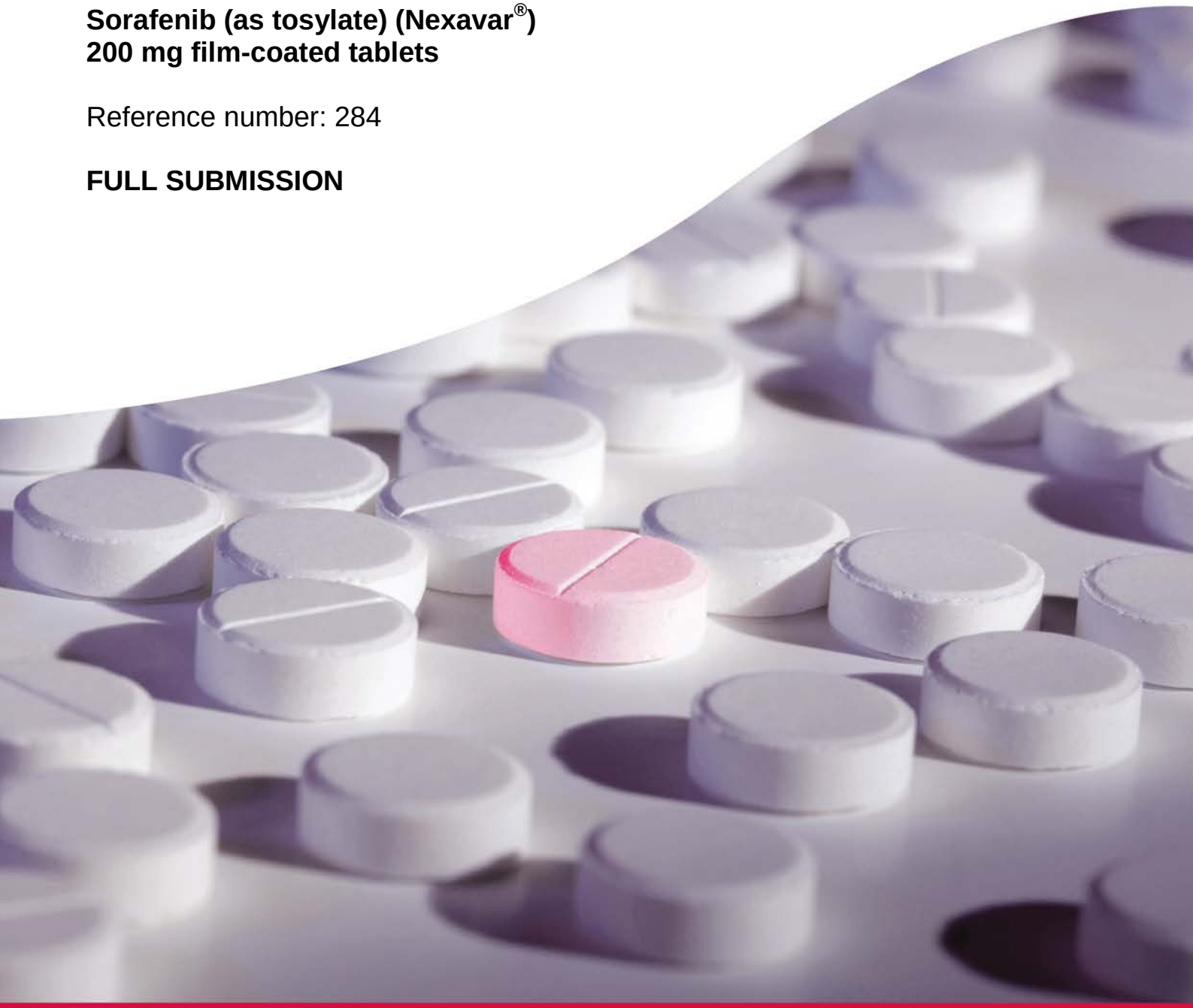
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Sorafenib (as tosylate) (Nexavar®) 200 mg film-coated tablets

Reference number: 284

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Sorafenib (as tosylate) (Nexavar®) 200 mg film-coated tablets. Reference number: 284. February 2016.

AWMSG Secretariat Assessment Report
Sorafenib (as tosylate) (Nexavar®) 200 mg film-coated tablets

This assessment report is based on evidence submitted by Bayer Healthcare Pharmaceuticals[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Sorafenib (as tosylate) (Nexavar®) for the treatment of hepatocellular carcinoma[2].
Dosing	The recommended dose of sorafenib in adults is 400 mg sorafenib (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Refer to the Summary of Product Characteristics for further dosing information[2].
Marketing authorisation date	29 October 2007 (licensed for advanced renal cell carcinoma on 19 July 2006; licence extension granted for differentiated thyroid carcinoma on 23 May 2014)[3].

