National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Pfizer	Guidance on the use of axitinib will facilitate patient access to a treatment for advanced renal cell carcinoma in which prior systemic therapy has failed. As there are no current NICE recommended treatments for this patient group, it is appropriate for axitinib to be appraised as an STA.	Comment noted. At the scoping workshop, consultees considered than STA was the most appropriate process to appraisal this topic and provide timely guidance to the NHS.
	Commissioning Support Appraisals Service (CSAS)	Yes, it is appropriate. There is no alternative second-line treatment option for this particular group of patients.	Comment noted.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	Yes	Comment noted.
Wording	Pfizer	The draft remit incorrectly refers to the anticipated license for axitinib, we suggest changing “after failure of prior systematic treatment” to “after failure of one prior systemic treatment”.	Comment noted. Consultees at the scoping workshop considered it prudent to not specify how many prior treatments need to have been tried before axinitib can be used because the wording of the marketing authorisation is still unclear. No changes to the draft remit have been made.

Section	Consultees	Comments	Action
	Commissioning Support Appraisals Service (CSAS)	In the title of this draft scope, and in the 2nd line of 2nd paragraph under the sub-title 'The Technology', 'systematic' treatment is written and this should presumably be 'systemic' treatment.	Comment noted. This is a typographical error which has been amended in the scope.
Timing Issues	Pfizer	Axitinib is currently under appraisal by the EMEA. It is expected that [redacted], with marketing authorisation anticipated [redacted] and UK availability from [redacted]. The likely timeframe based upon the STA process will enable guidance to be produced close to launch of this medicine in England and Wales. [**NB Confidential information has been removed**]	Comment noted. NICE aims to produce guidance soon after the technology is introduced in the UK.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	This drug is likely to be licenced soon and ideally a NICE appraisal would come out at the same time as the drug is licenced.	Comment noted. NICE aims to produce guidance soon after the technology is introduced in the UK.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Pfizer	We suggest updating this section. There are more recent data available on the number of new kidney cancers diagnosed in England and Wales[1] and also on the estimations regarding staging of patients presenting with RCC in England and Wales[2]. References: 1. Incidence of kidney cancer in England and Wales 2008. [updated 10/08/2011, cited 12/09/2011]. Available from: http://info.cancerresearchuk.org/cancerstats/types/kidney/incidence/ 2. The British Association of Urological Surgeons (BAUS), Cancer Registry Reports. Section of Oncology, Cancer Registry, Analysis of minimum data	Comment noted. The epidemiological information in the background of the scope has been updated in line with more recent data.

Section	Consultees	Comments	Action
		set for Urological Cancers, Available from: http://www.baus.org.uk/	
	Commissioning Support Appraisals Service (CSAS)	This is accurate.	Comment noted.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	Everolimus is almost 'routinely' used as a second line therapy for patients who progress on first line tyrosine kinase inhibitor therapy, as it is almost universally available and being used under the Cancer Drug Fund across England. This information should be reflected in the background to allow later indirect comparison with axitinib and to consider the relative positioning of therapy using these two agents and perhaps the sequential use.	Comment noted. In NICE technology appraisal TA219, everolimus is not recommended for the 2nd line use of renal cell carcinoma. Clinical specialists at the scoping workshop indicated that everolimus is commonly prescribed through the Cancer Drugs Fund as a second-line treatment for advanced renal cell carcinoma. It was noted that NICE has been advised by the Department of Health that treatments on the Cancer Drugs Fund should not be included as comparators. Clinical specialists at the scoping workshop expressed the need for a clinical guideline on the management of renal cell carcinoma. NICE will consider whether a clinical guideline on the management of renal cell carcinoma can be produced.
The technology/	Pfizer	The current description of the clinical trials for axitinib is confusing and inaccurate. Axitinib has not been compared with placebo and has also been studied in sorafenib refractory patients. We suggest	Comment noted. The scope has been updated to reflect that axitinib has not been studied

