All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA169)

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Final Appraisal Report

Sunitinib (Sutent®)
Pfizer

Advice No:0607 – August 2007

Recommendation of AWMSG

Sunitinib (Sutent®) should not be recommended for use within NHS Wales for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC).

The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 15th August 2007

The recommendation of AWMSG is:

- Sunitinib (Sutent®) should not be recommended for use within NHS Wales for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC). The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use.

Key factors influencing recommendation:

- The submission was only for first-line treatment as an alternative to cytokines which is the context of this appraisal.
- Currently clinical effectiveness data is limited to a pre-planned interim analysis of one Phase III trial and further results with survival outcome are still awaited.
- It is not clear yet how the objective response rate corresponds to subsequent survival advantage.
- The data available includes only those patients with good performance status and relatively little co-morbidity. The outcomes in patients with a greater number of risk factors or poorer performance status are unknown.
- The estimated incremental cost per QALY is based on the interim analysis of data from one clinical trial and does not, in the view of the AWMSG, demonstrate the cost-effectiveness of this treatment.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Sunitinib is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (mRCC) [1].

2.2 Dosing[1]:
The recommended dose of sunitinib is one 50mg dose orally, taken daily for four weeks, followed by a two-week rest period (schedule 4/2) to comprise a complete cycle of six weeks. Duration of treatment is until disease progression or unacceptable toxicity.

Dose adjustments in 12.5mg steps may be applied based on safety and tolerability. However, the daily dose should not exceed 87.5mg nor be decreased below 37.5mg.

Therapy should be initiated by a physician experienced in the treatment of renal cell carcinoma.

2.3 Market authorisation date: 11th January 2007 (first-line treatment of mRCC) [2]

2.4 UK Launch date: February 2007 (first-line treatment of mRCC) [2].

3.0 DECISION CONTEXT
Renal cell carcinoma (RCC) originates from cells of the proximal renal tubules and is the most frequently occurring solid tumour within the kidney [3]. The disease occurs in both a sporadic (nonhereditary) and a hereditary form with a number of familial syndromes now recognised [4]. If operable, then surgical excision is the primary treatment for RCC and may involve a radical nephrectomy, even in the presence of advanced disease[5]. It is estimated that 20 to 50 per cent of patients who have curative resection for earlier stages of RCC will develop recurrent or metastatic disease [5]. Furthermore, approximately 30% of newly diagnosed cases of RCC present with metastatic disease (stage IV) [7,8]. Without treatment, these patients have a median survival of only six to twelve months and a two-year survival rate of 10-20% [9].

Advanced/metastatic RCC (mRCC) is largely resistant to chemotherapy and is almost always incurable. Currently, standard treatment in the UK is with single-agent immunotherapy agents such as interferon-α (IFN-α) or interleukin-2 (IL-2), also known as adesleukin [10]. However, these agents are associated with only a modest response rate and effect on overall survival and can result, particularly with IL-2, in severe morbidity [7]. After treatment failure, use of the alternate agent is associated with response rates in fewer than 5% of patients[12]. The multi-kinase inhibitors sunitinib and sorafenib are both licensed in the US and the EU for use in advanced RCC after failure of immunotherapy having demonstrated significant benefit as single-agents in second-line therapy compared to best supportive care (BSC) [11,14]. Both are also licensed for first-line use, however in the case of sorafenib this is only indicated in patients who are considered unsuitable for cytokine therapy [1,13]. Other management options are limited to supportive care or treatment in clinical trials with unlicensed agents [10-12].

This report is a review of the evidence submitted by the company, and consequently is an assessment of the clinical and cost effectiveness of sunitinib (Sutent®) only in first-line therapy for the treatment of mRCC [2,15].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Evidence for first-line use of sunitinib in mRCC included in the company submission was based on one Phase III trial that demonstrated longer progression-free survival (PFS) and higher objective response rates in patients receiving sunitinib when compared to current standard therapy with interferon- alpha (IFN-α). Additional data on durability of response and long-term outcome would further clarify the survival benefit of sunitinib. Final survival analysis is expected to be available in 2008. The European Public Assessment Report states that the overall safety of tyrosine kinase inhibitors is considered generally acceptable in view of the target population; however further long-term safety data is required particularly with regards to cardiotoxicity. It is the opinion of WMP that this is desirable also in view of the submission being for first-line use.

Two Phase III trials are currently underway. The first will assess the efficacy and safety of sunitinib alone or in combination with IFN-α as first-line therapy in the treatment of mRCC. The second trial is currently enrolling patients to compare the efficacy of sunitinib with sorafenib (a main competitor) in patients with resected RCC.

4.2 Review of the evidence on cost-effectiveness

The estimated incremental cost of £29,199 per QALY gained for treatment with sunitinib, compared to IFN-α, is in the extreme upper range of what is considered to be a cost-effective therapy. This estimate is based on an interim analysis of data from one clinical trial. The generalisability of the results to other settings and patient populations should be considered given the model is based on the interim results of a single trial. The economic analysis explored the impact of uncertainty in some parameters and the impact of time horizon was noted, with a shorter five-year horizon increasing the cost per QALY estimate to £36,225. The impact of changes to the unit costs of sunitinib and IFN-α was not investigated in the sensitivity analysis. It is likely that sunitinib would exceed a cost-effectiveness threshold of £30,000 per QALY.