2.0 DECISION CONTEXT

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, and occurs predominantly in patients with chronic liver disease and cirrhosis; it is the third leading cause of cancer death worldwide[4,5,6]. Current options for the treatment of HCC depend upon the stage of the cancer at diagnosis and are outlined in a number of guidelines[5,7,8]. For patients diagnosed with early stage cancer (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A, see Glossary), there are curative options: resection, radiofrequency ablation or liver transplantation[7]. For intermediate cancer (BCLC stage B 3) transarterial chemoembolisation is an option. In patients with advanced (BCLC stage D) HCC, the treatment options listed are sorafenib or best supportive care[5,7,8]. Systemic therapy with cytotoxic medicines are not considered to have a proven survival benefit and can be poorly tolerated due to underlying disease[5,8,9].

Sorafenib is an oral multikinase inhibitor which inhibits tumour cell proliferation and tumour vascularisation[10]. It blocks vascular endothelial growth factor, platelet-derived growth factor receptors and cKit and RAF signalling pathways on tumour cells and surrounding endothelial cells[5]. National Institute for Health and Care Excellence (NICE) has previously assessed and not recommended the use of sorafenib for the treatment of hepatocellular carcinoma[11]. An updated All Wales Medicines Strategy Group (AWMSG) application has been made for sorafenib, which includes a Wales Patient Access Scheme (WPAS) and additional information[1]. The applicant company has highlighted that the submission focuses on the use of sorafenib for patients with advanced HCC where surgical or locoregional treatments have failed or are unsuitable[1].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC)[1].

2.3 Guidance and related advice

- NICE pathway. Liver cancers. Last updated 2015[12].
- Verslype C et al. Hepatocellular carcinoma: European Society for Medical Oncology-European Society for Digestive Oncology (ESMO–ESDO) Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012[5].
- European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer (EASL-EORCT) Clinical practice guidelines: Management of hepatocellular carcinoma. 2012[7].
- Scotland Cancer Networks Managed Clinical Network for HepatoPancreatoBiliary Cancers. Scottish clinical management guideline for the managment of hepatocellular carcinoma (HCC). 2011[8].
- NICE technology appraisal (TA) 189. Sorafenib for the treatment of advanced hepatocellular carcinoma. 2010[11].
- Ryder SD. British Society of Gastroenterology Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. 2003[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from two phase III clinical studies and a real world UK retrospective study[1]. The SHARP study evaluated the clinical effectiveness of sorafenib compared with placebo in patients with advanced HCC in Europe, North America, South America and Australasia and is described in more detail below[13]. The Asia-Pacific study evaluated the clinical effectiveness of sorafenib in patients from China, Korea and Taiwan; this study will not be discussed in detail[14]. The UK-based retrospective study (Palmer *et al*, 2013) is described in Section 3.2 below.

3.1 SHARP Study

This was a multicentre, phase III, double-blind, placebo-controlled study in patients with advanced-stage HCC who had not received previous systemic therapy. Patients were included if they were not eligible for or had disease progression after surgical or locoregional therapies[13]. Patients (n = 602) were randomly assigned to receive sorafenib 400 mg twice daily (n = 299) or placebo (n = 303). Treatment continued until radiologic and symptomatic progression or the occurrence of unacceptable adverse events (AEs) or death[13].

There were two primary endpoints: overall survival (OS) and time to symptomatic progression (TTSP) from the date of randomisation to death from any cause or the first documented event of symptomatic progression respectively[13]. Symptomatic progression was defined as a decrease of four or more points on the Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index 8 (FHSI8) questionnaire, deterioration in Eastern Cooperative Oncology Group (ECOG) performance status (see Glossary) to four, or death. TTSP was assessed at baseline, every three weeks during treatment and at end of treatment for patients who had discontinued without symptomatic progression. Secondary endpoints included time to radiologic progression, disease control rate, quality of life and safety[1,13].

The second planned interim analysis was conducted when 321 deaths had occurred (143 in the sorafenib group and 178 in the placebo group) shortly after which the study was stopped; therefore these are the final results[13]. Median OS was significantly longer in the sorafenib group compared with placebo (10.7 months versus 7.9 months; hazard ratio [HR], 0.69; 95% confidence interval [CI] 0.55–0.87; $p < 0.001$). The other primary endpoint, median TTSP, did not differ significantly between the sorafenib group and the placebo group (4.1 months and 4.9 months respectively; HR, 1.08; 95% CI, 0.88–1.31; $p = 0.77$)[13].

