

## Resubmission

**axitinib, 1mg and 5mg, film-coated tablets (Inlyta<sup>®</sup>)** **SMC No. (855/13)**

**Pfizer**

04 October 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**axitinib (Inlyta<sup>®</sup>)** is accepted for use within NHS Scotland.

**Indication under review:** for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

In a phase III, open-label study, axitinib improved progression-free survival significantly more than another targeted therapy when used after first-line sunitinib or a cytokine. There was no significant improvement in overall survival.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of axitinib. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

## Indication

For the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

## Dosing Information

Axitinib 5mg orally twice daily approximately 12 hours apart with or without food. Axitinib tablets should be swallowed whole with a glass of water. Treatment with axitinib should be conducted by a physician experienced in the use of anticancer therapies.

## Product availability date

October 2012

## Summary of evidence on comparative efficacy

Axitinib is a new oral, selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGF) receptors which are involved in the pathologic angiogenesis, tumour growth and metastatic progression of cancer. It has a marketing authorisation for the second-line treatment of advanced RCC for patients who have received prior cytokine or sunitinib therapy for advanced disease.

The key evidence to support the use of axitinib in RCC comes from one open-label, phase III study comparing the efficacy and safety of axitinib with another protein kinase inhibitor, sorafenib; in the second-line treatment of RCC (AXIS study).<sup>1,2,3</sup> Eligible patients were aged at least 18 years and had histologically or cytologically confirmed RCC, with a clear-cell component. They had progressive disease defined by Response Evaluation Criteria in Solid Tumours (RECIST) after receiving one previous first-line treatment with sunitinib, bevacizumab plus interferon alfa, temsirolimus or a cytokine. All patients had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1. Patients were randomised, with stratification for type of previous first-line treatment and ECOG performance status, to receive axitinib (n=361) or sorafenib (n=362) in an open-label manner. The initial axitinib dose was 5mg twice daily which could be titrated by the investigator to 7mg twice daily and then 10mg twice daily in patients with no adverse events >grade 2 for ≥2 weeks unless blood pressure was >150/90 mmHg or antihypertensive treatment was being used. The doses of both axitinib and sorafenib could be reduced if necessary for adverse events. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever happened first. Further post-study treatment was then permitted at the discretion of the investigator.<sup>1,4</sup>

The primary outcome was progression-free survival (PFS), defined as the time from randomisation to either first disease progression (according to RECIST criteria assessed on independent radiological review) or death from any cause. At the primary PFS analysis, after 402 primary events, and median treatment durations of 6.4 months with axitinib and 5.0 months with sorafenib, progression of disease had occurred in 53% (192/361) of axitinib and 58% (210/362) of sorafenib patients. Median PFS was significantly longer in the axitinib compared with the sorafenib group: 6.7 months versus 4.7 months respectively; hazard ratio (HR) 0.66

(95% confidence interval [CI]: 0.54 to 0.81),  $p < 0.0001$ . In the subgroup of patients who had received prior sunitinib treatment ( $n=389$ ), median PFS was also significantly longer in the axitinib group: 4.8 months versus 3.4 months respectively; HR 0.74 (95% CI: 0.57 to 0.96),  $p=0.0107$ . In the subgroup of patients who had received prior cytokine treatment ( $n=251$ ), median PFS was also significantly longer in the axitinib group: 12.1 months versus 6.5 months respectively; HR 0.46 (95% CI: 0.32 to 0.68),  $p < 0.0001$ . There were small numbers of patients previously treated with bevacizumab ( $n=59$ ) and temsirolimus ( $n=24$ ) and the between group differences were not significant. The HR for PFS numerically, if not significantly, favoured axitinib over sorafenib across all baseline demographic subgroups except in patients who had received previous treatment with bevacizumab, when it numerically favoured sorafenib.<sup>1,4</sup>

The secondary outcome of overall survival did not differ significantly between axitinib and sorafenib in either the total study population or in the subgroups of patients who had received prior first-line sunitinib or cytokine therapy. At the final survival analysis, 58% (211/361) axitinib and 59% (214/362) sorafenib patients had died. The median overall survival was 20.1 months versus 19.2 months respectively; HR 0.97 (95% CI: 0.80 to 1.17). In the subgroup of patients previously treated with sunitinib, median overall survival was 15.2 months versus 16.5 months respectively: HR 1.00 (95% CI: 0.78 to 1.27), and in the subgroup of patients previously treated with a cytokine, 29.4 months versus 27.8 months respectively: HR 0.81 (95% CI: 0.56 to 1.19).<sup>1,4</sup>