5.0 LIMITATIONS OF DECISION CONTEXT:

- This assessment of sunitinib is restricted to those patients with treatment naïve mRCC.
- Data are currently limited to one ongoing Phase III trial.
- Studies with sunitinib have included those patients with a good performance status (ECOG 0 or 1) only; therefore the efficacy and also safety in patients with poor performance status are unknown.
- The majority of patients in studies had kidney cancer of clear-cell type. Although 85% of kidney cancer is of this type, the potential implications for efficacy or safety in different subtypes of mRCC are also unknown.
- At present, the safety and efficacy of sunitinib in paediatric patients has not been established; nor has it been studied in those with impaired renal function, or patients with Child-Pugh Class C hepatic impairment.
- Although there is a Phase III trial currently underway, at present there is no published data that compares the efficacy of sunitinib with sorafenib (a main competitor) in patients with resected RCC.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

The indication covered by the company submission is for first-line treatment of mRCC only. Therefore, evidence included in the submission is based on the results of a second pre-planned interim analysis of an ongoing Phase III trial, and does not include the two Phase II studies in patients with cytokine-refractory mRCC on which marketing authorisation for sunitinib was originally based [11,14,15].

6.1 Clinical efficacy:

6.1.1 Trial A6181034: Sunitinib versus IFN-α in metastatic renal-cell carcinoma [16].

This multi-centred, randomised, open-label, active-controlled, Phase III trial compares the efficacy and safety of sunitinib versus IFN-α in the first-line treatment of patients with metastatic clear-cell RCC.

The analysis included in the submission was performed when approximately 354 PFS events had occurred (approximately 75% of the total number of expected events in the trial overall). At the data cut off date (15th November 2005) 750 adult patients had been randomised to receive sunitinib (six week cycles of 50mg orally once daily for four weeks and then two weeks without treatment; n=375) or IFN-α (three times a week subcutaneous injections at 3MU per dose for the first week, then 6MU per dose the second week and 9MU per dose thereafter; n=375). Treatment was continued in both groups until disease progression, unacceptable adverse events or withdrawal of patient consent.

Key eligibility criteria, which included the presence of an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as well as adequate organ function, are outlined in appendix 1.

The primary endpoint of the study was PFS, defined as the time from randomisation to disease progression or death from any cause. Secondary endpoints included the objective response rate, overall survival, patient-reported outcomes, and safety (refer to Appendix 1). A blinded central review of radiological images was used to assess the primary endpoint and the objective response rate.

Results:
Demographic and baseline characteristics were similar between treatment arms with regard to sex, race, baseline Eastern Cooperative Oncology Group (ECOG) performance status, and age. The mean age of patients was 60 years and the median time since initial diagnosis was 46 weeks for patients treated with sunitinib and 44 weeks for patients treated with IFN-α[15]. Previous treatment included partial, or radical nephrectomy for 91% of patients treated with sunitinib and 89% of patients treated with IFN-α. Radiotherapy had been received by 14% of patients treated with sunitinib and 14% of patients treated with IFN-α.

At the time of analysis, the median duration of treatment was six months (range, one to 15) in the sunitinib group and four months (range, one to 13) in the IFN-α group. Treatment was ongoing among 248 patients in the sunitinib group (66%) and 126 patients in the IFN-α group (34%). Reasons for discontinuing treatment were progressive disease (in 25% of the patients in the sunitinib group and 45% in the IFN-α group, $p<0.001$), adverse events (8% and 13%, respectively; $p = 0.05$), withdrawal of consent (1% and 8%, respectively; $p<0.001$), and protocol violation (less than 1% in each group) [16].

At the data cut-off date, 92 patients in the sunitinib group compared to 170 patients receiving IFN-α were reported by Motzer and colleagues to have progressive disease [16]. Median PFS was 11 months (47 weeks) in the sunitinib group (95% confidence interval [CI]: 10 to 12 months) and five months (22 weeks) in the IFN-α group (95% CI: four to six months), corresponding to a hazard ratio of 0.42 (95% CI: 0.32 to 0.54; $p<0.001$) [16].

Sunitinib treatment was associated with a higher objective response rate than IFN-α, with 31% (103/335) in the sunitinib group (95% CI: 26 to 36) in contrast to 6% (20/327) in the IFN-α group (95% CI: four to nine percent); p<0.001 [16]. Median duration of response with sunitinib was calculated to be 41 weeks (95%CI: 30 to 54 weeks) [15]. At the time of the analysis, median overall survival had not been reached in either group; 13% (49/375) of patients in the sunitinib group and 17% (65/375) in the IFN-α group had died. Although there was a trend toward improved survival with sunitinib (hazard ratio for death, 0.65; 95% CI: 0.45 to 0.94; p= 0.02), the comparison did not meet the pre-specified level of significance for this interim analysis.

Health-related quality of life was significantly better in the sunitinib group than in the IFN-α group (p<0.001), as reported by patients in post-baseline assessments with the use of both FACT-G and FKSI questionnaires (refer to Appendix 1). The higher scores in the sunitinib group for kidney cancer–related symptoms and overall quality of life were clinically meaningful, on the basis of established guidelines [16].