The primary analysis of time to radiologic progression was based on an independent review of radiologic data and defined as time from randomisation to disease

progression according to the Response Evaluation Criteria in Solid Tumours (RECIST)[13]. The median time to radiologic progression was significantly longer in the sorafenib group than the placebo group (5.5 months versus 2.8 months respectively; HR, 0.58; 95% CI 0.45–0.74; p < 0.001)[13]. After the cut-off date for the primary independent analysis further radiological assessments were carried out by investigators; the median time to radiologic progression was 3.9 months in the sorafenib group and 2.7 months in the placebo group (HR, 0.6889; 95%CI, 0.56–0.84; p < 0.001)[15]. There was no significant difference between response rates in the sorafenib group compared with the placebo group, 2% and 1% of patients achieved partial response and 71% and 67% of patients had stable disease respectively. No patients in either group had complete response. Disease control rate was significantly higher in the sorafenib group compared with the placebo group (43% versus 32%, p = 0.002)[13]. The median duration of treatment was 5.3 months (range, 0.2–16.1) in the sorafenib group and 4.3 months (range, 0.1–16.6) in the placebo group[13].

Health-related quality of life was measured according to Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) response rates; approximately 8% more placebo patients than sorafenib patients achieved the eight-point minimally important difference at cycle three, day one or end of treatment visit [commercial in confidence data removed][1,15]. Results of the physical well being subscale analysis showed a significantly higher proportion of patients achieving a better/same response in the placebo group over the sorafenib group (p = 0.0004)[1]. There was no significant difference between groups for the functional well being subscale[1,15].

3.2 Palmer *et al*, 2013

This was a multicentre retrospective study conducted at two specialist hepatobiliary oncology units in the UK[6]. Funding applications were made to local funding bodies for patients with advanced HCC for whom sorafenib was considered appropriate. The main criteria for application were: a good World Health Organisation performance status (WHO-PS 0–2); well compensated background chronic liver disease; and not a suitable candidate for locoregional therapies. Patients were either granted funding or not; the primary outcome measure was overall survival, the secondary outcome was overall survival in patients receiving at least one dose of sorafenib[6].

A total of 133 applications were made to 42 funding bodies in England and Wales: 57 (43%) were approved and 76 (57%) were declined[6]. The patient demographics and prognostic factors were well balanced across the two groups with no statistical differences between any of the variables.

In the primary analysis, the median survival from the date of application for funding was 4.1 months when funding was declined and 9.5 months when funding was approved (HR, 0.48; 95% CI 0.3186–0.7276; p = 0.0005)[6]. Out of the 57 patients for whom funding was granted 14 patients did not receive sorafenib due to deterioration in clinical condition to the extent that treatment could not commence. Of the 43 patients who did receive at least one dose of sorafenib the median survival was 10.7 months (HR 0.38; 95% CI, 0.25–0.59; p < 0.0001), the mean duration of treatment was 5.1 months[6].

3.3 Safety

The most frequently reported treatment-related AEs in the SHARP study in patients receiving sorafenib were mostly of grade one or two in severity and gastrointestinal, constitutional or dermatologic in nature[13]. Treatment related AEs were more frequent in the sorafenib group compared to placebo (80% versus 52%, respectively). Specifically diarrhoea, weight loss, hand-foot skin reaction, alopecia, anorexia and voice changes occurred more frequently in the sorafenib group compared with placebo (p < 0.001). In the sorafenib group, discontinuation of study medicine due to AEs were due to gastrointestinal events (6%), fatigue (5%) and liver dysfunction (5%), the rate of discontinuation of study medicine was similar in both treatment groups. Dose

reductions occurred in 26% of patients in the sorafenib group and 7% of the placebo group, and dose interruptions occurred in 44% and 30% of patients respectively[13].

Deaths assessed as related to study medicine were reported in 6 (2%) placebo patients and 4 (1.3%) sorafenib patients. The four deaths in the sorafenib group were due to bleeding oesophageal varices (1); haemorrhage into the abdominal cavity (1); visceral arterial ischaemia (1) and renal failure (1)[1].

