NICE National Institute for Health and Care Excellence

CDF Rapid Reconsideration

Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219) [1015]

Committee papers

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Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Cancer Drug Fund Reconsideration of TA219 **Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma [ID1015]**

CDF Comittee Meeting, 29th November 2016, London

Chair: Andrew Stevens

Single Technology Appraisal

Lead Team (NICE TA219, Comittee C):

Evidence Review Group: BMJ Group

NICE Technical Team: Frances Sutcliffe, Jenniffer Prescott, Marcela Haasova, Andrew Kenyon, Jenna Dilkes, Caroline Hayto

Company: Novartis

Slides handouts for public

General issues for consideration

- Has the company addressed all the committee's preferred assumptions stated in FAD?
- Are the company's and ERG's estimates of the ICER plausible?
- Does everolimus meet the criteria for a 'life-extending treatment at the end of life'?
- Taking into account the patient access scheme, should everolimus be:
  - recommended for routine commissioning in the NHS?
  - not recommended for routine commissioning in the NHS?
  - recommended for use in the Cancer Drug Fund (CDF)?

Marketing Authorisation

Everolimus

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF) - targeted therapy.

- Oral mammalian target of rapamycin (mTOR) inhibitor
- Oral agent, dose: 10 mg once daily
- List price:

  Afinitor 2.5mg tablets (30 tbts): £1,200

  Afinitor 5mg tablets (30 tbts): £2,250

  Afinitor 10mg tablets (30 tbts): £2,673 →price per day: £98.1
- Also marketed for treatment of unresectable or metastatic pNETs, and HER-2 negative advanced breast cancer.

Note: list price decreased from £2,970 to £2,673 since the original submission.

Impact on patients and carers

- Renal cell carcinoma is the commonest kidney cancer
- 11,873 new cases of kidney cancer in the UK in 2013; almost 50% have advanced disease at diagnosis (TNM stages III and IV)[1]
- One-year survival relates to TNM stage at diagnosis: 37% for TNM IV (versus 95% for TNM I)[1]
- Tyrosine kinase inhibitors and everolimus improve outcomes, but most people have side effects
- Benefit of 2nd-line and subsequent treatments usually modest
- Response varies so it is important to have a range of treatments

1 Cancer Research UK. Kidney cancer statistics. Accessed November 2016. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer

TA219 everolimus history

- 1st appraisal committee meeting: 13th January 2010
- Appraisal consultation document 1 issued: Not recommended
- 2nd appraisal committee meeting: 9th March 2010
- 3rd appraisal committee meeting: 12th May 2010
- Final appraisal determination 1 issued: Not recommended
- 4th appraisal committee meeting: 11th August 2010
- 5th appraisal committee meeting: 13th October 2010
- Final appraisal determination 2 issued: Not recommended
- Appeal hearing: 28th February 2011: Dismissed
- Final guidance published: 19th April 2011: **Not recommended**

EVL on CDF list for the treatment of metastatic RCC where all the following criteria are met:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy;
2. biopsy proven renal cell carcinoma;
3. use in patients who have had prior treatment with only one previous TKI; and
4. contraindication to 2nd line axitinib therapy OR excessive toxicity to axitinib necessitating discontinuation of axitinib within 3 months of starting therapy and at which time there is no evidence of disease progression.

Treatment pathway

- ***TA 219**: BSC as a comparator*
- ***CDF review of TA219**: BSC + axitinib as comparators*
- ***Nivolumab guidance** published on 23rd November 2016*

1st line	**Pazopanib** ★ TA215	**Sunitinib** ★ TA169		
2nd line	**Everolimus** ✪ Not NICE recommended (TA219). Available via CDF if contraindication or toxicity to **axitinib**	**NEW Axitinib** ★ TA333	**NEW Nivolumab** ◆ **TA400**	**Best supportive care**
3rd line	**Best supportive care**	**NEW Nivolumab** ◆ **TA400**		

★: oral tyrosine kinase inhibitors; oral treatment
✪: oral mammalian target of rapamycin (mTOR) inhibitor; oral treatment
◆: human monoclonal antibody; intravenous treatment
Key: BSC, best supportive care; CDF: Cancer Drug Fund.

Scope TA219 vs CDF reconsideration

Decision problem	
Population	People with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.
Intervention	Everolimus
Comparators	Best supportive care Axitinib
Outcomes	overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life.
Economic evaluation	Cost utility from NHS and PSS perspective

Company submission matched scope

Comparators: Axitinib TA333

- Axitinib **is** recommended as an option for treating adults with advanced RCC **after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine**, only if the company provides axitinib **with the discount** agreed in the patient access scheme.