Points to note from the study:

- Cytokine treatment is standard therapy for mRCC in the UK. Therefore the choice of IFN-α as a comparator is valid.
- Outcomes were determined by investigator assessment and also independent review. Results were similar, and Motzer and colleagues have published both[16]. The results shown above are those determined by independent review.
- Fifteen patients (4%) randomised to receive IFN-α withdrew consent before starting treatment; the remaining 360 patients received at least one dose of study drug. However, the primary endpoint was analysed in all patients assigned to a study group, according to the intention-to-treat principle. Therefore, 375 patients assigned to the IFN-α group underwent analysis for PFS.
- Duration of response for IFN-α could not be calculated because none of the 20 patients with a confirmed response had subsequent progression or death at the time of analysis.
- The benefit of sunitinib over IFN-α was observed regardless of the patients' baseline features or prognostic factors [16].
- Results from this trial are lower for those responding to the standard therapy with IFN-α (5%)
- After the interim analysis had been performed and discussed with the data and safety committee, patients in the IFN-α group with progressive disease were allowed to cross over to the sunitinib group [16].
- Additional data on the durability of the response to sunitinib and the long-term outcome would further clarify the survival benefit associated with each treatment [16].
- A final survival analysis will be reported for this trial when the data become mature. This is not expected to be available until 2008 [15].
- A Phase II study involving 60 patients has assessed the efficacy and safety of sunitinib in bevacizumab-refractory mRCC and suggests that sunitinib may be of some benefit. However further trial work is necessary [17]. For other relevant ongoing trials refer to section 8.2.
- Adverse events reported for this trial are discussed under section 7.2. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0) [18].

6.2 Safety:

- In the Phase III study the proportion of patients with Grade III or IV adverse events was relatively low in both groups. However, treatment-related serious

adverse events were reported in 18% (66/375) of patients treated with sunitinib and in 5% (18/375) patients receiving IFN-α. Other treatment-related adverse events were reported as occurring in the majority of both treatment arms (sunitinib: 95% (357/375) versus IFN-α: 91% (329/375) [15,16];although, more patients treated with sunitinib compared to IFN-α required a dose reduction due to adverse events (32% versus 21%, respectively) [16].

- Important treatment-related serious adverse events associated with sunitinib are thrombocytopenia, leucopenia and hypertension. In the Phase III study all these SAEs occurred more often in the sunitinib group than in the IFN-α group ($p<0.05$ for all comparisons). Grade III or IV neutropenia was observed in 12% of patients in the sunitinib group and in 7% of those in the IFN-α group; the condition was associated with fever in two patients receiving sunitinib. Grade III lymphopenia occurred with greater frequency in patients treated with IFN-α ($p<0.05$).
- An important risk identified with sunitinib is cardiac toxicity. Patients who presented with cardiac events within 12 months prior to sunitinib administration were excluded from clinical studies. It is unknown if patients with concomitant cardiac conditions may be at higher risk of developing drug-related left ventricular dysfunction. Therefore patients should be carefully monitored for signs of congestive heart failure while receiving sunitinib, with baseline and periodic evaluations of left ventricular ejection fraction. In patients without cardiac risk a baseline ejection fraction is suggested [1].
- Tyrosine kinase inhibitors are considered to have a generally favourable safety profile considering the target population [19,20]. Nevertheless, further data regarding long-term safety is required, especially for cardiotoxicity [19].
- Caution is recommended when administering sunitinib with potent CYP3A4 inducers (such as rifampicin) or inhibitors (such as ketoconazole), which may decrease or increase sunitinib plasma concentrations respectively[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

Therapeutic options for treatment-naïve patients with mRCC are currently limited to the following:

- Radical nephrectomy
- Cytokine therapy with IFN-α, or sometimes IL-2.
- Sorafenib (only licensed for first-line therapy when patients are considered unsuitable for cytokine therapy)

Other unlicensed therapies being evaluated in clinical trials for potential use in mRCC include, amongst others [10]:

- bevacizumab
- gefitinib
- erlotinib
- temsirolimus

7.2 Comparative effectiveness:

- Comparative efficacy and safety data are limited. A Phase III, randomised, open-label, controlled trial is ongoing to assess the efficacy and safety of sunitinib alone or in combination with IFN-α as first-line therapy in the treatment of mRCC (the Renal EFFECT Trial). A further Phase III study is currently enrolling patients to compare the efficacy of sorafenib versus sunitinib in patients with resected RCC. The primary objective of this trial will be to compare the disease-free interval between the two tyrosine kinase inhibitors and placebo[21].

- Although IFN-α is the current standard therapy in the UK, the Phase III trial included in the company submission demonstrated that progression-free survival was longer and objective response rates were higher in patients with mRCC who received sunitinib than those receiving IFN-α [15,16]. However, such head-to-head comparative data is currently limited to this one trial.
- There is no evidence to suggest that the patients enrolled in the trial included in the submission do not reflect the patient population or current clinical practice in Wales. The trial was an international study that included five UK sites. Nevertheless, it should be noted that current studies with sunitinib have included those patients with a good performance status (ECOG 0 or 1) only; therefore the efficacy and also safety in patients with poor performance status are unknown. In addition, the majority of patients had kidney cancer of clear-cell type. Although 85% of kidney cancer is of this type, the potential implications for efficacy or safety in different subtypes of mRCC are unknown [19].
- Both sunitinib and IFN-α can be administered at home. However, the fact that sunitinib is an oral therapy may be an advantage when compared to IFN-α which is administered as a subcutaneous injection.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider:

The key economic issue for AWMSG to consider are:

1. whether the additional benefits offered by sunitinib compared to current therapy justify the additional cost, and if so,
2. whether the total budgetary impact of supporting the use of sunitinib is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard searches by WMP did not identify any published economic evaluation studies of the use of sunitinib.