Objective response rate was also a secondary endpoint, defined as those with a confirmed complete or partial response according to RECIST criteria. This was achieved in significantly more axitinib than sorafenib patients: 19% (70/361) versus 9.4% (34/362) respectively,  $p=0.0001$ . All responses were partial. In patients previously treated with sunitinib, the objective response rates were 13% (25/194) and 8.7% (17/195) respectively ( $p=0.09$ ), and in patients previously treated with a cytokine, 36% (45/126) and 17% (21/125) respectively ( $p=0.0003$ ). In the total study population, the duration of response was 11 months in the axitinib group and 10.6 months in the sorafenib group.<sup>1,4</sup>

Quality of life was measured by the Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI) and its subscale, FKSI-DRS and the EuroQol (EQ-5D). There were no significant differences between axitinib and sorafenib in those outcomes.<sup>3,4</sup>

## Summary of evidence on comparative safety

During the pivotal AXIS study, treatment-related adverse events were reported in 91% (325/359) axitinib and 95% (336/355) sorafenib patients and these were  $\geq$  grade 3 in 49% (177/359) and 53% (189/355) of patients respectively.<sup>2</sup> Discontinuation due to adverse events was reported in 9.2% (33/359) axitinib and 13% (46/355) sorafenib patients. Updated analysis, using data to 1 February 2011, indicated that 4.7% of axitinib and 9.3% of sorafenib patients discontinued due to treatment-related adverse events.<sup>4</sup>

The most frequently reported treatment-related adverse events in the axitinib group versus the sorafenib group respectively were: diarrhoea (51% versus 50%), hypertension (39% versus 29%), fatigue (35% versus 26%), nausea (29% versus 18%), decreased appetite (28% versus 25%), dysphonia (28% versus 12%) and palmar-plantar erythrodysesthesia syndrome (27% versus 51%). Hypertension (as above), nausea (as above), dysphonia (as above) and hypothyroidism (18% versus 6.8%) occurred more frequently in the axitinib group and palmar-

plantar erythrodysesthesia syndrome (as above), alopecia (3.3% versus 32%) and rash (12% versus 31%) occurred less frequently in the axitinib group. The most frequently reported serious adverse events were hypertension, diarrhoea and fatigue in the axitinib group and palmar-plantar erythrodysesthesia syndrome, hypophosphataemia, lipase elevation and hypertension in the sorafenib group. In the axitinib group, there were a number of serious adverse events including haemorrhage (11%: including gastrointestinal haemorrhage, cerebral haemorrhage and haemoptysis), venous thromboembolic events (1.9%), arterial thromboembolic events (1.1%), posterior reversible encephalopathy syndrome (0.4%), gastrointestinal perforation and fistula formation (0.3%) and hypertensive crisis (<1%).

The key AXIS publication reported that there were no treatment-toxicity deaths in the axitinib group and two in the sorafenib group: one due to tumour necrosis causing retroperitoneal bleeding in a patient also receiving dalteparin and one due to a gastro-intestinal bleed. The publication also notes that there were four reported treatment-related or causality-unknown deaths in the axitinib group (one each due to asthenia, gastro-intestinal bleed, sepsis and disease progression and renal-cell carcinoma) and five in the sorafenib group (one each due to unknown cause, blood creatinine increased and c-reactive protein increased, general physical health deterioration, retroperitoneal bleed and gastro-intestinal bleed).<sup>1</sup>

Axitinib can adversely affect blood pressure and thyroid function. The summary of product characteristics (SPC) recommends monitoring blood pressure and thyroid function before and during treatment.

