BSC in people with advanced HCC. The model had four distinct health states: first-line treatment – non-progressive advanced disease; first-line treatment – progressive disease; BSC – progressive disease; and death. The model had a cycle length of 1 month and a lifetime time horizon. The time horizon was assumed to cover up to an additional 14 years of life for a patient population with an average starting age of 67 years. Time horizons of 2, 5 and 10 years were explored in sensitivity analyses.

3.11 The model used effectiveness data from the SHARP study, extrapolated to a lifetime horizon. Several distributions were tested. Based on the Akaike information criterion for goodness of fit to the observed data, a log-normal distribution was chosen for extrapolating time to disease progression and overall survival (based on the trial investigators' assessment). It was assumed that the rate of adverse events was constant over time, and the disutilities associated with adverse events were additive (that is, they could be estimated by calculating the difference between a health state with an adverse event and the same health state without the adverse event). Only common adverse events were included in the model. Adverse events occurring in fewer than 10% of patients were excluded.

3.12 The utility values used in the model were derived using a mapping approach. HRQoL was measured with the FACT-hep instrument. The manufacturer mapped these responses using an algorithm developed by Dobrez et al. (2007) to obtain health-state utility estimates. This mapping algorithm used the generic portion of the FACT-hep instrument (FACT-G) to map to a set of time trade-off utility values. The algorithm did not include information gained from the 'hep' subset of the FACT-hep questionnaire.

3.13 The model included costs for drug treatment for HCC (sorafenib), and treatment costs for different health states and adverse events. Resource use and cost parameters in the model were estimated from primary (SHARP trial) and secondary sources. The estimates of resource use and costs of adverse events were based on a survey of UK clinicians. The model also included the costs of sorafenib for 7.7% of patients who continued treatment with sorafenib after progression for a median of 129 days, as observed in the SHARP study.

3.14 Sorafenib compared with BSC produced a base-case incremental cost-effectiveness ratio (ICER) of £64,754 per QALY gained. One-way sensitivity analyses demonstrated that the ICER was most sensitive to estimates of time to progression and overall survival from SHARP, and to utility values. Probabilistic sensitivity analysis provided a similar result to the deterministic base case (£65,244 per QALY gained). The manufacturer carried out subgroup analyses that included age (65 years and older), and measures of performance status; Child–Pugh liver function grade A; tumour node metastasis [TNM] I–III; BCLC stage B; BCLC stage C), resulting in ICERs that ranged from £32,701 to £76,592 per QALY gained. Other disease-specific subgroups and scenario analyses were examined and resulted in ICERs both higher and lower than the base-case ICER; these results are currently commercial in confidence.

3.15 The manufacturer proposed a PAS which was accepted by the Department of Health in England and the Department of Health and Social Services in Wales for consideration by NICE. The manufacturer submitted revised cost-effectiveness analyses incorporating a PAS in which every fourth pack of sorafenib is provided free or rebated to the NHS. In the revised model, the cost of one cycle of sorafenib was removed every fourth cycle for patients still receiving sorafenib over the 14-year time horizon of the model. In the PAS, all patients stop treatment at the point of progression, as determined according to investigator assessment, as in the SHARP trial. The manufacturer stated that this was consistent with clinical practice. The revised model therefore assumed that patients would not continue treatment after progression, which differs from the analysis without the PAS, in which 7.7% of patients continued treatment after progression. The benefits in the model were not adjusted. All other assumptions remained the same as in the original model. The revised base-case ICER (taking the PAS into account) for the trial population was £51,899 per QALY gained. The manufacturer carried out subgroup analyses (taking the PAS into account) that included age (65 years and older) and measures of performance status; Child–Pugh liver function grade A; tumour node metastasis [TNM] I–III; BCLC stage B; BCLC stage C), resulting in ICERs that ranged from £28,105 to £60,681 per QALY gained. Other disease-specific subgroups and scenario analyses were examined, and resulted in ICERs both higher and lower than the base-case ICER (£51,899 per QALY gained); these results are currently commercial in confidence. Further documentation was provided in confidence to the Department of Health.

3.16 The ERG stated that the manufacturer's submission was of acceptable overall quality and it generally followed the NICE reference case. The two RCTs used to derive effectiveness data

were of sufficient power to demonstrate that sorafenib plus BSC statistically significantly improved overall survival and time to radiological disease progression compared with placebo plus BSC. The ERG stated that the manufacturer provided a reliable, internally valid model that was appropriate for the decision problem and was based primarily on robust clinical data from the SHARP RCT.