Section	Consultees	Comments	Action
intervention		amending this description to more accurately reflect how axitinib has been developed as follows: We recommend amending this section to more accurately reflect the trial populations of the axitinib Phase II studies and pivotal Phase III clinical trial as follows: "Axitinib has been studied in clinical trials including two Phase II studies in cytokine and sorafenib refractory advanced or metastatic RCC patients. The phase III pivotal trial (A4061032) compared axitinib with sorafenib, as second-line treatment of advanced or metastatic RCC after failure of one prior first-line regimen of sunitinib or bevacizumab + INF□ or temsirolimus or cytokine therapy." References 1. Rixe O, Bukowski RM, Michaelson MD, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol 2007; 8: 975-84 2. Rini BI, Wilding G, HudesG, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 4462-8	compared with placebo. A more detailed description of the clinical trials for axitinib will be included in the manufacturer's evidence submission.
	Commissioning Support Appraisals Service (CSAS)	The description is accurate.	Comment noted.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	Yes	Comment noted.
Population	Pfizer	Suggest altering the population description to reflect the phase III clinical trial population – "patients with advanced or metastatic RCC after failure of one prior systemic treatment". The population within the Phase III trial is mixed in terms of previous therapies received, it may be considered appropriate to conduct sub-	Comment noted. Clinical specialists at the scoping workshop considered that the population should remain unchanged in line with the remit for this appraisal because the

Section	Consultees	Comments	Action
		group analysis based on prior therapy.	specific marketing authorisation for axitinib is currently unknown. No changes to the population in the scope have been made.
	Commissioning Support Appraisals Service (CSAS)	It is not clear from the population description if axitinib is to be considered for people in whom immunotherapy was not suitable. From the wording it is assumed that efficacy in these people will not be assessed. This is an area where the scope could be expanded.	Comment noted. NICE can only make recommendations in line with the marketing authorisation for axitinib. They acknowledged that specific guidance for people in whom immunotherapy is unsuitable may not be possible depending on the final wording of the marketing authorisation.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	The population should also be broken down into the type of prior therapy received, eg temsirolimus, bevacizumab, prior cytokine therapy, also by prognostic Motzer score group. If the data is available the outcome of treatment with axitinib in relation to outcomes on first line treatment (eg PFS) would also guide where it mightr be most useful (eg is it more useful if there has been a benefit from TKI as opposed to primary resistance?). The data for axitinib for patients who failed first line cytokine therapy is very impressive. This represents less than 100 patients per year in the UK, but nevertheless is an important sub-group and the recommendations should be considered overall and for this particular sub-group.	Comment noted. If evidence allows, subgroups according to type of prior therapy received, and prognostic score (for example ECOG or Motzer) will be considered.
Comparators	Pfizer	Although other therapies are licensed for patients whose disease has progressed following prior therapy; none of these have been recommended by NICE. Consequently, the only relevant comparator for this appraisal is best supportive care.	Comment noted. Consultees at the scoping workshop agreed that because NICE has not recommended any other therapies as second-line treatment options for renal cell

Section	Consultees	Comments	Action
			carcinoma, that best supportive care is the most likely comparator for this appraisal. Consultees acknowledged that everolimus is commonly prescribed through the Cancer Drugs Fund for this indication, but were advised that the Department of Health has confirmed that treatments on the Cancer Drugs Fund should not be included as comparators.
	Commissioning Support Appraisals Service (CSAS)	These are appropriate, but Technology Appraisal, No. 178, includes sorafenib (first- and second-line) and sunitinib (second-line) for the treatment of advanced and/or metastatic renal cell carcinoma. As it is expected to be reviewed in October 2011, it might be relevant to include the use of sorfenib or sunitinib second line as comparator treatments. Alternatively, a multiple technology appraisal of second-line treatments for advanced and/or metastatic RCC might be particularly helpful.	Comment noted. TA169 and TA178 were considered for review in November 2011. During consultation, consultees indicated that there is no significant new evidence to warrant a review at this time. Consequently, TA169 and TA178 will be transferred to the static guidance list. Therefore sorefenib and sunitinib will not be in routine use as second-line treatments when an appraisal of axitinib begins, and therefore they are not considered to be appropriate comparators for this appraisal. Consultees at the scoping workshop highlighted the need for a clinical guideline on the management of renal cell carcinoma. NICE will consider