## Summary of clinical effectiveness issues

The pivotal study compared axitinib with the active comparator, sorafenib, primarily in terms of PFS and the benefit was significant. The evidence to support the marketing authorisation comes from subgroup analyses of the AXIS study. However, the difference in PFS in the subgroup of patients who had received previous sunitinib (a tyrosine kinase inhibitor) was significant but small (median of 4.8 months versus 3.4 months: absolute difference of 1.4 months).<sup>1</sup> The European Medicines Agency European Public Assessment Report (EPAR) notes that a number of divergent members of the Committee for Medicinal Products for Human Use (CHMP) considered the benefit-risk balance in this subgroup of patients to be negative and raised the possibility of cross-resistance in patients previously treated with sunitinib.<sup>4</sup> The treatment effect was greater in the subgroup of patients who had received prior treatment with cytokines (median of 12.1 months versus 6.5 months: absolute difference 5.6 months). However, the use of cytokines as first-line therapy for advanced disease has largely been replaced by VEGF-targeted therapy, so there are likely to be small numbers of patients who would be eligible for second-line treatment with axitinib following failure of a first-line cytokine in clinical practice. In the pivotal study, the numbers of patients previously treated with temsirolimus and bevacizumab were considered too small to confirm efficacy and the licensed indication does not include these patients.

Pazopanib is licensed and has been accepted by SMC for the first-line treatment of advanced RCC. The AXIS study did not include patients who had progressed on first-line pazopanib treatment and so axitinib is not licensed for use second-line after pazopanib. This may have implications for Scottish clinical practice.

In the AXIS study, the PFS benefit was not associated with a significant improvement in overall survival. However, treatment effects on overall survival may have been confounded by further post-study treatment which was permitted on disease progression.<sup>1,2,4</sup>

There are a number of limitations of the study which may affect the generalisability of the results to clinical practice. The pivotal study compared axitinib with sorafenib in a sample of patients with mixed previous treatment history. Sorafenib is licensed for second-line use following cytokine treatment, and this is the position recommended by two European guidelines.<sup>5,6</sup> In the UK, the National Institute of Health and Care Excellence (NICE) did not recommend sorafenib for second-line use.<sup>7</sup> The use of sorafenib as a comparator may not be relevant to current clinical practice although, at the time of the study, sorafenib was considered appropriate. The study was of open-label design which could have introduced bias. However, the primary outcome of PFS was performed by independent review. During the study, dosing of axitinib, but not sorafenib, could be increased if tolerated and this occurred in 37% of axitinib patients<sup>1</sup>; this reflects the licensed doses of each. Study patients had an ECOG performance status of  $\leq 1$  so the efficacy of axitinib in patients with a poorer performance status is not known. In addition, the pivotal study recruited RCC patients with a clear-cell component so the efficacy of axitinib in patients with advanced and/or metastatic RCC other than clear-cell histology is not known. Finally, patients with central nervous system metastases were excluded from entry into the AXIS study.<sup>1</sup>

Other medicines licensed for second-line use in RCC include everolimus (after VEGF receptor therapy), sorafenib, sunitinib (after cytokines), and pazopanib (first-line but also second-line after cytokines). These medicines are not recommended for second-line use in NHS Scotland on the basis of SMC advice /NICE Multiple Technology Appraisal. SMC clinical experts have therefore identified an unmet need for second line treatment options. The introduction of axitinib would offer a second-line treatment option for patients with advanced RCC, of good performance status, whose disease has progressed after first-line sunitinib, or cytokine therapy. Although there are likely to be more patients eligible for axitinib after first-line sunitinib, the benefit of axitinib was markedly less in these patients. Some CHMP members expressed uncertainty about the rationale for selecting another tyrosine kinase inhibitor second-line after initial treatment with a tyrosine kinase inhibitor because of the possibility of cross resistance.

The company submission includes two indirect comparisons of axitinib versus best supportive care (BSC) in terms of PFS and overall survival: one in cytokine-refractory and one in sunitinib-refractory patients. Both comparisons are limited to data from two studies. In cytokine-refractory patients, data were used from the subgroup of patients from the AXIS study (axitinib versus sorafenib) who had failed on previous cytokine treatment<sup>1</sup> and from the TARGET study (sorafenib versus placebo, where placebo was used as a proxy for BSC).<sup>8,9</sup> There were a number of differences between the studies including previous treatment, Memorial Sloan-Kettering Cancer Centre (MSKCC) risk scores, ECOG performance status and post-study treatment. Results indicated that axitinib significantly improved PFS and overall survival compared with BSC but the results for overall survival may be less robust due to cross-over and post-study treatment.