3.17 The ERG highlighted the following key areas of concern with the manufacturer's submission:

- using investigator assessment of time to disease progression rather than independent assessment
- the generalisability of the SHARP population to the overall UK HCC population
- using BSC as the sole comparator
- relying on expert opinion for estimating resource use and costs of adverse events
- the methods used to determine the HRQoL information for sorafenib and BSC and the algorithm used to obtain health-state utility estimates
- the definition and the modelling of the PAS.

3.18 The ERG stated that there were clear discrepancies between the analyses of independent and investigator assessment of time to disease progression. Although the investigator analysis indicated less extension in time to disease progression than the independent analysis, it generated a greater proportion of live patients in the progressive state who incurred low costs, which could bias the ICER in favour of sorafenib. The ERG carried out additional sensitivity analyses on the impact of using the independent assessment of time to disease progression rather than the investigator assessment. These analyses produced an ICER of £76,067 per QALY gained (not including the PAS), which was

higher than the ICER estimated in the base case using the investigator analysis (£64,754 per QALY gained).

3.19 The ERG noted that the effectiveness evidence from the SHARP study related almost exclusively to patients with relatively good liver function (Child–Pugh grade A). Furthermore, it noted that the manufacturer's submission referenced results from a recent uncontrolled open-label study by Abou-Alfa et al. (2008) that was relevant to the decision problem. The ERG noted that patients with Child–Pugh grade B liver function may gain less survival benefit from sorafenib than patients with Child–Pugh grade A liver function. It noted that if patients with Child–Pugh grade B liver function were included in the analysis this would have reduced the overall effectiveness of sorafenib. Therefore, the average estimates of survival gain for sorafenib for the population defined in the decision problem are likely to be an overestimate if based only on the results from the SHARP study (in which patients had predominantly Child–Pugh Grade A liver function).

3.20 The ERG noted that although the manufacturer's submission considered that doxorubicin was not a valid comparator, it was considered a viable therapy in a recent study comparing sorafenib plus doxorubicin versus doxorubicin alone. The ERG also noted that the European Medicines Agency (EMEA) considered a phase III RCT of nolatrexed versus doxorubicin in advanced HCC (n = 445) in the European Public Assessment Report on sorafenib. The EMEA concluded, on the basis of the observed 2.3-month median survival advantage for doxorubicin, that on balance it was likely to be an effective intervention. The ERG highlighted that although doxorubicin is not licensed specifically for advanced HCC, it is licensed for the treatment of solid tumours, which could include HCC. It was unclear to the ERG what proportion of patients in the UK is treated with doxorubicin and why this therapy was not considered a valid comparator for the economic evaluation.

3.21 The ERG highlighted that the description of the pack-length and dosage of sorafenib in the SPC differed from that in the manufacturer's modelled PAS. In the manufacturer's model of the PAS, sorafenib use was based on the average dose in the SHARP study (710.5 mg per day) rather than the recommended SPC dose (800 mg per day). The pack-length of sorafenib listed in the SPC at the recommended dosage would last 28 days rather than 30.4 days, as was modelled. The ERG calculated that if the PAS was strictly modelled according to the SPC recommended dosage and pack length, the manufacturer's base case would increase from £51,899 to £58,147 per QALY gained. The ERG highlighted that the manufacturer's revised analyses did not take into account the administrative costs to the NHS of the PAS. It stated that including any administration costs would increase the manufacturer's cost-effectiveness estimates.

3.22 The ERG also noted that in the revised model incorporating the PAS, based on the SHARP study, a cycle of sorafenib lasted 31.5 days for an average patient, whereas in the model a cycle lasted for 1 month (equivalent to 30.4 days). The ERG stated that the modelling approach used by the manufacturer was equivalent to every fourth month free rather than every fourth 'treatment-cycle' free. Modelling every fourth 'treatment-cycle' free would increase the ICER minimally. Furthermore, the ERG noted that the cost of sorafenib for the 7.7% of patients continuing treatment after progression (as observed in the SHARP study) was removed from the model, but the benefits in the model were not adjusted. The ERG calculated that if the costs of sorafenib treatment after disease progression were included, then the manufacturer's base case would increase from £51,899 to £54,509 per QALY gained. The ERG also highlighted that there were inconsistencies in the costs associated with the modelled treatment duration. In the revised analyses submitted by the manufacturer, sorafenib costs

per model cycle were calculated based on 30 days of treatment (equivalent to £2836 per cycle). The ERG noted that the model cycle length is actually 30.4 days (equivalent to sorafenib costs of £2878 per cycle); increasing the manufacturer's base-case ICER from £51,899 to £52,641 per QALY gained.

