National Institute for Health and Clinical Excellence
Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma

Comment 1: the draft remit

Section	Consultees	Comments	Response
Appropriateness	Novartis Pharmaceuticals	Guidance on the use of everolimus will facilitate patient access to a treatment which is effective in patients with metastatic renal cancer whose disease has progressed despite prior VEGFr-TKI therapy. Currently there are no proven treatment options for patients at this stage of their disease.	Comment noted. No changes to the scope required.
	Bayer	Recently licensed therapies for this treatment are currently being evaluated as part of an MTA. Therefore it is important and appropriate that everolimus is referred to NICE. However, consideration should be given as to the usefulness of the Phase 3 trial (NCT00410124; clinicaltrials.gov) given that the recent MTA ACD for RCC treatments has not recommended sorafenib or sunitinib.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.
	Wyeth	It will be appropriate to evaluate Everolimus in view of the ongoing appraisal of other new agents for RCC and others that have recently been referred.	Comment noted. No changes to the scope required.
	Royal College of Nurses	There is no current national standard second line treatment for mRCC, it is therefore appropriate that all new drugs are given equal opportunity for evaluation by NICE.	Comment noted. No changes to the scope required.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Not yet licensed in the UK but strong RCT evidence (now reported at international meetings) that it is efficacious second line after first line treatment failure with tyrosine kinase inhibitors. The appraisal will only be relevant if NICE approves sunitinib etc. in its current appraisal.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.

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Wording	Novartis Pharmaceuticals	The draft remit does not adequately reflect the licensed indications for everolimus. The draft remit should reflect the anticipated licensed indication as follows, "... for the treatment of patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed despite prior VEGFr-TKI therapy."	Comment noted. The draft remit is for the appraisal of everolimus "within its licensed indications" and therefore no changes are required.
	Bayer	No comment	Comment noted. No actions required.
	Royal College of Nurses	Wording is appropriate.	Comment noted. No changes to the scope required.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Yes, but see above.	Comment noted. See response above.
Timing Issues	Novartis Pharmaceuticals	The likely timeframe based on a STA being conducted will enable guidance to be issued close to product launch. However, as everolimus is licensed post - VEGFr-TKI therapy, some consideration may need to be given to the timing for publication of guidance relating to the ongoing appraisal of sunitinib, sorafenib, bevacizumab and temsirolimus for mRCC.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.
	Bayer	Guidance should be provided at the earliest opportunity, preferably as near to launch as possible.	Comment noted. The Institute is committed to providing guidance that is as timely as possible
	Royal College of Nurses	NICE is currently cocnsidering other technologies for second line use in mRCC. It is therefore appropriate that this is also considered.	Comment noted. No changes to the scope required.

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	NCRI Renal CSG, RCP, RCR, ACP, JCCO	No timings given but should follow closely the appraisal of sunitinib etc first line (if this is positive).	Comment noted. The Institute is committed to providing guidance that is as timely as possible
Additional comments on the draft remit	Novartis Pharmaceuticals	In order to avoid confusion references to, "second-line treatment" as stated in the title of the document should be removed. This should be amended in line with the licensed indication ie for the treatment of patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed despite prior VEGFr-TKI therapy.	Comment noted. The term “second-line” has been removed and everolimus will be appraised “within its licensed indications”

Comment 2: the draft scope

Section	Consultees	Comments	Response
Background information	Bayer	No comment	Comment noted. No action required.
	Royal College of Nurses	This appears to be accurate and complete.	Comment noted. No changes to the scope required.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	No comments.	Comment noted. No action required.
The technology/ intervention	Novartis Pharmaceuticals	The last sentence of this section states, "It is being studied in clinical trials for metastatic RCC that has progressed on VEGF receptor tyrosine kinase inhibitors (first –line therapy with sunitinib and/or sorafenib, or prior therapy with bevacizumab plus IFN-α) compared to placebo." In order to avoid confusion we propose that this is amended to, "It is being studied in clinical trials in patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed despite prior VEGFr-TKI therapy."	Comment noted. This was discussed at the scoping workshop and consultees agreed that the description was appropriate. No changes have been made to the scope.
	Bayer	See comment below regarding bevacizumab plus IFN-α.	See response below