Section	Consultees	Comments	Action
			whether a clinical guideline on the management of renal cell carcinoma can be produced.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	There is clinical equipoise regarding second line therapy for metastatic renal cell carcinoma patients who relapse after sunitinib therapy. Axitinib has been found superior to sorafenib in a randomised trial of second line therapy and this trial will form the basis of the NICE appraisal. The obvious problem is that sorafenib cannot be used as a comparator, because sorafenib is rarely used as second line therapy in the UK and is not funded for this indication. In the UK, there is no standard second line therapy funded, although the vast majority of patients either continue with sunitinib therapy despite progression, or access everolimus via the Cancer Drugs Fund in England (although the drug is not available routinely in Wales). It could be argued that a comparison to sorafenib is a reasonable close approximation as to what actually happens in clinical practice in the UK (that is, continuation of a 1st generation anti-VEGF TKI therapy past relapse). It should be acknowledged that the treatment landscape has altered since the main, large axitinib trial, in that pazopanib and sunitinib are currently available first line in the metastatic setting and also everolimus second line (Cancer Drug Fund). It would be necessary and important to also do an indirect comparison of everolimus and axitinib, based on current available trial data on both agents. The sequential use of axitinib and everolimus should also be considered. As all these estimates will have wide confidence limits, consideration of all these parameters when making the final judgements will help make decisions which have transparency and clinical credibility. A judgement against BSC alone will not.	Comment noted. Consultees at the scoping workshop agreed that because NICE has not recommended any other therapies as second-line treatment options for renal cell carcinoma, that best supportive care is the most likely comparator for this appraisal. Consultees acknowledged that everolimus was not recommended for second-line treatment of renal cell carcinoma in TA219 but that it is commonly prescribed through the Cancer Drugs Fund for this indication, but were advised that the Department of Health has confirmed that treatments on the Cancer Drugs Fund should not be included as comparators.

Section	Consultees	Comments	Action
		We would therefore recommend consideration of a range of different comparators: 1. axitinib should be benchmarked against everolimus, which is the internationally recognised standard 2nd line therapy, and the drug for which a comparison against BSC is available. 2. it should be compared to the continuation of anti-VEGF therapy 3. an indirect estimate of cost effectiveness compared to BSC.	
Outcomes	Pfizer	The outcome measures listed are accurate and capture the most important health related benefits.	Comment noted.
	Commissioning Support Appraisals Service (CSAS)	These are appropriate, but it is particularly important to consider overall survival and explicit measures of quality of life. Progression-free or disease-free survival, or time to progression are less useful outcome measures.	Comment noted. Clinical specialists at the scoping workshop highlighted that a 20% improvement in response rate is considered clinically meaningful for patients with metastatic renal cell carcinoma.
Economic analysis	Pfizer	No comment	Comment noted.
	Commissioning Support Appraisals Service (CSAS)	The time horizon should be long enough to demonstrate any overall survival benefit, but given the poor 5-year survival rates for metastatic disease, it is unlikely that the time horizon should extend beyond 5 years.	Comment noted.
Equality and Diversity	Pfizer	No comment	Comment noted.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	Seems adequate.	Comment noted.
Innovation	Pfizer	Axitinib is an oral small-molecule receptor tyrosine kinase inhibitor (TKI) that targets angiogenesis. It is a more potent inhibitor of	Comment noted. Consultees at the scoping workshop considered

Section	Consultees	Comments	Action
		vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3 in vitro compared with currently licensed TKI VEGFR inhibitors for mRCC. The mechanism for the superior efficacy of axitinib versus sorafenib after failure of a tyrosine kinase inhibitor, while unclear may be due to axitinib's higher selectivity and affinity for VEGFRs than sorafenib. We believe that axitinib, compared to best supportive care, will positively impact the treatment and survival of patients that have failed previous therapy. As there are no NICE approved drugs for this patient group, axitinib will address this unmet need.	that axitinib represents a step-change in the management of patients with renal cell carcinoma, as there are currently no funded second-line treatments available through the NHS.
	Commissioning Support Appraisals Service (CSAS)	No, this is another example of a class of drugs that has been reviewed by NICE for this indication.	Comment noted.
	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	Although it will not be a step change in therapy, it may well offer some useful additional benefit in that it is a well-targeted TKI and may also be better tolerated than other agents currently available. In terms of additional benefit not included in a QALY calculation, a response rate with axitinib of 20% in a second line metastatic setting would be felt to be a very worthwhile clinical benefit to patients by renal cancer consultants. As indicated above it would be useful to tease out of the data if there may be groups who benefit more or less than others if the numbers are large enough.	Comment noted. Consultees at the scoping workshop considered that axitinib represents a step-change in the management of patients with renal cell carcinoma, as there are currently no funded second-line treatments available through the NHS.
Other considerations	Pfizer	No comment	Comment noted.
	Commissioning Support Appraisals Service (CSAS)	The price has not yet been determined, but it should be possible to estimate costs of administration to allow modelling of probable costs.	Comment noted. The manufacturer will include all relevant costs in its evidence submission.
Questions for	Pfizer	*Have the most appropriate comparators for the treatment of*	Comment noted. Consultees at