3.4 AWTTC critique

- In Europe, HCC is an orphan disease most commonly seen in patients with cirrhosis. Early stage disease is potentially curative with surgery or ablation; however, there are limited systemic treatment options[10]. Chemotherapy is often poorly tolerated due to the underlying cirrhosis and is generally not recommended in clinical guidelines. Sorafenib is the first licensed product specifically for the treatment of HCC; it is listed as the standard systemic therapy for patients with advanced HCC and well-preserved liver function in a number of guidelines[5,7,8]. Sorafenib is currently available via an alternative commissioning route in England; therefore, the applicant company highlight the current unmet need in Wales as it is not routinely available[1,11,16]. Clinical expert opinion sought by AWTTC emphasises the current unmet need in Wales where there is a lack of treatment options for patients who present with advanced disease.
- The company provided clinical evidence for patients with advanced HCC for whom surgical or locoregional therapies had failed or were not suitable. This a subpopulation of the licensed indication; however, this is in line with the positioning of sorafenib for treatment of HCC in a number of clinical guidelines and was accepted as the scope for the technology appraisal by NICE.[1,5,7,11].
- Advanced HCC, according to the BCLC stages, is associated with a poor prognosis and a median survival of 4–8 months. The SHARP study demonstrated increased overall survival with sorafenib of 2.8 months over placebo (best supportive care)[13]. There was also a statistically significant difference in median time to radiological disease progression for patients treated with sorafenib compared to those receiving placebo. However, in the pivotal SHARP study, there was a second primary endpoint, time to symptomatic progression, which did not demonstrate any significant difference between sorafenib and placebo. It was suggested that this may have been due to the patient orientated outcome measurement which may have been influenced by symptoms related to AEs of the medicine, tumour related symptoms and symptoms related to liver failure which would progress regardless of effects on tumour stabilisation or regression[11,13].
- Additional information has been provided in the AWMSG submission compared to that considered by NICE. In the retrospective study by Palmer *et al* in the 'intention to treat' analysis mean overall survival was 5.4 months longer in the group where funding was approved than in those where funding was declined[6]. The study authors highlight that a greater number of patients in the trial had adverse prognostic factors than those in the SHARP trial resulting in a relatively worse outcome for those patients not receiving treatment with sorafenib. Also, it was suggested that the growing experience of managing toxicities and dose intensity of sorafenib in the two oncology units since the publication of the SHARP trial data may have contributed to the improved overall survival. However, being a retrospective study the trial was not randomised or blinded, and therefore potential for bias should be considered and results interpreted with caution. The authors state that funding applications were made using the same criteria for suitability for sorafenib and baseline demographics between the two groups were balanced[6].
- There is very little evidence in patients with impaired liver function. In the SHARP study, 97% of patients had well preserved liver function (Child-Pugh

class A)[13]. The study authors note that if the trial had included patients with more advanced liver failure (Child-Pugh class B or C), deaths related to advanced liver disease may have masked any significant activity of sorafenib[13]. In the UK retrospective study, the majority (82%) of patients had good liver function (Child-Pugh class A); however, the authors highlight that a greater number of patients had adverse prognostic features compared to those recruited in the phase III studies. These features included poorer performance status and greater tumour burden, despite this survival advantage was favourable compared to the phase III studies[6].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis (CUA) comparing 400 mg sorafenib (2 x 200 mg tablets) twice daily, with BSC, for adults with advanced HCC who are unsuitable for surgical or locoregional therapies. BSC is defined according to medical judgement and does not include other systemic treatments; an approach accepted in NICE TA189[11].

The CUA takes the form of a Markov decision model, which adopts an NHS Wales perspective, monthly (four week) cycles and a time horizon of 15 years. The model is characterised by three health states: progression-free, progressed, and death. Patients are modelled to receive sorafenib until they progress or discontinue due to unacceptable toxicity. A proportion of patients (7.7%) in the active arm are assumed to continue to receive treatment after progression for a median duration of 129 days, to mirror the events of the SHARP trial[15]. Costs and outcomes accrued beyond one year are discounted at a rate of 3.5% per annum.

Efficacy data used to populate the model are sourced from the SHARP study[15]. Given the limited duration of the trial, the observed data from the study have been extrapolated for time to progression (TTP) and OS. A number of distributions were considered for extrapolation; the lognormal model was deemed to provide the best fit according to Akaike and Bayesian information criteria. Medians for TTP and OS from the model and the trial were compared for validity. Only grade 3 and 4 AEs resulting from treatment, which were reported in at least 10% of patients in the intervention group, and were considered by clinical experts to have costs and quality of life consequences, are included in the model. The model implicitly assumes that the probability of AE remains constant over time.

The medicine acquisition cost of sorafenib is based on a confidential discount offered to all patients in Wales via the Wales patient access scheme (WPAS). The mean cost per cycle/month is based on the SHARP study[15] data (710.5 mg mean dose per day), which includes dose reductions and interruptions. No medicine acquisition costs have been apportioned to the comparator cohort. Resource use associated with the medical management of patients and AEs is informed via a resource survey conducted with three UK-based oncology experts, given that a systematic review of the literature reportedly did not identify appropriate data. Unit costs have been sourced from NHS Reference Costs[17], the Personal Social Services Research Unit[18], British National Formulary (BNF)[19] and Monthly Index of Medical Specialities (MIMS)[20].