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	Royal College of Nurses	Accurate	Comment noted. No changes to the scope required.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Yes.	Comment noted. No changes to the scope required.
Population	Novartis Pharmaceuticals	In order to avoid confusion we propose that this section is amended to, "It is being studied in clinical trials in patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed despite prior VEGFr-TKI therapy."	Comment noted. This was discussed at the scoping workshop and consultees agreed that the description was appropriate. No changes made to the scope.
	Bayer	The above trial relates to patients who have progressed after treatment with sorafenib and/or sunitinib. Patients who have had prior therapy with bevacizumab plus IFN-α are included but should also have had received sorafenib and/or sunitinib. Therefore it may not be appropriate to compare the technology in patients who have only progressed on bevacizumab plus IFN-α and not received sorafenib and/or sunitinib.	Comment noted. The wording of the population has been amended to more accurately reflect the prior therapies received by the trial population.
	Wyeth	The population studied in the Phase III trial includes patients with clear cell histology only. Moreover, 95% of patients have had nephrectomy. Population mainly with good/intermediate prognosis. The population is very mixed in terms of the previous therapies received. Thus, it is unlikely that sub-group analyses can be carried out	Comment noted. This was discussed at the scoping workshop, however it was agreed that evidence on subgroups is available from the key trial therefore it is appropriate to include these in the scope.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Subgroup analysis will be difficult due to small numbers.	Comment noted. This was discussed at the scoping workshop, however it was agreed that evidence on subgroups is available from the key trial therefore it is appropriate to include these in the scope.
Comparators	Novartis Pharmaceuticals	No other treatments are licensed for patients whose disease has progressed despite prior VEGFr-TKI therapy. The appropriate comparator is best	Comment noted. This was discussed at the scoping

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		supportive care.	workshop. Consultees agreed that the comparators are dependent on the outcome of the recent MTA.
	Bayer	The above trial only compares against placebo. Furthermore, the recent ACD for RCC treatments does not recommend the new clinically effective treatments for RCC. Although sorafenib and sunitinib may be considered best alternative care they are not regularly used in the NHS. Consequently, the only relevant comparator to the NHS would be best supportive care. For comparative purposes, BSC should be defined as per definition in the MTA evaluation report.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that the comparators are dependent on the outcome of the recent MTA.
	Wyeth	The comparator in Phase III is placebo plus BSC. Possibly should be Sorafenib although Sorafenib data was in cytokine failure rather than TKI failure.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that the comparators are dependent on the outcome of the recent MTA.
	Royal College of Nurses	Sunitinib and Sorafenib can be considered appropriate comparators for treatment of second line mRCC.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that the comparators are dependent on the outcome of the recent MTA.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Unless sunitinib/sorafenib are approved by NICE 1st line then the only comparator is best supportive care.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that the comparators are dependent on the outcome of the recent MTA.
Outcomes	Novartis Pharmaceuticals	Yes	Comment noted. No changes to the scope required.

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	Bayer	The standard measure of capturing HRQoL by NICE is the utility value that is then used to estimate QALYs. The utility value has several well documented limitations and is unlikely to capture the true overall benefit of any of the therapies in the specific disease area.	Comment noted. This was discussed at the scoping workshop. It was agreed that as there are no current viable alternatives to QALYs, then the economic analysis should be conducted as per the NICE reference case. No changes to the scope have been made.
	Wyeth	Primary outcome is PFS : OS would be a more powerful measure of efficacy. Benefit at this time is relatively small (4 months vs 1.9 months on placebo).	Comment noted. This was discussed at the scoping workshop and consultees agreed that all identified outcomes are important. Therefore no changes to the scope have been made.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Need to take account of progressive free survival and QOL - nothing else works in this condition. OS improvements are modest.	Comment noted. This was discussed at the scoping workshop and consultees agreed that all identified outcomes are important. Therefore no changes to the scope have been made.
Economic analysis	Novartis Pharmaceuticals	No comment	Comment noted. No actions required.
	Bayer	Using the QALY as the main unit of measurement in oncology treatments has several limitations. In particular it does not take into account patient's increased value of time when they have only a few months of life left.	Comment noted. This was discussed at the scoping workshop. It was agreed that as there are no current viable alternatives to QALYs, then the economic analysis should be conducted as per the NICE reference case. No changes to the scope have been made.
	Wyeth	Only a generic description is provided and no details have been given.	Comment noted. The scope is intended to provide a brief

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			description of the decision problem. No changes have been made to the scope.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	QALYs are not considered an appropriate measure for metastatic RCC where survival is short and any improvement modest (quality v quantity).	Comment noted. This was discussed at the scoping workshop. It was agreed that as there are no current viable alternatives to QALYs, then the economic analysis should be conducted as per the NICE reference case. No changes to the scope have been made.
Equalities	Novartis Pharmaceuticals	No comment	Comment noted. No action required.
	Bayer	No comment	Comment noted. No action required.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Renal cancer is uncommon and deserves as much attention as other more common cancers. There is nothing that works in metastatic RCC and any therapy that improves outcomes must be accorded high priority.	Comment noted. This was discussed at the scoping workshop and consultees agreed that there are no specific equality issues.
Other considerations	Novartis Pharmaceuticals	Subgroup analyses for progression free survival (PFS) were performed based on MSKCC risk group (favourable, intermediate, poor). In addition, exploratory analyses were performed based on age (>=65 years and < 65 years), gender, prior VEGF TKI therapy (sorafenib only, sutent only or both) and region. The PFS results from this analysis demonstrate homogeneity across all of the subgroups analysed.	Comment noted. This was discussed at the scoping workshop and the consultees agreed that the subgroups identified are appropriate.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	None.	Comment noted. No changes to the scope required.
Questions for consultation	Novartis Pharmaceuticals	Have the most appropriate comparators for the treatment of metastatic RCC been	Comment noted. This was discussed at the scoping