At the time of publication (February 2015), axitinib has a UK MA only for use after failure with first-line sunitinib or a cytokine. If it is considered for use after any other first-line treatments, the prescriber should obtain and document informed consent and follow the relevant guidance published by the General Medical Council.[1]

Because the remit referred to NICE by the DoH for this TA only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding.

[1]For further information see the General Medical Council's Prescribing guidance: prescribing unlicensed medicines.

TA219 Evidence available

- Evidence from 1 double-blind phase III randomised controlled trial RECORD-1:

  everolimus+BSC (n=277) vs placebo+BSC (n = 139)
- Prior immunotherapy (IFNα or IL-2) or bevacizumab allowed
- Baseline characteristics similar
- Pts receiving placebo plus BSC with radiological progression could cross-over to receive open-label everolimus
- 76% of patients had crossed over from the placebo plus BSC arm to the everolimus plus BSC by Feb 08 (81% by Nov 08)

TA219 RECORD-1

Population	Median progression-free survival			
	1st interim analysis		2nd interim analysis	
	Everolimus + BSC vs. BSC	HR (95% CI)	Everolimus + BSC vs. BSC	HR (95% CI)
All (n = 416)	**4.9 vs. 1.9**	0.33 (0.25 - 0.43)	Not reported	0.30 (0.22 - 0.44)

Source: ACM 4 11th August 2010

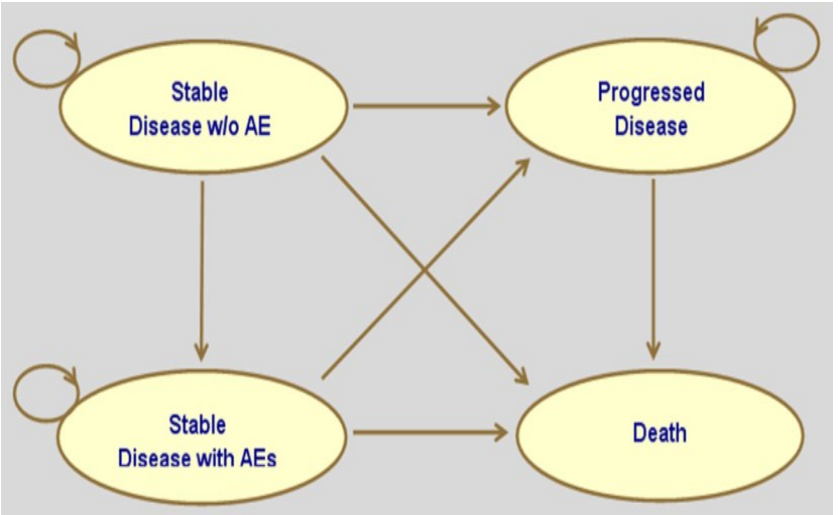
- ERG: the main factor affecting cost-effectiveness was the estimate of OS used in the economic model.

Overall survival	Mean/median EVL (Months)	Mean/median BSC (Months)	Difference (Months)
ITT	14.8	14.4	0.4
IPWC	16.2	9.6	6.6
RPSFT	16.1	7.9	8.2
ERG RPSFT	**16.7**	**10.8**	**5.9**

Source: ACM 5 13th October 2010

TA219 original model:

- everolimus 10mg per day + BSC vs. BSC alone
- 4-state Markov model: stable disease (no AEs); stable disease (with AEs); progressed disease and death
- utility values for states: 0.76; 0.71; 0.68 and 0 respectively
- hypothetical cohort having progressed on VEGF-targeted therapy
- 8-week cycles with a time horizon of 18 cycles
- IPCW analyses to determine OS
- mortality hazard rate multiplier (applied to mortality probabilities in BSC only)
- PAS – [redacted] *
- 91.8% dose intensity (RECORD-1)
- Discounting of 3.5% after the first year
- Treatment given until disease progression



*new PAS was introduced at ACM 4: [redacted]

TA219 Results ACM 5

Variable	Inc. cost £	Inc. QALY	ICER £	Prob. ICER < £50K
Original Base Case*	[redacted]	[redacted]	58,316	NA
NEW Base Case #	[redacted]	[redacted]	49,186	NA
NEW Base Case # **+ admin costs (£28)**	[redacted]	[redacted]	**49,272**	**NA**
NEW Base Case # + admin costs of 2 hours (£56)	[redacted]	[redacted]	49,358	NA