3.23 The ERG highlighted that the economic evaluation relied heavily on expert opinion for estimating resource use for the treatments in the model, and the manufacturer did not comment on or assess the validity of the resulting estimates. The ERG stated that using expert opinion as a primary source for a wide range of resource use estimates significantly increased the uncertainty associated with the overall model results. The ERG noted that the economic evaluation also relied heavily on expert opinion for estimates of the costs of adverse events. It also noted a number of other, more minor, omissions and errors in the manufacturer's approach to including adverse events in the economic model.

3.24 The ERG noted that the economic evaluation relied on mapping estimates of HRQoL using an algorithm developed by Dobrez et al. (2007) to obtain health-state utility estimates. The ERG stated that although the algorithm developed by Dobrez et al. (2007) was methodologically valid, it may not be the most appropriate approach to estimating utility scores. This is because it is based on preferences of a population with cancer, not preferences of the general population, as specified in the NICE reference case. The ERG also noted that in the manufacturer's submission the mean utility before disease progression was marginally lower (0.69) than the mean utility after disease progression (0.71), which seemed counterintuitive. It commented that this lack of face validity may be because of a potential error in the Dobrez algorithm used to calculate utility values, resulting in higher utility values being assigned to more-severe health states (that is, once disease progression has occurred), and therefore the utility estimates

presented in the manufacturer's submission should be treated with caution. Sensitivity analyses were carried out in the manufacturer's submission to explore the effects of the utilities from the mapping algorithm. The analyses used utility values from the ongoing NICE technology appraisal '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' for sorafenib with BSC before progression (0.76) and after progression (0.68). This produced a similar ICER to the base case, of £63,992 per QALY gained (not including the PAS).

3.25 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx [this will be available on publication]

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of sorafenib for HCC, having considered evidence on the nature of HCC and the value placed on the benefits of sorafenib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the UK treatment pathway for patients with HCC. The clinical specialists described that in UK clinical practice one third of HCC patients would be eligible for procedures such as local resection, radiofrequency ablation or chemoembolisation. They noted that these procedures are not considered 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 BCLC staging

classification and treatment schedule as presented by Llovet et al. 2008. The clinical specialists agreed that the BCLC staging system is used in UK clinical practice.

4.3 The Committee was aware that the licensed indication for sorafenib was HCC without specific restrictions. However, the clinical effectiveness evidence from the SHARP study related to patients with advanced HCC for whom 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 manufacturer's decision problem. The Committee noted that the manufacturer presented evidence from the SHARP study 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 performance status (0–2). The Committee considered how the clinical-effectiveness evidence observed in the SHARP trial related to the total UK population with advanced HCC, particularly with regard to patients with Child–Pugh grade B liver function. The Committee heard from the clinical specialists that patients with Child–Pugh grade B liver function would be considered for systemic therapy with sorafenib, 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 HCC (defined as BCLC stage C) 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 manufacturer's decision problem focussed on advanced HCC and was in accordance with the scope

4.4 The Committee then discussed possible comparators used in the UK for advanced HCC in clinical practice. It noted the ERG's comments that doxorubicin could be a relevant comparator, although the extent of its use was unclear. The clinical specialists

stated that, before sorafenib was introduced, patients with advanced HCC usually received BSC. Conventional chemotherapy with systemic agents such as doxorubicin was occasionally used. However, the clinical specialists highlighted that there were a number of adverse events associated with doxorubicin therapy (such as hair loss, nausea and vomiting, lower resistance to infection, bruising or bleeding) that limited its use to relatively fit patients. Furthermore, the clinical specialists discussed some studies that had shown doxorubicin not to have apparent benefit based on radiological assessment. 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 HCC (defined as asymptomatic tumours without vascular invasion or hepatic spread) is transarterial chemoembolisation, in line with current clinical guidelines. The Committee were mindful that this subgroup was outside the decision problem as presented by the manufacturer. Therefore BSC was accepted as an appropriate comparator for the majority of patients with advanced HCC.