8.3 Review of company submission on cost-effectiveness

8.3.1 Summary of the evidence:

The company submission included a cost-utility evaluation that compared sunitinib to IFN-α as a first-line treatment for patients with advance and/or mRCC. IFN-α represented the current standard treatment for this patient group in Wales. The model did not address the use of sunitinib as a second-line therapy. The analysis was undertaken from the perspective of NHS Wales.

The decision analytic model was populated with data derived from trial A6181034, which is an international open-label, randomised controlled trial currently in progress; final results are expected in 2008. The study enrolled adults with previously untreated advanced and/or mRCC with an ECOG performance score of 0 or 1 and the analysis was carried out over the remaining life expectancy of the individual patient, with a time horizon of six years.

In the model, the overall survival and PFS input parameters were derived by extrapolation of the interim results (15 months follow-up) of trial A6181034. At the time of analysis, the median overall survival had not been reached for either group. For the sunitinib regimen, PFS was estimated by applying the hazard ratio to the PFS survival curve created for the IFN-α regimen. For the IFN-α regimen, the PFS was extrapolated based on a Weibull survival curve. For the sunitinib regimen, overall survival was estimated by again applying the hazard ratio to the overall survival curve created for the IFN-α regimen. For the IFN-α regimen, the overall survival was estimated by

regression analysis. The submission acknowledges the considerable uncertainty in modelling these survival outcomes.

The reported model outputs were life years gained, progression free years and quality adjusted life years (QALYs) gained. EQ-5D utility scores obtained from the trial participants were used to estimate the QALYs gained for each regime, and according to whether or not the disease had progressed. The visual analogue scores (EQ-VAS) were used alone in the sensitivity analysis. However, the utility values gained were not compared with utilities reported from other studies. Treatment-related adverse effects were included in the model if there was a statistically significantly difference between regimes, and, if they were deemed by expert opinion as likely to incur resource use costs.

A change in the NHS price of sunitinib, effective from 1st April 2007, was noted. Further communication clarified that the analysis used the new price and took account that the first cycle of sunitinib was provided free of charge to the NHS. However, it is unclear whether this arrangement is permanent, or for a limited time only. Further changes in the unit acquisition cost, or the cost of the first cycle would impact on the cost to NHS Wales. However, the impact of changing these parameters was not explored in the sensitivity analyses. In addition, IFN-α was assumed to incur greater administration costs compared with sunitinib, and these differences are discussed in appendix 2.

Costs and outcomes were discounted at 3.5% per annum in the base case analysis and varied in the one-way sensitivity analysis.

8.3.2 Summary of key findings:
In the base case analysis, the incremental cost per progression-free year gained with the sunitinib regime compared to the IFN-α regime was £53,909. The incremental cost per life year gained was £24,801. The incremental cost per QALY gained was £29,199. This was based on sunitinib providing an additional 0.38 progression-free years, an additional 0.82 years of life and an additional 0.69 QALYS at an additional cost of £20,283 per patient.

Five one-way sensitivity analyses were conducted which indicated that the time horizon, and the annual discount rate were the most sensitive parameters (of those tested). However, the impact of the cost assumptions, that may have an influence on the results, were not assessed. Probabilistic sensitivity analysis was conducted to assess the joint effects of uncertainty across key parameters. From a Monte Carlo simulation of 2,000 iterations, the mean incremental cost per QALY was reported at £28,709; (95% confidence intervals were not provided). The probability of sunitinib being cost-effective at a willingness to pay threshold of £100,000 per QALY was 95%, and, at a threshold of £30,000 per QALY was 48%.

8.4 Review of evidence on budget impact

8.4.1 Summary of the evidence and key findings:
The perspective adopted by the budget impact analysis was that of the NHS Wales. Welsh population estimates (by five year age groups and gender) between 2004 and 2011 were combined with Welsh rates of kidney cancer for 2003 to estimate the number of incident cases and prevalent cases of advanced and/or mRCC in Wales in 2007. Using an assumed increase in patient numbers of 2% per year, it was anticipated that between 2007 and 2011 the total number of patients with advanced and/or mRCC would increase from 349 to 393.

The company submission assumed that 75% of advanced and/or metastatic RCC patients eligible for first-line therapy would be fit for treatment. Therefore, in 2007 an estimated 130 patients in Wales would be eligible for treatment, and assuming a 2% increase in cases each year, the budget impact analysis estimates that by 2011, the number of patients eligible for treatment with sunitinib would rise to 146.

Sunitinib was estimated to cost £23,366 per patient per year (average duration of treatment; 0.83 years) compared to £6,634 for IFN-α (average duration of treatment; 0.45 years). The reported cost of sunitinib assumed that the first treatment cycle was free of cost, and used the acquisition cost at the time of writing prior to the change in the NHS price effective 1 April 2007.The budget impact analysis assumes that in 2007, 16 (12%) of the 130 patients eligible for treatment in Wales would receive sunitinib at a cost of £303,181. After allowing for savings from the displaced 12% share of IFN-α, the net cost of introducing sunitinib to this client group in Wales, in 2007, was estimated to be £256,452.

The rate of adoption of sunitinib was assumed to increase each year as follows; in 2008, sunitinib was expected to be used to treat 15% of patients eligible for first-line therapy at a cost of £389,779 (net £329,703); in 2009, 20% of eligible patients at a cost of £534,196 (net £451,861); in 2010, 25% of patients at a cost of £687,322 (net £581,386); in 2011, 30% of eligible patients at a cost of £848,672 (net £717,868).