Note the new base case ICER of £49,272 was rounded up to £49,300 in the FAD

*[redacted]

#[redacted]

Source: ACM 5 13th October 2010; ERG analyses

TA219 Committee preferred assumptions

1. 8-week cycles with a time horizon of 39 cycles
2. ERG RPSFT analyses to determine OS. Extrapolation of survival curves by fitting Weibull distribution to both everolimus and BSC arms: mean OS of 10.8 months for BSC vs. 16.7 months everolimus (inc. diff. 5.9 months). Transition probabilities from the ERG's model applied to the model.
3. Discounting of 3.5% from second cycle

Resulting in:

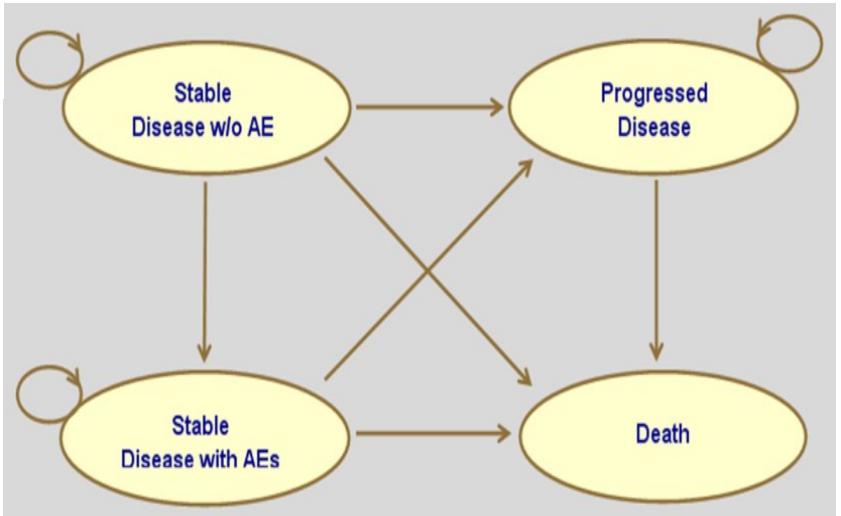
- **Base case ICER of £49,273* (including admin cost of £28)**
- **The mean probabilistic ICER of £51.661**

*PAS: [redacted]

Note the ICERs were rounded up to £49,300 and £51.700 in the FAD.

CDF Reconsideration Model

- Everolimus 10mg per day + BSC vs. BSC alone
- 4-state Markov model: stable disease (no AEs); stable disease (with AEs); progressed disease and death
- utility values for states: 0.76; 0.71; 0.68 and 0 respectively
- hypothetical cohort having progressed on VEGF-targeted therapy
- 8-week cycles with a time horizon of 39 cycles (6 years)
- RPSFT adjusted survival analysis based on ERG revisions to transition probabilities (mortality hazard rate multiplier is no longer used)
- New PAS – [redacted]
- 91.8% dose intensity (RECORD-1)
- Discounting of 3.5% from the first cycle.
- Treatment given until disease progression



CDF Reconsideration Results

	Old list price £2,970 + original PAS*		List price £2,673 + original PAS*		List price £2,673 + new PAS#	
	EVL	BSC	EVL	BSC	EVL	BSC
Intervention cost (£)	19,714	N/A	17,743	N/A	[redacted]	**N/A**
Other costs (£)	16,766	17,494	16,765	17,494	**16,765**	**17,494**
Total costs (£)	36,480	17,494	34,508	17,494	[redacted]	**17,494**
Difference in total costs (£)	N/A	18,986	N/A	17,014	**N/A**	[redacted]
LYG	1.169	0.738	1.169	0.738	**1.169**	**0.738**
LYG difference	N/A	0.431	N/A	0.431	**N/A**	**0.431**
QALYs	0.843	0.517	0.843	0.517	**0.843**	**0.517**
QALY difference	N/A	0.326	N/A	0.326	**N/A**	**0.326**
ICER/QALY	N/A	£58,316	N/A	£52,261	**N/A**	[redacted]

*[redacted]

#[redacted]

CDF probabilistic sensitivity analysis
(corrected for errors identified by ERG)

	Deterministic results + new PAS#		Probabilistic results + new PAS#	
	EVL	BSC	EVL	BSC
Intervention cost (£)	[redacted]	N/A	[redacted]	N/A
Other costs (£)	16,765	17,494	16,804	17,728
Total costs (£)	[redacted]	17,494	[redacted]	17,728
Difference in total costs (£)	N/A	[redacted]	N/A	[redacted]
LYG	1.169	0.738	1.166	0.741
LYG difference	N/A	0.431	N/A	0.425
QALYs	0.843	0.517	0.846	0.523
QALY difference	N/A	0.326	N/A	0.324
ICER/QALY	N/A	[redacted]	N/A	[redacted]