Clinical effectiveness

4.5 The Committee considered the clinical-effectiveness data presented by the manufacturer. It noted that evidence from the clinical studies of sorafenib plus BSC suggested that it increased median survival by more than 2.8 months compared with placebo plus BSC. The Committee also noted that there was a statistically significant difference in median time to radiological disease progression for patients receiving sorafenib (an extension 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 the SHARP trial, but was mindful that the study was stopped early, potentially

underestimating the survival benefit attributable to sorafenib. The Committee heard from clinical specialists and patient experts that the observed benefits in overall survival and time to radiological disease progression were clinically meaningful. The Committee was mindful that there were differences between the analyses using independent and investigator assessment for time to radiological disease progression. It noted that a statistically significant difference was not observed for time to symptomatic disease progression for sorafenib compared with placebo. However, the Committee accepted the manufacturer's and 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 HCC.

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 specialists confirmed that similar adverse events have been observed 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 affect health-related quality of life, they could be tolerated because of the trade-off with the benefits in terms of extension in life.

4.7 Based on the clinical-effectiveness evidence and the testimony from clinical specialists and patient experts, the Committee concluded that sorafenib was a clinically effective treatment for advanced (BCLC stage C) HCC in patients for whom surgical or locoregional therapy had failed or was not suitable.

Cost effectiveness

4.8 The Committee discussed the cost effectiveness of sorafenib for treating patients with advanced HCC for whom surgical or locoregional therapies had failed or were not suitable. The Committee noted that the base-case ICER presented by the manufacturer was originally £64,754 per QALY gained and when the PAS was included this went down to £51,900 per QALY gained; both 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 manufacturer's base case was dependent 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 noted that although the log-normal curve was the best fit amongst these overall and 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 the better fit. The Committee concluded that both curve fits were reasonable. 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, and the Weibull extrapolation of survival data produced an ICER, which was substantially higher than the base-case.

4.10 The Committee then discussed the ERG critique of the manufacturer's PAS submission. The Committee noted concerns about the discrepancies between the descriptions of the pack length and dosage of sorafenib in the PAS as modelled and as described in the SPC. It agreed that the descriptions in the SPC represented a strict definition of treatment intensity and that the treatment intensity modelled in manufacturer's submission (based

on the SHARP study) 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. 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, and the corresponding (commercial in confidence) ICER using the Weibull extrapolation of survival data. The Committee also noted that the manufacturer's model did not take into account the administration costs to the NHS of the PAS and concluded that this would further increase the ICERs.

4.11 The Committee was mindful of the concerns raised by the ERG about inconsistencies in the utilities used in the manufacturer's model. However, it noted that when alternative utility values from a previous renal cell carcinoma assessment report (from Technology Appraisals No. 169 & 178) were used in a sensitivity analysis, the base-case ICER was not significantly affected. The Committee also 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 manufacturer's base case was dependent on investigator (rather than independent) assessment. The Committee noted that the ERG's analyses demonstrated that the original cost per QALY gained increased substantially when using the independent assessment of time to radiological disease progression (see section 3.21). The Committee considered that this further indicated that both the ICER derived using log-normal extrapolation (£52,600 per QALY gained without any PAS administration costs) and the corresponding ICER

derived using Weibull extrapolation of survival data (without any PAS administration costs) were uncertain and likely to be higher. Therefore, it concluded that sorafenib, as a treatment for advanced HCC in patients for whom surgical or locoregional therapies had failed or were not suitable, would not be a cost-effective use of NHS resources.

4.12 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.

4.13 The Committee discussed whether the benefit provided by sorafenib in HCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It noted from the clinical studies that normal 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 the SHARP study, which was stopped early. The Committee considered that evidence from the clinical studies of sorafenib plus BSC suggested that it increased median survival by more than 2.8 months compared with placebo

plus BSC, and the manufacturer's economic model predicted a mean gain in overall survival of 6.1 months. Although the Committee noted that sorafenib is licensed for an indication other than HCC, the Committee considered sorafenib to fulfil the small population criterion for an end-of life treatment. In summary, the Committee was satisfied that the population and sorafenib met the criteria for an appraisal of a life-extending, end-of-life treatment, and that the evidence presented was supported by robust data.

4.14 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 HCC in patients for whom surgical or locoregional therapies had failed or were not suitable would not be a cost-effective use of NHS resources.