Literature searched by the company did not identify utility values for this particular patient population. Utility values were therefore estimated via mapping four items, focused on physical and functional wellbeing, from the FACT-HEP data collected in the SHARP study[15] to time trade-off (TTO) utilities, using a pre-existing validated algorithm[21]. The TTO utilities were provided by a large sample of cancer patients for their current health state. Quality of life data were collected at baseline and at the start

of the third treatment cycle in the SHARP trial[1,15]. In the event of an AE happening 30 days prior to the two data collection points or missing data, it is assumed that an AE has occurred. The mean utility values from the mapping exercise were found to be similar between different health states and treatment arms; in fact, they were higher in the post-progression state than they were in the pre-progression state.

Probabilistic sensitivity analyses were conducted to test the robustness of the model and account for uncertainties of the following parameters:

- Utility and disutility values associated with health states and AEs
- Probability and costs of AEs
- Costs associated with health states

One way sensitivity analyses explore the impact of variations in health state utility values, disutility and costs associated with AEs, costs of treatments, time to progression, and overall survival, to ascertain which parameters have most influence over base case results. Scenario analyses were conducted to evaluate the effects of using alternative: data sources, parametric functions for overall survival, time horizons (five years and ten years), no continuation of sorafenib post-progression, and utility values.

4.1.2 Results

The results of the base case analysis of the CUA are present in Table 1. When the WPAS price is applied, twice daily oral administration of 400 mg sorafenib exceeds the usual cost-effectiveness threshold of £20,000 to £30,000 per quality-adjusted life-year (QALY) compared to BSC. The incremental cost-effectiveness ratio (ICER) produced equates to [commercial in confidence data removed] per QALY gained.

Table 1. Results of the base case analysis (WPAS price)

	Sorafenib	BSC	Difference
Total costs	¶¶	¶¶	¶¶
Total life-years	1.569	1.047	**0.522**
Total QALYs	1.104	0.737	**0.367**
ICER (£/QALY gained)	¶¶		

BSC: Best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
¶¶ commercial in confidence data removed

The results of the one-way sensitivity analyses indicate that the ICER is most sensitive to variations in: OS related to both sorafenib and BSC; the utility associated with first line treatment with sorafenib; and time to progression when treated with sorafenib. The majority of ICERs produced via these analyses exceed £30,000 per QALY gained.

Probabilistic sensitivity analyses reveal that with a WPAS price and at the higher threshold of £30,000 per QALY, sorafenib has a 26% chance of being the most cost-effective treatment option.

Table 2 summarises the results for the most noteworthy and/or plausible scenario analyses.

Table 2. Results of scenario analyses applying the WPAS price only

Scenarios	ICER	Plausibility
Using multicentre retrospective real-life UK data[6] for costs and QALYs	¶¶	Whilst the data used for this scenario were retrospective, it has the advantage of being real world data, from a large patient population, collected over a longer time frame than the RCT used to populate the base case analysis.
Applying a log-logistic parametric model for extrapolation of OS: a) SHARP trial b) Palmer *et al*, 2013	¶¶ ¶¶	The log-logistic distribution appears to be the next best fit for the OS data according to the statistical tests, and is therefore worthy of consideration.
Applying a Weibull parametric model for extrapolation of OS: c) SHARP trial d) Palmer *et al*, 2013	¶¶ ¶¶	The Weibull distribution offers a good visible fit for the OS extrapolation data at the tail end of the survival curve, and is therefore a plausible alternative for consideration.
Altering time horizon to: e) 5 years f) 10 years	¶¶ ¶¶	Given the limited life expectancy of this group, the 10 year time horizon is a plausible alternative to the base case 15 year time horizon.
No continuation of sorafenib post progression	¶¶	This scenario reflects the licensed administration guidance for sorafenib.
Equalised utility values for the pre and post progression states	¶¶	Despite there being no statistically significant difference in utility between trial arms, the equalisation of utility values arguably does not offer any added benefit to the evaluation.
Lower utility values for the progressed health state	¶¶	The base case model is characterised by similar utility values for pre-progression and post-progression. This may be somewhat attributed to the timing of data collection, rather than a true reflection of patient utilities. This scenario may therefore offer a plausible alternative for consideration.
Hybrid assessment of TTP	¶¶	The base case model is based on investigator assessment of TTP rather than the independent assessment which was the primary analysis in the pivotal study.
Independent assessment of TTP	¶¶	This scenario uses the independent assessment hazard ratio for TTP, obtained for the pivotal study. This scenario is potentially limited in plausibility, given that the data collected to inform this ratio did not continue beyond the first interim analysis time-point.
12 year time horizon, Weibull parametric model for extrapolation and no continuation of sorafenib post progression	¶¶	This AWTTC generated scenario combines plausible alternatives for the time horizon, the survival extrapolation distribution and the pattern of sorafenib administration.
AWTTC: All Wales toxicology and Therapeutics Centre; ICER: incremental cost effectiveness ratio; OS: overall survival; QALY: quality-adjusted life-year; RCT: randomised control trial; TTP: time to progression ¶¶ commercial in confidence data removed		