In sunitinib-refractory patients, a new method (simulated treatment comparison) used data from the subgroup of patients from the AXIS study (axitinib versus sorafenib) who had failed on previous sunitinib treatment<sup>1</sup> and from the RECORD-1 study (everolimus versus BSC).<sup>10,11</sup> Predictive equations were calculated for the AXIS study and were used to add the missing BSC arm, estimating results expected from a head-to-head comparison. There were a number of differences between the studies including a number of lines of previous treatment (patients in

RECORD-1 had been heavily pre-treated) and post-study treatment. Results indicated that the benefits of axitinib on PFS and overall survival were greater when compared with BSC than when compared with sorafenib. The results for overall survival may be less robust due to cross-over and post-study treatment. Calculated PFS was lower than expected for BSC. Some measures of uncertainty around the absolute differences were presented. There is also some uncertainty in the robustness of this new method.

## Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing axitinib with best supportive care for the second line treatment of patients with advanced renal cell carcinoma (aRCC) whose cancer had progressed after first line therapy with either sunitinib or a cytokine. Separate cost-effectiveness results were presented for the sunitinib and cytokine refractory patients. The comparator of BSC was justified on the grounds that there are no medicines accepted by SMC for second line use in aRCC. SMC clinical experts have confirmed that BSC represents an appropriate comparator. The predominant first line treatment used in Scotland is sunitinib, so the economic analysis of axitinib in the sunitinib-refractory patient population is of most relevance for clinical practice. The cost-effectiveness of axitinib in pazopanib-refractory patients has not been assessed as this is outwith the licensed indication for axitinib.

The economic model consisted of a three health state model, consisting of progression free survival (PFS), progressive disease (PD) and death, with a 10 year base case time horizon. The primary clinical data source for axitinib used in the economic model was the sunitinib and cytokine refractory sub-groups of the phase III AXIS study. However, as this study contained sorafenib as the comparator arm, indirect comparison methods were used to compare axitinib with BSC in the two patient populations as described in the clinical effectiveness section above. PFS and overall survival (OS) outcomes for axitinib were extrapolated in the two patient populations by fitting parametric survival functions to the individual axitinib patient data from the AXIS study. The functions applied in the base case were the Weibull for both PFS/OS in the cytokine refractory population, and the Weibull for PFS and lognormal for OS in the sunitinib refractory population. In order to extrapolate BSC outcomes in each patient population, the proportional hazards assumption was applied. Utility associated with the PFS and PD health states for both axitinib and BSC were based on EQ-5D values for the axitinib patients in the AXIS study, producing mean estimates of 0.69 for PFS and 0.61 for the PD health state.

Costs for axitinib covered drug acquisition costs and the costs of managing grade 3/4 adverse events. The dose of axitinib used in the model was 10mg per day adjusted by a relative dose intensity of 102% derived from the AXIS study. A per cycle discontinuation rate derived from the AXIS trial was used which produced estimates of 0.8% and 1.26% per 4 week cycle for the cytokine and sunitinib refractory patients respectively. The company clarified that this corresponded to an average duration of treatment with axitinib of 266 and 203 days for the cytokine and sunitinib refractory patients respectively. Clinical management costs for PFS and PD states covering GP and nurse visits, CT scans, blood tests and pain medication derived from a previous HTA review were estimated at £91 and £319 respectively per 4 week cycle, and a one-off cost of £3,923 based on a published study was included for terminal stage palliative care.



A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a confidential discount was given on the list price of the medicine.

With the PAS, the base case incremental cost effectiveness ratio (ICER) for axitinib vs BSC for the sunitinib refractory population was estimated at £33,837 per quality adjusted life year (QALY) gained. The results were sensitive to the methods and data used for performing the indirect comparison. Using an alternative observational data source from Sweden for treatment outcomes associated with BSC for aRCC patients with prior sunitinib use produced an increased ICER dependent on type of parametric function fitted. Using an alternative approach to performing the simulated treatment comparison whereby the BSC estimate was derived based on prior sunitinib refractory patient data in RECORD-1 produced an improved ICER for axitinib. The results were also sensitive to varying the parameters in the parametric functions used for extrapolation. Applying a lower relative dose intensity of 80%, which the company claimed was more representative of expected clinical practice, reduced the ICER. SMC clinical experts in general were supportive that this lower RDI was reasonable for clinical practice, although caution should be exercised in interpreting the ICER as it does not take account of any possible reduction in efficacy associated with a lower dosing.