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- The National Cancer Research Institute (NCRI) Renal Clinical Studies Group has prepared the following position statement: "Existing standard therapies for metastatic renal cell cancer are inadequate. Both sorafenib and sunitinib significantly prolong progression free survival in metastatic renal cell cancer and should now be made routinely available in the management of this disease in the UK" [12]. Other related advice is highlighted in section 10.3 below.
- Should this product be endorsed for use in NHS Wales, a physician experienced in the treatment of renal cell carcinoma should initiate therapy.
- It is the opinion of WMP that sunitinib is not currently suitable for shared care.

9.2 Related advice:

The European Association of Urology published guidelines on RCC in 2006 [3].

9.3 AWMSG/NICE advice

Current advice published by the National Institute for Health and Clinical Effectiveness (NICE) relates to improving outcomes in urological cancers [5]. However, technology appraisals planned to be assessed by NICE as part of the 14th wave include bevacizumab and also sorafenib for the treatment of mRCC [22].

In March 2007 the All Wales Medicines Strategy Group appraised sorafenib in the treatment of patients with mRCC who had previously failed cytokine therapy or were unsuitable for such therapy [23,24].

9.4 Medical Expert

Medical expert opinion was sought and provided prior to the meeting.

9.5 Patient Interest Groups

Patient interest group submissions by the Rarer Cancers Forum and Kidney Cancer UK were provided.

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Appendix 1. Additional Clinical Information

Main inclusion/exclusion criteria for Trial A6181034 [15,16]

Inclusion Criteria

- Histologically confirmed RCC, clear cell histology with metastases
- Evidence of measurable disease by radiographic technique
- Male or female, 18 years or older
- ECOG performance status 0 or 1(see explanation below)
- Resolution of all acute toxicities of prior therapies
- Adequate organ function

Exclusion Criteria

- Prior systemic (including adjuvant or neoadjuvant) therapy of any kind for RCC
- Major surgery or radiation therapy within 4 weeks
- Severe haemorrhage within 4 weeks
- Diagnosis of a second malignancy within the last 5 years
- History of or known brain metastases, spinal cord compression or carcinomatous meningitis
- Serious acute or chronic illness or recent history of significant cardiac abnormality
- Pre-existing thyroid abnormality with thyroid function that cannot be controlled by medication
- Known HIV or AIDS-related illness
- Current treatment on another clinical trial

ECOG Performance Status Scales [25]

ECOG PERFORMANCE STATUS	
Grade	ECOG
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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Assessments Tools used in Trial A6181034

The objective response rate:
Tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST[26]).

Health-related quality of life assessments [27,28]**:**
Patient-reported outcomes were assessed using Functional Assessment of Cancer Therapy – General FACT-G and FACT- Kidney Symptom Index (FKSI) questionnaires which were administered before randomisation, on days 1 and 28 of each cycle, and at the end of treatment.

The FACT system is widely used in cancer trials. The FKSI is a clinically relevant symptom index, which was developed and validated specifically for patients with kidney cancer. One hundred and forty one kidney cancer patients (identified from a national patient and support advocacy organisation) were enrolled in a study to validate the FKSI-15 and its shorter version the FKSI-10 (comprised of the first 10 items only).

FKSI items were derived from the Functional Assessment of Chronic Illness Therapy (FACIT) item bank, literature reviews and FACT-G plus consultations with three kidney cancer experts. Thirty-four symptoms and concerns related to kidney cancer were compiled. Patients provided input in the final selection of the items, and experts provided validation of the items selected by the patients. The final version of the FKSI is comprised of 15 statements as detailed in the table below.

FACT Kidney Symptom Index (FKSI) [28]

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
	I have a lack of energy	0	1	2	3	4
	I am bothered by side effects of treatment	0	1	2	3	4
	I have pain	0	1	2	3	4
	I am losing weight	0	1	2	3	4
	I have bone pain	0	1	2	3	4
	I feel fatigued	0	1	2	3	4
	I am able to enjoy life	0	1	2	3	4
	I have been short of breath	0	1	2	3	4
	I worry that my condition will get worse	0	1	2	3	4
	I have a good appetite	0	1	2	3	4
	I have been coughing	0	1	2	3	4
	I am bothered by fevers	0	1	2	3	4
	I am able to work (includes work from home)	0	1	2	3	4
	I have had blood in my urine	0	1	2	3	4
	I am sleeping well	0	1	2	3	4

APPENDIX 2: Health Economic Review

Summary of relevant published economic evidence

Standard searches conducted by WMP across multiple databases and information portals have not identified any published economic evaluation studies of the use of sunitinib.

Company submission – economic evidence

1.0 Description and critique of company submission

The company submission included a cost-utility analysis that compared sunitinib to IFN-α as a first-line treatment for patients with advanced and/or mRCC[15]. A decision analytic model was developed to determine the lifetime expected costs and benefits of treatment with sunitinib versus IFN-α. The model included a disease progression model that included three health states; progression-free, progressed, or dead. Following progression, patients were assumed to receive best supportive care. This model structure appears to be a reasonable simplified representation of the disease. The model did not account for possible spontaneous remission, which is known to occur occasionally in untreated patients[5]. However, the rate of spontaneous remission is not reported.

The company submission did not include a diagram of the decision tree nor the disease progression model.

The model used the data from a single trial. Consequently the validity of the results is dependent on factors including the design of the original trial (such as open-label versus masked) and the number of withdrawals from the study. The generalisability of the results to other settings and patient populations should also be considered given the model is based on the results of a single trial.