4.1.3 AWTTC critique

The CUA model based on the company's base case analysis predicts an ICER of [commercial in confidence data removed] per QALY gained for sorafenib versus BSC. Whilst the model is characterised by a number of strengths, it also has its limitations owing to a number of assumptions. These have the potential to introduce bias and uncertainty, as described below.

Strengths:

- The submission gives a detailed and transparent account of the methods, data sources and analyses undertaken.

- The comparator, time horizon and perspective used for the analyses appear appropriate.
- Sensitivity and scenario analyses comprehensively explore plausible alternatives to accommodate the uncertainty surrounding model parameters and assumptions.
- All standard parametric models have been considered and compared for the purpose of extrapolation of TTP and OS. The parametric function was fitted to OS data based on appropriate criteria, and was then extrapolated. The extended survival prediction for a small proportion of the patient resulting from use of the log-normal curve was verified as being consistent with clinical expert experiences.

Limitations:

- The CUA has been modelled using an average daily dose of 710.5 mg. This is reflective of the mean dose taken during the SHARP study (it factors in dose reductions and interruptions) but does not reflect the licensed 800 mg dose that will be prescribed in practice.
- In the model, 7.7% of patients continue to receive sorafenib for a median duration of 129 days after progression. This is in line with the conduct of the SHARP study but it is unclear if this is applicable to clinical practice in Wales.
- The TTO, onto which the FACT-G quality of life responses were mapped, was based on responses from cancer patients, and not the general public. There are limitations to using patient preferences, which may differ appreciably from those of the public (which is the preferred approach).
- The similarities in utilities between health states and treatment arms derived from the mapping exercise may be influenced by the timing of data collection (just two time points) and/or low sensitivity of the algorithm to poor health states[1]. However, sensitivity analyses have been conducted to address these potential shortcomings.
- The AEs included in the model and associated resource use are based on expert clinical opinion. This has the potential to introduce bias in AE selection and contributes to uncertainty surrounding cost implications. The model also implicitly assumes a constant AE risk, which is not reflective of the AE patterns observed in the SHARP trial, where AEs occured with greater frequency in earlier cycles and lesser frequency in latter cycles. This assumption may therefore introduce a small bias against sorafenib.
- Given the lack of published data, estimates of resource use associated with the management of HCC patients were determined via a resource use survey conducted with three clinical experts in Greater London. This limited sample and relevance to Wales results in uncertainty and the potential for bias in these estimates.
- The ICER is particularly sensitive to the extrapolations. If the Weibull distribution is alternatively considered the best fit in terms of longer term survival, this significantly increases the ICER (see Table 2).
- A small number of patients are predicted to survive for a long time; this will inevitably impact on the calculation of mean life years gained.

4.2 Review of published evidence on cost-effectiveness

A literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) identified two published papers[22,23] that report on the cost-effectiveness of sorafenib compared with BSC. Both papers have authors affiliated with the company, and present the findings from the SHARP study[15] adopting a US third party payer perspective. They conclude that sorafenib is cost-effective and that the incremental life years gained were between 0.49[22] and 0.53[23]. These papers have limited value in terms of informing decision making from a UK perspective, but have been included for

the sake of completeness given the paucity of relevant evidence published in the UK and Europe.