The base case incremental ICER for axitinib vs BSC for the cytokine refractory population was estimated at £56,343 per QALY gained with the PAS. The ICERs in this patient population were also quite sensitive to the extrapolation method used, with use of a lognormal parametric function increasing the ICER to £61.1k with PAS. Reducing the dose intensity to 80% produced a lower ICER of £44.4k with PAS.

There are a number of key issues with the economic analyses:

- The ICERs for both the sunitinib refractory and cytokine refractory patient populations are high and there is uncertainty in the base case ICERs according to a number of key outcome variables.
- As the sunitinib refractory population is the most important for clinical practice, the primary concern is with the reliability of the BSC results produced from the simulated treatment comparison (STC). This is a novel method not previously seen in SMC reviews which has the potential for bias associated with the comparison of axitinib and BSC using single treatment arms. To provide some indication of the impact of uncertainty, the company was requested to provide an analysis assuming a  $\pm 20\%$  variation in OS for BSC, which resulted in an ICER range of £27.9k to £44.1k with PAS.
- The EQ-5D utilities are based on a non-UK valuation tariff. The company provided analysis using the UK tariff, which reduced the PFS and PD utilities to 0.66 and 0.55 respectively, thereby increasing the ICERs to £36.5k in sunitinib refractory patients, and to £58.8k in cytokine refractory patients and with the PAS. In the view of SMC, these figures represent the base case cost per QALY estimates to which other sensitivity analyses should then have been applied.
- Post progression costs may have been underestimated, and as there is longer post progression time estimated for axitinib in the sunitinib refractory patients, the impact of assuming higher costs would increase the ICER in this patient group. The company provided an additional analysis assuming a doubling of post progression costs which increased the ICER to £36.5k with PAS for sunitinib refractory patients. When this analysis was applied to the base case ICER which used the UK EQ-5D tariffs, the result was £39.4k per QALY.

- The utility estimate for progressive disease may be overestimated as it is based on EQ-5D values derived just after the end of axitinib treatment and so does not take account of a potential decline in quality of life with disease progression over time. Assuming a 10% lower utility for progressive disease increases the ICER £35.2k with PAS in sunitinib refractory patients. When this adjustment was applied to the UK EQ-5D tariff base case, the ICER was £37.9k per QALY. In addition, the utility of BSC in the PFS state may be underestimated as it is based on EQ-5D data for axitinib which therefore includes any disutility associated with treatment related AEs. However, as the results are not sensitive to variation in PFS utilities, it is unlikely that this has a significant impact on the ICERs in the two patient populations.
- To account simultaneously for some of the key issues identified, the company was asked to provide some further analysis for the sunitinib refractory group. Taking into account the combined effect of using the UK EQ-5D tariff, higher costs of progressive disease and lower utility in progressive disease, the ICER rose to £40.9k per QALY. The company also provided analysis to show the impact of assuming a 20% increase in overall survival for BSC patients on this ICER in order to try to represent the uncertainty around the survival benefit for axitinib from the indirect comparison. This resulted in an ICER of £48.7k.

SMC considered the likely range of cost-effectiveness ratios for axitinib in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of axitinib in the context of the SMC decision modifiers and agreed that the criteria for a substantial improvement in life expectancy and an absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS were satisfied. Although there were some limitations in the economic analysis, the committee agreed that the relatively high cost per QALY was acceptable given the expected benefits of the treatment and in the context of the decision modifiers.

It is SMC policy to include the estimated QALY gain and the incremental cost in the detailed advice document for all submissions. The submitting company has advised, however, that publication of these figures, when considered alongside other cost-effectiveness data for axitinib in advanced renal cell carcinoma in the public domain, could reveal the level of discount that is available under a Patient Access Scheme elsewhere in the UK. For this reason SMC has been unable to publish these data for axitinib.