2.0 Population

The study population comprised a hypothetical cohort of patients diagnosed with advanced and/or mRCC, based on participants in trial A6181034. This is an ongoing phase III, international, multi-centred, open-label, randomised controlled trial that enrolled 750 adult patients (aged 18 years or older), with previously untreated advanced and/or mRCC. These patients had RCC with a clear-cell histological component. The study enrolled patients with an ECOG performance status of 0 or 1. Therefore, the outcome in patients with a poorer performance status is uncertain. It was not stated what percentage of the patients were UK-based[16]. The patient population enrolled in the trial is likely to adequately represent patients diagnosed with RCC in Wales.

3.0 Perspective and time horizon

The analysis was conducted from the perspective of the NHS in Wales. Only the direct costs to the NHS Wales were included which was appropriate given the stated perspective.

The analysis was carried out over the remaining life expectancy of the individual patient. The time horizon selected for the base case analysis was six years and a one-way sensitivity analysis investigated the impact of reducing the time horizon to five years. The justification for using this time horizon was based on results of extrapolating data from the first 15 months of trial A6181034. This trial is still in progress and final results are anticipated in 2008. Considerable uncertainty was involved in extrapolating

overall survival curves and this was acknowledged[15]. Given this uncertainty while mature data is awaited, and that the two-year survival rate for patients with metastatic RCC is 10-20%[7], a thorough investigation of the effects of a shorter time horizon in the sensitivity analysis was justified.

4.0 Comparator

The economic evaluation compared sunitinib to IFN-α, which represents the current standard treatment practiced in Wales for this patient group. This was an appropriate comparator as indicated by NICE guidance[5]. Treatment is continued until disease progression and then patients are assumed to receive best supportive care. Following disease progression the model did not allow patients to switch from one treatment to another.

Aldesleukin (also known as IL2) and sorafenib, are also used to treat RCC in the UK but were not included in the study. One trial, currently in progress, is comparing sunitinib alone versus in combination with IFN-α[7]. A second trial is recruiting to compare the disease-free survival of patients with locally advanced renal cell carcinoma treated with adjuvant sunitinib versus sorafenib versus placebo[21]. Other treatments being evaluated for potential use in advanced and/or mRCC include bevacizumab (which has been suggested for appraisal by NICE in the 14th wave) [22], gefitinib, erlotinib, and temsirolimus[12]. Although they are currently not licensed for RCC, this does not necessarily exclude them as appropriate comparators for assessment of clinical and cost effectiveness.

5.0 Clinical inputs

5.1 Efficacy

The hypothetical cohort was assumed to have the same ECOG performance status of 0 or 1 as observed in patients enrolled in trial A6181034[16].

In the model, the overall survival and PFS input parameters were derived by extrapolation of the interim results of this single trial that enrolled participants from August 2004 until October 2005. This scheduled data analysis was undertaken in November 2005, at which time the median overall survival had not been reached for either group.

For the IFN-α regimen, the PFS was extrapolated based on a Weibull survival curve. For the sunitinib regimen, progression free survival (PFS) was estimated by applying the hazard ratio from the trial to the PFS survival curve created for the IFN-α regimen.

For the sunitinib regimen, overall survival was estimated by again applying the trial hazard ratio to the overall survival curve created for the IFN-α regimen. For the IFN-α regimen, the overall survival was estimated by regression analysis. A comparison of empirical and modelled data from two earlier trials was made to support the validity of the method used [6,29].

The submission acknowledges the considerable uncertainty in modelling these survival outcomes, which extrapolated from data at 15 months follow-up to estimate the six-year time horizon.

5.2 Health outcomes

The reported model outputs were life years gained, progression free years and quality adjusted life years (QALYs) gained. The majority of the input data for the model was derived from data from trial A6181034. The primary health outcome in the trial was PFS. Secondary outcomes included overall survival, and, health-related quality of life assessed by administration of FACT-G, FKSI health status tools and the EQ-5D utility

instrument. The choice of tools was appropriate. The EQ-5D results were grouped according to the treatment received and, stable or progressed disease status. The utility scores were used to determine the anticipated QALYs gained for each regime and according to the health status. The effect of using either the EQ-5D questionnaire or the EQ-VAS was investigated in a sensitivity analysis and utility values were one of the parameters included in the probabilistic sensitivity analysis. However, the utility values gained were not compared with utilities from alternative sources.

5.3 Adverse events

The costs of managing the adverse effects of treatment with sunitinib and IFN-α were incorporated into the model. The percentage of patients that experienced these effects was obtained from trial A6181034 data, reported by Motzer and colleagues[16]. These rates varied from those in the Summary of Product Characteristics[1]. The model considered treatment-related adverse effects which were statistically significantly different between regimes, and, that were determined by expert opinion as likely to incur resource use costs. However, in the model supplied, the percentages of patients experiencing neutropenia, and vomiting, which fit both of these requirements, were not clearly reported. The impact of uncertainty in the frequency of adverse effects was not investigated in the sensitivity analysis.

6.0 Healthcare resource utilisation and cost

The model considered only direct healthcare resources and costs incurred by NHS Wales. The direct costs incurred by the patient were not included in the study.

Healthcare resource use was based on expert opinion and on data from trial A6181034, as reported below. The costs included were the cost of acquisition, administration, adverse effects and the cost of best supportive care after cessation of active treatment. Published UK health care costs for 2005[30] were used, and adjusted to 2006 prices.