The search also uncovered NICE and Scottish Medicines Consortium (SMC) guidance relating to the cost-effectiveness of sorafenib when compared with BSC[11,24]. The NICE TA guidance expressed greatest concerns surrounding: the high ICERs generated, which were deemed too high even when end-of-life QALY weighting considerations were undertaken (base case ICER of £64,800 at list price and £51,900 with PAS); the uncertainty surrounding which probability distribution should be used for extrapolation; and the use of investigator rather than independent investigator assessments of TTP[11]. The SMC guidance expressed the same concerns, in addition to issues relating to generalisability to the Scottish population[24]. The model structure and probability distributions used remain largely unchanged in the AWMSG submission[1]. However, the company has attempted to address some of the issues surrounding uncertainty by including additional statistical tests to measure the goodness of fit of the Kaplan Meier curve data. Also, the AWMSG submission includes a WPAS, which reduces the ICER for the base case, the various scenarios and the sensitivity analyses[1].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Incidence data for Wales are sourced from the Welsh Cancer Intelligence and Surveillance Unit[25,26]. Given that the average survival following diagnosis of HCC is less than 12 months, the company considers the incidence rate to also be representative of prevalence. In 2013 there were 273 cases of liver cancer in Wales[25,26]; 252 of these were HCC[27]. The company has calculated the mean increase in incidence over the period 2001–2013[26] to forecast incidence for the next five years. It is assumed that 30% of HCC patients are eligible for treatment[1]. It is further estimated that 15% of these eligible patients will receive sorafenib in 2016, with this rising to 60% in 2019. The estimated number of days on treatment used for the budget impact analysis is 226 days. This captures the average number of days pre-progression, in addition to the extended treatment of 7.7% of patients who are expected to receive sorafenib post-progression. The budget impact considers medicine acquisition costs only and BSC has been considered as having no associated medicine costs.

5.1.2 Results

The estimated cost per patient treated at the WPAS price [commercial in confidence data removed] has been multiplied by the number of patients forecasted to receive sorafenib to calculate the net cost of treatment. Table 3 details the projected 5 year budget impact on the basis of acquisition costs only. Table 4 presents the results of the sensitivity analysis conducted.

Table 3. Company-reported costs associated with use of sorafenib for the treatment of advanced HCC

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Forecasted incidence of HCC in Wales (estimated as 85% of all liver cancers)	296	313	330	348	367
Number of eligible patients[*] (Indication covered in this submission)	89	94	99	104	110
Uptake (%)	15%	30%	45%	60%	60%
Treated patients	13	28	45	63	66
Net costs – WPAS pricing					
Medication cost of sorafenib[†]	¶¶	¶¶	¶¶	¶¶	¶¶
Overall net cost[§]	¶¶	¶¶	¶¶	¶¶	¶¶
Cumulative net cost over 5 years	¶¶				

[*]assumed to be 30% of HCC patients
[†]assuming that 7.7% of patients will continue treatment post-progression for a median of 4.24 months
[§]BSC is considered to have zero associated medicine costs.
BSC: best supportive care; HCC: hepatic cellular carcinoma; WPAS: Wales patient access scheme
¶¶ commercial in confidence data removed

Table 4. Results of the sensitivity analyses – varying the number of eligible patients (increased by 10%) and the uptake of sorafenib

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients (Indication covered in this submission)	98	103	109	114	121
Uptake (%)	20%	35%	50%	65%	65%
Treated patients	20	36	55	74	79
Overall net cost (WPAS price)	¶¶	¶¶	¶¶	¶¶	¶¶

WPAS: Wales patient access scheme
¶¶ commercial in confidence data removed

5.1.3 AWTTC critique

Strengths and limitations of the budget impact analysis are as follows:

- The submission provides a detailed and transparent account of the methods and data sources used in the budget impact analysis.
- The incidence data used to represent prevalence are from a reliable source.
- The costing assumes that 7.7% of patients will continue to receive sorafenib post-progression. If in practice sorafenib is stopped at point of progression, as per the licensed indication, the calculated budget impact may be an overestimate.
- The sensitivity analyses explore the impact of altering the assumptions relating to eligibility for treatment and the expected market share for sorafenib. Whilst

such analyses are generally beneficial, it is not clear how the ranges for market share have been selected. It is therefore unclear how realistic the forecasted budget impact is.

5.2 Comparative unit costs

Sorafenib represents the first and only licensed systemic treatment specifically for HCC. Based on the recommended dose of 400 mg twice daily the approximate monthly (28 days) cost of sorafenib per patient is £2,980[19].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, sorafenib (Nexavar®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that sorafenib (Nexavar®) will be supplied by a home healthcare provider[1].

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 5 November 2015
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

The company submission indicates that the use of sorafenib in the given patient population meets the end of life criteria set by the AWMSG policy on appraising life-extending, end-of-life medicines[28]. These criteria are detailed in Table 5. During their appraisal in 2010, NICE considered sorafenib, within the agreed scope, to have met the criteria for appraisal of a life-extending, end-of-life treatment[11].