*Other data were also assessed but remain commercially confidential.\**



## Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- James Whale Fund for Kidney Cancer
- Kidney Cancer UK

## Additional information: guidelines and protocols

The European Association of Urology (EAU) published updated EAU Guidelines on Renal Cell Carcinoma in March 2013.<sup>5</sup> A general recommendation for therapy with targeting agents in patients with metastatic RCC is given. For the first-line treatment of low or intermediate risk metastatic RCC the following treatments are specifically recommended: sunitinib, bevacizumab plus interferon-alpha or pazopanib. Recommendations for second-line treatment after prior cytokine therapy include sorafenib, pazopanib and axitinib. Axitinib and everolimus are recommended as a second-line treatment after failure of tyrosine kinase inhibitors.

The European Society for Medical Oncology (ESMO) published clinical practice guidelines “Renal cell carcinomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up” in June 2012.<sup>6</sup> This guideline makes recommendations for systemic treatment of metastatic disease for:

- Second-line treatment after cytokines (decreasing number of patients since VEGF-targeted therapy is now first-line standard of care) with sorafenib, pazopanib, axitinib and sunitinib.
- Second-line treatment after VEGF-targeted therapy with everolimus and axitinib.

The National Institute of Health and Clinical Excellence (NICE) published; Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (multiple technology appraisal guidance 178) in August 2009.<sup>7</sup> Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma. Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

The National Institute of Health and Clinical Excellence (NICE) published; Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (multiple technology appraisal guidance 169) in March 2009.<sup>12</sup> Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

## Additional information: comparators

Other medicines licensed for second-line use in RCC include everolimus (after VEGF receptor therapy), sorafenib, sunitinib (after cytokines), and pazopanib (first-line but also second-line after cytokines).

## Cost of relevant comparators

Drug	Dose Regimen	Cost per 28 days (£)	Cost per 28 weeks (£)
<b>Axitinib</b>	<b>5mg orally twice daily</b>	<b>3,517</b>	<b>24,619</b>
Sunitinib*	50mg orally daily for 4 weeks and then 2 week rest (6-week cycle)	3,139	14,648
Sorafenib*	400mg orally twice daily	2,980	20,860
Everolimus*	10mg orally daily	2,772	19,404
Pazopanib*	800mg orally daily	2,093	14,648

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs (11 June 2013). All medicines are given continuously until disease progression with the exception of sunitinib which is given in 6-week cycles (4 weeks on and 2 weeks off treatment). Therefore to allow comparison, costs are presented for 28 days of treatment and then for 28 weeks (median duration of axitinib treatment during AXIS study was 6.4 months). \*Not recommended for second-line use by SMC/NICE MTA.

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 110 in all 5 years.

The submitting company has advised that publication of the budget impact estimates, when considered alongside other data in the public domain, could reveal the level of discount that is available under a Patient Access Scheme elsewhere in the UK. For this reason SMC is unable to publish the budget impact estimates for axitinib.

Other data were also assessed but remain commercially confidential.\*

## References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Rini BI, Escudier B, Tomczak P et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011; DOI:10.1016/S0140-6736(11)61613-9.

2. Motzer RJ, Escudier B, Tomczak P et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552-62.

3. Cella D, Escudier B, Rini B et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. British Journal of Cancer 2013;108:1571-8.

4. European Medicines Agency European Public Assessment Report (EPAR) for Inlyta® EMEA/H/C/002406 [www.ema.europa.eu](http://www.ema.europa.eu) [accessed 7 November 2012]

5. Ljungberg B, Bensalah K, Bex et al. European Association of Urology Guidelines on Renal Cell Carcinoma (2013). Available from [www.uroweb.org](http://www.uroweb.org) [Accessed 10 June 2013]

6. Escudier B, Eisen T, Porta C et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 (suppl 7):vii65-vii71.

7. National Institute for Health & Clinical Excellence. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 178. August 2009.

8. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-34.

9. Escudier B, Eisen T, Stadler WM et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009; DOI: 10.1200/JCO.2008.19.5511.

10. Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.

11. Motzer RJ, Escudier B, Oudard S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma. Cancer 2010;116:4256-65.

12. National Institute for Health & Clinical Excellence. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 169. March 2009.

This assessment is based on data submitted by the applicant company up to and including 13 September 2013.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

[http://www.scottishmedicines.org.uk/About\\_SMC/Policy\\_Statements/Policy\\_Statements](http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements)

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*