6.1 Acquisition costs

The drug costs were reported as cost per cycle. The cost of a six-week cycle of IFN-α was reported as £780, and this was taken from the Electronic Monthly Index of Medical Specialities in December 2006. There was a lack of clarity with respect to the reported acquisition cost of sunitinib. The cost of one 6-week cycle of sunitinib was reported as £3,048, but the source of the cost of sunitinib was not explicitly stated. It was noted that a change in the NHS price would be effective from 1st April 2007. Further communication established that the base-case analysis for the model used the new cost. In the analysis, there was no charge to the NHS for the first cycle of sunitinib but it was unclear whether this arrangement was permanent or would exist for a limited period only. The effect of a change in the cost of sunitinib or IFN-α was not explored in the one-way or probabilistic sensitivity analysis even though it is highly likely to affect the results. A change in the relative acquisition costs of the drugs, including cessation of the provision of the first cycle free of charge, would lead to greater costs to the NHS Wales and an ICER different to that reported in the study.

6.2 Administration costs

Administration costs for sunitinib comprised a maximum of seven outpatient visits in the first six months. Administration costs of IFN-α comprised a maximum of eight outpatient visits in the first six months, and district nurse visits. The rationale for allocating more outpatient visits for IFN-α than sunitinib was to allow for the assessment of efficacy and toxicity. In fact, in the trial, adverse effects were seen more often in the sunitinib group. On the basis of clinical opinion, it was assumed that 50% of patients would require the assistance of a district nurse to administer their subcutaneous IFN-α dose. However, this figure appears high and was not varied in the sensitivity analysis. The higher rate

of administration costs applied to IFN-α could potentially bias the results in favour of sunitinib.

6.3 Cost of adverse effects

The cost of adverse effects was estimated by applying unit costs to healthcare resources consumed by event. The resource use was based on estimates from unpublished data from the trial A16181034. Hospital admission as a result of an adverse event was reported in hospitalisation costs. The greater number of in-hospital days for sunitinib than IFN-α was taken from actual trial data. The unit cost of the healthcare resources consumed was taken from published UK sources. The use of UK, rather than Welsh sources, is unlikely to affect the outcome of the analysis.

6.4 Best supportive care

The cost of best supportive care was included for the estimated remaining survival time following cessation of active treatment. This was based on a published study of women with stage IV breast cancer in the UK[31], in which physicians were surveyed about their treatment strategies for the client group.

7.0 Discounting

In the base case analysis, costs and outcomes were discounted at 3.5% per annum. A one-way sensitivity analysis explored the impact of changing the discount rate.

8.0 Results

8.1 Base-case analysis of the cost-effectiveness model

Over a time horizon of six years and using a discount rate of 3.5%, the incremental cost per progression-free year gained with treatment with sunitinib compared to IFN-α was £53,909. The incremental cost per life year gained was £24,801. The incremental cost per QALY gained was £29,199. This was based on sunitinib providing an additional 0.38 progression-free years, an additional 0.82 years of life and an additional 0.69 QALYS at an additional cost of £20,283 per patient.

8.2 Sub-group analysis

No sub-group analysis was presented in the company submission.

9.0 Sensitivity analysis

Sensitivity analyses were restricted to parameter uncertainty and discount rate. Five one-way sensitivity analyses were conducted (see sections 9.1 – 9.5 below) which indicate that the time horizon, and the annual discount rate were the most sensitive parameters. A probabilistic sensitivity analysis was also presented in the company submission (refer to section 9.6). The sensitivity analysis did not explore the effect of the cost of sunitinib.

9.1 Time horizon

Reducing the time horizon from six years as in the base case analysis, to five years increased the incremental cost per QALY gained from £29,199 (base-case) to £36,225. This suggested that the model is sensitive to the time horizon applied. No further analyses were reported.

9.2 Duration of IFN-α treatment

The duration of treatment with IFN-α was reduced from the base-case input of disease progression (22.3 weeks, based on data from trial A618034) to three months (based on clinical opinion). This resulted in a moderate increase in the incremental cost per QALY gained to £29,680.

9.3. QALY valuation with EQ-5D versus EQ-VAS

In the sensitivity analysis the utility scores were treated in three different ways. Firstly, EQ-5D utility scores for stable and progressed disease were combined within treatment regimes to produce an incremental cost per QALY gained of £30,216. Secondly, the EQ-VAS scores were also presented by combined health state for each treatment regime. This resulted in an incremental cost per QALY of £26,480. When the EQ-5D scores were grouped by disease progression health state within each regime, the incremental cost per QALY increased to £30,002.

9.4. Duration of overall survival

A sensitivity analysis was conducted in order to investigate uncertainty in the estimation of overall survival. Alternative survival curves were estimated by applying the hazard ratio for sunitinib to survival data from the two previously published studies[6,29] of IFN-α treatment for mRCC. Using this methodology the following results were obtained: the costs per life year gained were £22,312 and £23,942; the costs per progression-free life year gained were £56,706 and £54,845 and, the costs per QALY gained were £27,026 and £28,334.

9.5. Annual discount rate

The discount rate applied to the benefits and the costs was varied between 0% and 6%. The resulting worst-case incremental cost per QALY was £32,487 (costs discounted at 6%; benefits at 0%) and the best incremental cost per QALY was £26,470 (costs discounted at 0%; benefits at 6%).

9.6. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted by assigning distributions to parameters of the base-case model. A multivariate normal distribution was applied to survival parameters and a lognormal distribution was assigned to the survival hazard ratio. Beta distributions were assigned to health state utilities and relative dose intensity, and, gamma distributions were assigned to costs that seem appropriate. The PSA did not appear to assign distributions to the cost of both interventions, which does not seem appropriate.