Section	Consultees	Comments	Action
consultation		*advanced RCC after failure of prior systemic treatment been included in the scope?* As stated previously the appropriate comparator for this group of patients is best supportive care. While other treatments have been licensed for this group of patients, none of these have been recommended by NICE for use in England and Wales.	the scoping workshop agreed that because NICE has not recommended any other therapies as second-line treatment options for renal cell carcinoma, that best supportive care is the most likely comparator for this appraisal. Consultees acknowledged that everolimus is commonly prescribed through the Cancer Drugs Fund for this indication, but were advised that the Department of health has confirmed that treatments on the Cancer Drugs Fund should not be included as comparators.
Any additional comments on the draft scope	Royal College of Physicians (on behalf of: NCRI/RCR/ACP/JCCO)	In the future, a useful clinical trial in the UK would be to compare everolimus with axitinib directly in the second line setting, though this may not be supported by the relevant commercial organisations. Likewise formal testing of sequential use of both agents would be very valuable in making treamtent choices. Further details on the breakdown of patients from the main axitinib trial presented at ASCO in terms of performance status breakdown and Motzer score breakdown and type of prior therapy breakdown and relative response rates would be very valuable for the appraisal.	Comment noted. In NICE technology appraisal TA219, everolimus is not recommended for the 2nd line use of renal cell carcinoma, therefore it will not be included as a comparator in an appraisal for axitinib. NICE will consider whether a clinical guideline on the management of renal cell carcinoma can be produced. If the evidence allows, subgroups will be considered based on prior therapy received, and prognostic score (for example ECOG or Motzer).

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Welsh Government
Royal College of Nursing
The National Kidney Federation
Healthcare Improvement Scotland
Medicines and Healthcare products Regulatory Agency

Comment 3: the provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	**Proposal made by:**		**Action taken:** **Removed/Added/Not included/Noted**	**Justification:**
1.	Remove CANCERactive from the matrix under Patient / carer Groups	NICE Secretariat		Removed	This organisation has disbanded. CANCERactive has been removed from the matrix of consultees and commentators
2.	Add Association of Renal Industries to the matrix under 'Professional Groups'	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria the Association of Renal Industries has been included in the matrix of consultees and commentators.

3.	Add Association of Renal Technologies to the matrix under ‘Professional Groups’	NICE Secretariat		Added	This organisation’s interests are closely related to the appraisal topic and as per our inclusion criteria the Association of Renal Technologies has been included in the matrix of consultees and commentators.
4.	Add Association of The Urology Foundation to the matrix under ‘Professional Groups’	NICE Secretariat		Added	This organisation’s interests are closely related to the appraisal topic and as per our inclusion criteria The Urology Foundation has been included in the matrix of consultees and commentators.
5.	Add Association of National Kidney Research Fund to the matrix under ‘Professional Groups’	NICE Secretariat		Added	This organisation’s interests are closely related to the appraisal topic and as per our inclusion criteria the National Kidney Research Fund has been included in the matrix of consultees and commentators.
6.	Add Association of Cochrane Renal Group to the matrix under ‘Relevant Research Groups’	NICE Secretariat		Added	This organisation’s interests are closely related to the appraisal topic and as per our inclusion criteria the Cochrane Renal Group has been included in the matrix of consultees and commentators.