#[redacted]

CDF probabilistic sensitivity analysis

(corrected for errors identified by ERG)

[redacted]

ERG critique

- Company incorporated the Committee preferred assumptions
- Plus new PAS and updated costs (some parameters not justified or systematically identified)
- The new method estimating clinical effectiveness (RPSFT not IPCW) was not assessed by ERG
- PSAs not reliable (not sufficient information provided, list price and PAS varied in PSAs etc.)
- However the company's new base case ICER is similar to the original ERG's proposed ICER in TA219
- ERG's PSA results similar to the company's PSAs
- Corrected PSAs submitted by company consistent with both the previous PSAs and ERG's PSAs

Key: ICER, incremental cost-effectiveness ratio; IPCW, Inverse Probability of Censoring Weight ; PAS, patient access scheme; PSA, probabilistic sensitivity analyses; RPSFTM, Rank Preserving Structural Failure Time Model.

CDF new comparator axitinib

- Separate exploratory analyses
- No model submitted
- Clinical effectiveness data: RECORD-1 data subgroup of patients who had previously received sunitinib and data from AXIS trial (comparing axitinib and sorafenib)

Parameter	Everolimus	Axitinib
PFS	MAIC using IPD from RECORD-1 subgroup (n=43) and AXIS (axitinib vs sorafenib) trial (AD; n=194) Median PFS: [redacted]	MAIC using IPD from RECORD-1 subgroup (n=43) and AXIS (axitinib vs sorafenib) trial (AD; n=194) Median PFS: [redacted]
OS	An assumption of equal OS based on RECORD-1 OS data. The Weibull survival distribution was chosen for both PFS and OS. MAIC was not preformed as no statistically significant result were reported in RECORD-1 and AXIS trials for OS	

AD; aggregate data; IPD, individual patient data; MAIC, matched indirect comparison; OS, overall survival, PFS, progression-free survival.

CDF comparator axitinib continued

Parameter	Everolimus	Axitinib
Treatment dosing	Everolimus: 10 mg once daily Everolimus: [redacted] (mean dose intensity across all patients calculated using patient-level data for the matched population from the RECORD-1 trial	Axitinib: 5 mg twice daily Axitinib: 102% (mean dose intensity obtained from the axitinib ODAC briefing document)
Duration of active treatment	Everolimus: [redacted] (calculated from the RECORD-1 trial)	Axitinib: 6.67 months (obtained from the axitinib ODAC Briefing Document
Post-progression treatments	Treatments were based on those for the everolimus arm in RECORD-1 and the axitinib arm in AXIS (from the ODAC briefing document)	
Utilities	Swinburn et al., 2010: 0.795 for stable disease and 0.355 for disease progression.	
Time horizon	12 years; cycle length: 30.42 (average month)	

Company's CDF axitinib PFS

Kaplan-Meier progression-free survival curves for axitinib and weighted everolimus patients.

Company's CDF axitinib results

	List prices + no PAS	
	everolimus	axitinib
Intervention cost (£)	NR	NR
Other costs (£)	NR	NR
Total costs (£)	23,576	42,533
Difference in total costs (£)	18,956	
LYG	1.132	1.132
LYG difference	0	
QALYs	0.649	0.631
QALY difference	0.017	
ICER/QALY	EVL dominant	

Company's cost minimisation analyses:

"*It could be argued that there is no difference in efficacy between the two treatments and therefore assuming the same PFS and OS will be more plausible. This reduces the analysis to cost minimisation implying that we can ignore the QALY gains and ICERs reported in the table and focus on costs alone.*"

ERG critique

- Other estimates of PFS available:
  - Sherman et al. 2015 MAIC (Novartis funded): PFS 4.7 months EVL (95%CI 3.5 to 10.6) vs 4.8 moths AXT (95%CI 4.5 to 6.4)
  - Dranitsaris et al. 2013 NMA PFS HR (95%CrI): EVL vs. AXT 1.32 (0.88 to 2.0)
- Modelling subsequent treatments is questionable (no NICE approved 3rd line treatment)
- The choice of utility for progressed disease (0.36) is not consistent with TA219, and TA335 (0.68 and 0.61 respectively)
- The dose of intensity of everolimus (88%) is not consistent with TA219 (91.8%)
- ERG unable to assess the PFS and OS distribution
- Unclear how cost minimisation values were reached
- No model available

Key: EVL, everolimus; AXT, axitinib; MAIC, matched indirect comparison; NMA, network meta-analysis; OS, overall survival, PFS, progression-free survival.