A Monte Carlo simulation of 2,000 iterations was run on the model and a cost effectiveness acceptability curve (CEAC) was generated. In the submission, the mean incremental cost per QALY was reported at £28,709; 95% confidence intervals were not provided. The CEAC shows the probability of sunitinib being cost-effective at a willingness to pay threshold of £100,000 per QALY was 95%, and, at a threshold of £30,000 per QALY was 48%.

Company submission – budget impact analysis

1.0 Description and critique of company submission

The company submission provided a budget impact analysis from 2007 to 2011. The model compared the anticipated costs if sunitinib were available on formulary compared to it being unavailable. Full details of the data sources, underlying assumptions and methods of calculation were provided, and figures were based on Welsh sources as far as possible.

The analysis was based on the projected incidence of renal cancer in Wales, which was calculated by combining Welsh population estimates between 2004 and 2011 with observed rates of kidney cancer among the Welsh population and allowing for an assumed 2% increase in the incidence rate. It was estimated that each year, 85% of the new cases of kidney cancer would be diagnosed as RCC. Of these, they estimated

that 30% of cases would present as advanced RCC, and of the remainder, an estimated 40% would be early disease that would progress to advance RCC within three years. The budget impact model assumed that as sunitinib would be used as a first line therapy, consequently, only newly diagnosed patients would be eligible for treatment. Of these, it was estimated that 25% would be too unfit or fragile for treatment and would instead receive best supportive care. A differential rate of adoption was applied, to sunitinib. The costs of treatment with sunitinib and IFN-α were obtained from the economic model. As discussed earlier, no sensitivity analysis was performed to investigate the implications for NHS Wales of variations in the acquisition cost of sunitinib. Phase II studies of sunitinib as a second-line treatment of advanced and/or mRCC have been undertaken, and extension to include these eligibility criteria would increase the number of patients eligible for therapy.

2.0 Perspective and time horizon

The perspective adopted by the budget impact analysis was that of NHS Wales. The analysis was conducted over the five years from 2007 to 2011.

3.0 Data sources

3.1 Incident cases

The number of anticipated incident cases was calculated by combining Government Actuary Department Welsh population estimates (by five year age groups and gender) between 2004 and 2011 with rates of kidney cancer taken from the Welsh Cancer Intelligence and Surveillance Unit, 2003 [32].

The 2% rate of increase in the incidence of cancer is taken from figures for the USA[33]. However, based on incidence figures recently released by the Welsh Cancer Intelligence and Surveillance Unit for 2004 and 2005, this appears to be a reasonable assumption[34].

The rates of advanced and/or mRCC among all cases of kidney cancer, presentation with advanced to disease and progression to advanced disease, were all based on statistics from the same, single source [35]; not a systematic review of the literature.

3.2 Prevalent cases

The number of prevalent cases in a given year was calculated by adding the estimated number of patients who had received treatment, and survived, in the preceding years. The number of survivors was estimated by combining the number of patients who had been eligible for treatment with the estimated survival after treatment with IFN-α for each succeeding year. The net number of patients was obtained by combining estimates of the number of prevalent and incident cases less the number of patients who recovered or died.

3.3 Market share

It was assumed that 25% of incident cases would not be eligible for treatment with sunitinib on the basis of their clinical condition. This estimate was derived from clinical opinion however; it was unclear whether the estimate reflected the opinion of one expert or a combination of expert opinions.

3.4 Rates of adoption

A differential rate of adoption was applied, increasing 12% of the eligible population in 2007, to 30% in 2011. No justification was given for these rates.

3.5 Displaced medicine(s)

In the analysis, displacement by sunitinib was anticipated to lead to a reduction in the number of patients receiving treatment with IFN-α. This would result in a decrease in the expenditure on IFN-α, which would offset and lower the net cost of sunitinib. However, no direct savings would be made.

4.0 Results

4.1 Base-case

Sunitinib was estimated to cost £23,366 per patient per year (average duration of treatment; 0.83 years) compared to £6,634 for IFN-α (average duration of treatment; 0.45 years). The budget impact analysis assumes that in 2007, 16 (12%) of the estimated 130 advanced and/or metastatic RCC patients eligible for first-line therapy in Wales would receive sunitinib at an acquisition cost to the NHS Wales of £303,181. The remaining 114 (88%) of the eligible patients would receive IFN-α at a further cost of £342,678: a total expenditure of £645,859 to treat the patient group. This compares with a total cost of £389,407 if all patients were treated with IFN-α. Taking into account the savings from the displaced 12% share of IFN-α, the net cost of introducing sunitinib in to this client group in Wales in 2007 was estimated to be £256,452.

Increasing rates of adoption of sunitinib were anticipated to result in sunitinib being used to treat up to 30% of patients eligible for first-line therapy in 2011. In 2008, sunitinib was expected to be used to treat 20 patients at a cost of £389,779 (net £329,703); in 2009, sunitinib was expected to be used to treat 28 patients at a cost of £534,196 (net £451,861); in 2010, sunitinib was expected to be used to treat 35 patients at a cost of £687,322 (net £581,386); in 2011, sunitinib was expected to be used to treat 44 patients at a cost of £848,672 (net £717,868).

4.2 Sub-group analysis

No sub-group analyses were reported.

5.0 Sensitivity analysis

No sensitivity analyses of the budget impact model were reported.