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		included in the scope? As stated previously the appropriate comparator for this group of patients is best supportive care. No other treatments are licensed post- VEGF TKI failure. Could second-line treatment with sunitinib and sorafenib be considered as appropriate comparators? Second-line treatment with sunitinib and sorafenib does not constitute an appropriate comparison as these therapies are not licensed for patients whose disease has progressed despite prior VEGF TKI failure. How should best supportive care be defined? A study will be conducted in the UK to define what constitutes BSC in this setting in the UK. Results from this study will be utilised in the health economic analysis. Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? See previous response on subgroup analyses. Which process would be the most suitable for appraising this technology, the single technology or multiple technology process? We believe that the STA process would be appropriate for the review of this technology as this will result in earlier guidance to the NHS.	workshop. Consultees agreed that the comparators are dependent on the outcome of the recent MTA. See response above. Comment noted. No changes to the scope required. See previous response. Comment noted. No changes to the scope required.
	Bayer	The STA approach is appropriate for the appraisal of everolimus, but should be evaluated in line with the RCC MTA currently under review. The STA submission should preferably be reviewed by the same group that undertook the MTA of new RCC treatments. If this is not possible, then the manufacturer should follow a similar modelling approach and input values as outlined in the MTA evaluation report.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is

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			important to follow the current STA process.
	Wyeth	Should consider place in treatment paradigm alongside the agents currently under evaluation in the MTA.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.
	Royal College of Pathologists	Multiple technology process would appear more appropriate. This treatment can only be appraised in the context of other available treatments for advanced and metastatic RCC; these will have a common need for investigaion - imaging and pathology- prior to commencement of treatment and to monitor the effect of treatment.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.
	Royal College of Nurses	Best supportive care in order to conlrol symtoms of disease can include the use of radiotherapy and drugs (steriods, bisphosphonates, analgesia, anti-emetics etc) along with support from the multidisciplinary team including palliative care professionals.	Comment noted. The scope is only intended to provide a brief description of the decision problem. The components of best supportive care can be captured within the framework of a full appraisal. No changes have been made to the scope.
		Special consideration should be given to these groups where possible.	Comment noted. No changes to the scope required.
		I am not aware of any issues that require special attention in light of the duty to have	Comment noted. No changes to the scope required.

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		due regard to the need to eliminate unlawful discrimination and promote equality. Given the current technology appraisals underway to evaluate the comparator drugs, a single technology appraisal may be most appropriate to prevent duplication of wrork.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.
	NCRI Renal CSG, RCP, RCR, ACP, JCCO	Best supportive care is that care given over and above active anti-tumour agents (usually chemotherapy but in the case of RCC - immunotherapy). It includes hormone therapy, radiotherapy, palliative care etc.	Comment noted. The scope is only intended to provide a brief description of the decision problem. The components of best supportive care can be captured within the framework of a full appraisal. No changes have been made to the scope.
Additional comments on the draft scope.	Bayer	Related NICE recommendations: pre-referral of TroVax (MVA-5T4). The status of this may have to be reviewed due to the latest interim review of the TRIST trial (http://cancerdrugnewsblog.blogspot.com/2008/07/trovax-hits-problems-in-trist.html)	Comment noted. No changes to the scope required.
	Wyeth	The appraisal of Everolimus should be considered as a MTA with other relevant therapies. However, in the event that VEGF receptor tyrosine kinase inhibitor treatments currently being appraised by NICE are not recommended for first-line use, the indication Everolimus is expected to be granted marketing authorisation for may be irrelevant to the current practice in the UK. Similarly, in the absence of a recommendation for their use as second-line treatment, the comparators in the scope should be revised to reflect current practice.	Comment noted. This was discussed at the scoping workshop. Consultees agreed that this topic is dependant on the outcome of the recent MTA, but that in order to have timely guidance for everolimus, it is important to follow the current STA process.
	Royal College of Pathologists	Terminology of RCC type: the common type is more appropriately termed "conventional RCC" rather than "clear cell" (see other considerations) if tumour type subgroups are considered then appropriate criteria for defining and assuring accuracy	Comment noted. The scope is only intended to provide a brief description of the decision

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		of tumour type allocation will be needed	problem. The definition of tumour type allocation can be captured within the framework of a full appraisal. No changes have been made to the scope.

Comment 3: Regulatory issues

Section	Consultees	Comments	Action
Remit	Novartis Pharmaceuticals	The draft remit does not adequately reflect the licensed indications for everolimus. The draft remit should reflect the anticipated licensed indication as follows, "... for the treatment of patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed despite prior VEGFr-TKI therapy."	Comment noted. The draft remit is for the appraisal of everolimus "within its licensed indications" and therefore no changes are required.
Current or proposed marketing authorisation	Novartis Pharmaceuticals	CONFIDENTIAL INFORMATION REMOVED	Confidential comments noted.

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

GlaxoSmith Kline
Macmillan Cancer Support
Marie Curie Cancer Care
National Public Health Service for Wales
NHS Quality Improvement Scotland
Royal College of Surgeons
Royal Pharmaceutical Society
The Research Institute for the Care of Older People