Table 5. End of life considerations for New Medicines Group (NMG)/AWMSG

Criteria for application of the EoL policy (all must apply)[28]	Sorafenib considerations
The most plausible ICER estimate exceeds £30,000 per QALY	The company selected base case ICER exceeds £30,000 per QALY gained. PSA indicates that the chance of sorafenib being the most cost-effective treatment option when applying a threshold of £30,000 per QALY is low, at just 26%.
The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).	Patients receiving placebo in the SHARP trial[15] experienced a median OS of 34.4 weeks (7.9 months), although the study was stopped early. The mean survival of patients modelled to receive BSC in the economic model was 12.6 months
There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival	In the SHARP trial[15], patients receiving sorafenib experienced a median extension to OS of 2.8 months. The UK observational study[6] presented in the submission showed a median survival difference of 5.4 months, The economic model (base case)projected an incremental life extension of 6.3 months, but this was as low as 3.2 months using the Weibull function.
AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small	NICE assumes a "small" population is equivalent to 7,000 patients in England. This equates to around 406 patients in Wales. Although NICE noted that sorafenib was licensed for renal cell carcinoma as well as HCC, they considered sorafenib to fulfil the small population criteria for an end-of-life treatment[11]. Since the appraisal by NICE sorafanib has additionally received a license for differentiated thyroid carcinoma. The company estimate that 18 patients with this condition will be eligible for treatment in 2016. The additional eligible patients with this condition are unlikely to have a significant impact for this criterion.
AWMSG: All Wales Medicines Strategy Group; BSC: best supportive care; EoL: end of life; ICER: incremental cost-effectiveness ratio; NMG: New Medicines Group; OS: overall survival; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years; RCT: randomised control trial	

Should NMG/AWMSG conclude that sorafenib should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[28,29]:

NMG/AWMSG will need to consider:

- The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age.
- The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the medicine to fall within the current threshold range.

In addition, NMG/AWMSG will need to be satisfied that:

- The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of

trials in which cross-over has occurred and been accounted for in the effectiveness review) and;
- The assumptions used in the economic modelling are plausible, objective and robust.

6.6 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

Sorafenib for its full licensed indications is designated as an orphan medicine by the EMA and is therefore used to treat conditions affecting not more than 5 in 10,000 persons in the EU (or 1,500 patients in Wales)[30].

For medicines designated orphan status, NMG/AWMSG may consider, if the cost per QALY is above the normal thresholds applied, additional criteria for appraising these medicines (see Table 6).

Table 6. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	Patients with HCC have a very poor prognosis.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	HCC is amongst the most chemo-resistant tumour types. Sorafenib emerged as the first licensed systemic treatment specifically for HCC and is currently the recommended standard of care for patients with advanced tumours in a number of clinical guidelines[5,7,8].
Whether the medicine can reverse or cure, rather than stabilise the condition	Sorafenib does not reverse or cure the condition.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	Not applicable.
The innovative nature of the medicine	Specific evidence not provided.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	Specific evidence not provided. Sorafenib is an oral agent and can therefore be administered at home, as opposed to a hospital setting.
Added value to the patient's family (e.g. impact on a carer or family life)	Specific evidence not provided.
HCC: hepatic cellular carcinoma; OS: overall survival; QALY: quality-adjusted life-year	

GLOSSARY

Barcelona-Clinic Liver Cancer (BCLC) classification[7,31,32,32]

A set of criteria to guide management of patients with HCC taking the following variables into account:

- performance status
- Child-Pugh score
- tumour size
- multiple tumours
- vascular invasion
- nodal spread and extrahepatic metastases

The classification system sorts patients into one of four categories:

- stage 0 (very early stage)
    - asymptomatic early tumours
    - resection
- stage A (early stage)
    - asymptomatic early tumours
    - resection, transplantation, percutaneous treatments
- stage B (intermediate stage)
    - asymptomatic multinodular tumours
    - intra-arterial therapies
- stage C (advanced stage)
    - symptomatic tumours and/or invasive tumours
    - sorafenib
- stage D (terminal stage)
    - best supportive care

Child-Pugh liver function[33]

A scoring system to measure the severity of chronic liver disease composed from several categories:

- total bilirubin, µmol/l (mg/dl)
    - < 34: 1 point
    - 34-50: 2 points
    - > 50: 3 points
- serum albumin, g/l
    - > 35: 1 point
    - 28–35: 2 points
    - < 28: 3 points
- INR
    - < 1.7: 1 point
    - 1.7-2.3: 2 points
    - > 2.3: 3 points
- presence of ascites
    - none: 1 point
    - mild: 2 points
    - moderate to severe: 3 points
- presence of hepatic encephalopathy
    - none: 1 point
    - grades I–II (or suppressed with medication): 2 point
    - grades III–IV (or refractory): 3 point

The point scores are then added up and classified as:

- class A: 5–6 points
- class B: 7–9 points
- class C: 10–15 points

Eastern Cooperative Oncology Group (ECOG) performance status[34]

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

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