4.15 The Committee considered whether there were any subgroups for which sorafenib would be considered a cost-effective use of NHS resources. The Committee noted that the scoping exercise stated that the prevalence of HCC is high in people from black and minority ethnic groups who have recently moved to the UK. These groups may have limited access to the NHS and therefore present with a more advanced stage of the disease, such as Child–Pugh B and C stages. However, the Committee noted that no specific analysis was presented for this subgroup, and that clinical-effectiveness data for Child–Pugh B and C were limited. The Committee was mindful that only three subgroups presented by the manufacturer related to the BCLC staging system's classification of advanced disease (that is, BCLC C, which is defined as presence

of macroscopic vascular invasion, extrahepatic spread, or cancer-related symptoms [ECOG performance status 1–2]). The Committee noted that the analyses of the three subgroups resulted in ICERs all higher than the base-case ICER (including the PAS). It was mindful that the ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources. The Committee also noted that the subgroups presented by the manufacturer 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. Furthermore, no adjustments were made for multiple comparisons. The Committee was mindful 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 ICERs were plausible. It concluded that it would not be appropriate to recommend sorafenib for specific subgroups of patients with advanced HCC.

4.16 The Committee noted that some people may already be receiving sorafenib for the treatment of advanced HCC. It recommended that these people should have the option to continue treatment until they and their clinician consider it appropriate to stop.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding

direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.

Audit support for monitoring local practice.

6 Related NICE guidance

- Microwave ablation of hepatocellular carcinoma. NICE interventional procedure guidance 214 (2007). Available from www.nice.org.uk/IPG214
- Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007). Available from www.nice.org.uk/IPG211
- Laparoscopic liver resection. NICE interventional procedure guidance 135 (2005). Available from www.nice.org.uk/IPG135

Radiofrequency ablation of hepatocellular carcinoma. NICE interventional procedure guidance 2 (2003). Available from www.nice.org.uk/IPG2

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in April 2012. 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.

David Barnett
Chair, Appraisal Committee
September 2009

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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.

Dr Kathryn Abel
Reader and Consultant Psychiatrist, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr David W Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Brian Buckley
Lay Member

Mr Mark Campbell
Director of Standards, Bury Primary Care Trust

Professor Mike Campbell
Professor of Medical Statistics, University of Sheffield

Mr David Chandler
Lay Member

Dr Peter Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Christine Davey
Senior Researcher, North Yorkshire Alliance R&D Unit

Dr Mike Davies
Consultant Physician, Royal Infirmary, Manchester

Mr Richard Devereaux-Philips
Public Affairs Manager

Professor Rachel Elliot
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Professor Peter Jones
Pro Vice Chancellor for Research and Enterprise, Keele University

Dr Henry Marsh
Consultant Neurosurgeon, St Georges Hospital, London

Professor Jonathan Michaels
Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne
Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell
Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Mrs Ruth Oliver-Williams

Head of Nursing, Quality Improvement Lead Surgical Services, Royal Derby Hospital, Derby

Dr Katherine Payne

RCUK Senior Research Fellow of Health Economics

Dr Danielle Preedy

Lay Member

Dr Philip Rutledge

Consultant in Medicines Management, NHS Lothian

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine

Professor Andrew Stevens (Vice Chair)

Chair of Appraisal Committee C

Dr Matt Stevenson

Technical Director School or Health and Related Research, University of Sheffield

Dr Cathryn Thomas

General Practioner

B NICE project team

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

Fay McCracken
Technical Lead

Rebecca Trowman
Technical Adviser

Laura Malone
Project Manager

Appendix B: Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration, The University of Birmingham:

- Connock M, Round J, Bayliss S et al., Sorafenib for advanced hepatocellular carcinoma, March 2009.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

Manufacturer/sponsor:

- Bayer (sorafenib)

Professional/specialist and patient/carer groups:

- British Association of the Study of the Liver
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Royal College of Radiologists
- British Liver Trust
- Hepatitis B Foundation UK
- Hepatitis C Trust
- Rarer Cancers Forum

Other consultees:

- Department of Health
- Oxfordshire PCT
- Welsh Assembly Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health , Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Bayer (doxorubicin)
- Eli Lilly & Co. (gemcitabine)
- Pfizer (doxorubicin, cisplatin)
- Foundation for Liver Research
- Medical Research Council (MRC) Clinical Trials Unit
- West Midlands Health Technology Assessment Collaboration
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)
- National Collaborating Centre for Cancer

The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on sorafenib for HCC by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr John Bridgewater, Senior Lecturer in Medical Oncology UCL Cancer Institute, nominated by NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Calum Polwart, Network Pharmacist Cancer Network Pharmacist Forum, nominated by the British Oncology Pharmacy Association – clinical specialist
- Stella Pendleton, Executive Director of Rarer Cancers Forum and Hepatitis B Foundation UK, nominated by the Rarer Cancers Forum and Hepatitis B Foundation UK – patient expert
- Sean O Brian, Patient, nominated by the Rarer Cancers Foundation – patient expert