ERG preferred assumptions

- PFS and OS assumed to be the same
- Treatment duration assumed to be the same (5 months)
- The dose intensity for axitinib is 102% as per TA333
- The dose intensity for everolimus is 91.8% as per TA219
- Scenario analysis with 100% dose intensity for everolimus (a scenario where all patients receive everolimus)

Key: OS, overall survival, PFS, progression-free survival.

ERG cost minimisation analyses

- Intervention cost: the list price of the drug per month * 5 months (ERG treatment duration assumption) * dose intensity

ERG cost minimisation analyses	List prices + no PAS		EVL PAS AXT List price		EVL PAS + AXT PAS	
	EVL	AXT	EVL*	AXT	EVL*	AXT#
Intervention cost (£)	12,474	19,539	[redacted]	19,539	[redacted]	[redacted]

- If 100% dose intensity for everolimus is the everolimus cost with PAS is £[redacted]*
- The company clarified that the cost minimisation analysis using the same cost calculation as the ERG is their preferred approach

* Everolimus [redacted]
# Axitinib [redacted]

Key: EVL, everolimus; AXT, axitinib.

Consultees comments

- NHS England:

"… notes that the relevance and importance of everolimus in the treatment of renal cancer has reduced, noting that the clinical expert input into the nivolumab appraisal clearly stated that there was clinical preference for the use of axitinib 2nd line rather than everolimus 2nd line. At present, the potential position of everolimus would be as 3rd line in the treatment pathway. This assessment may further change if nivolumab is recommended by NICE within its licensed indication and in which case everolimus would be positioned as a potential 4th line of treatment."

Consultees comments continued

- Kidney Cancer Support Network :

“There is a huge unmet need for a clinically effective drug in the second/third-line setting that has been proven to improve overall survival”

- NCRI-ACP-RCP-RCR:

“Everolimus is an oral agent which can be administered as an outpatient. It was previously widely available in England through the Cancer Drug Fund as second-line therapy post VEGF-targeted treatment failure. Although access to it is now more restricted, knowledge of its specific toxicities relative to alternative second-line therapies are recognised and considered manageable.”

Issues for consideration

- Is the company base case for everolimus versus best supportive care suitable for decision making
- Exploratory analyses limitations: can the ERG cost minimisation analyses be used for decision making
- End of life criteria
  - survival was assumed the same for everolimus and axitinib in the company's exploratory analyses and ERG cost minimisation analyses
  - TA219: everolimus met the end of life criteria
  - TA333: axitinib met the end of life criteria

Cost-effectiveness summary slide

Company base case	List price £2,673 + new PAS		
	Everolimus*	best supportive care	difference
Intervention cost (£)	[redacted]	N/A	
Total costs (£)	[redacted]	17,494	[redacted]
LYG	1.169	0.738	0.431
QALYs	0.843	0.517	0.326
ICER/QALY	[redacted]		

ERG cost minimisation analyses	List prices + no PAS		EVL PAS AXT List price		EVL PAS + AXT PAS	
	EVL	AXT	EVL*	AXT	EVL*	AXT#
Intervention cost (£)	12,474	19,539	[redacted]	19,539	[redacted]	[redacted]

*Everolimus [redacted]
#Axitinib [redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

January 2016

1 Introduction

1 All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2 In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3 The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4 The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5 A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6 Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7 The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8 Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9 The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

Name of the technology: Afinitor® (everolimus)

The proposed scheme will apply to all current and future indications:

- Current indications with marketing authorisations :
    - Hormone receptor-positive advanced breast cancer : Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor
    - Neuroendocrine tumours of pancreatic origin : Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease
    - Renal cell carcinoma: Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Future indication : the treatment of advanced Neuroendocrine Tumors (GI or Lung Origin)

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

To provide a cost-effective therapy to the NHS, thereby facilitating access for patients treated with Afinitor. *'Commercial in confidence information removed'*

3.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

'Commercial in confidence information removed'

3.4 Please provide specific details of the patient population to which the patient access scheme/ commercial

access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

'Commercial in confidence information removed'

3.5 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The PAS will apply following positive NICE guidance for Afinitor. It will apply when patients commence treatment. It is not dependent on any criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

'Commercial in confidence information removed'

3.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

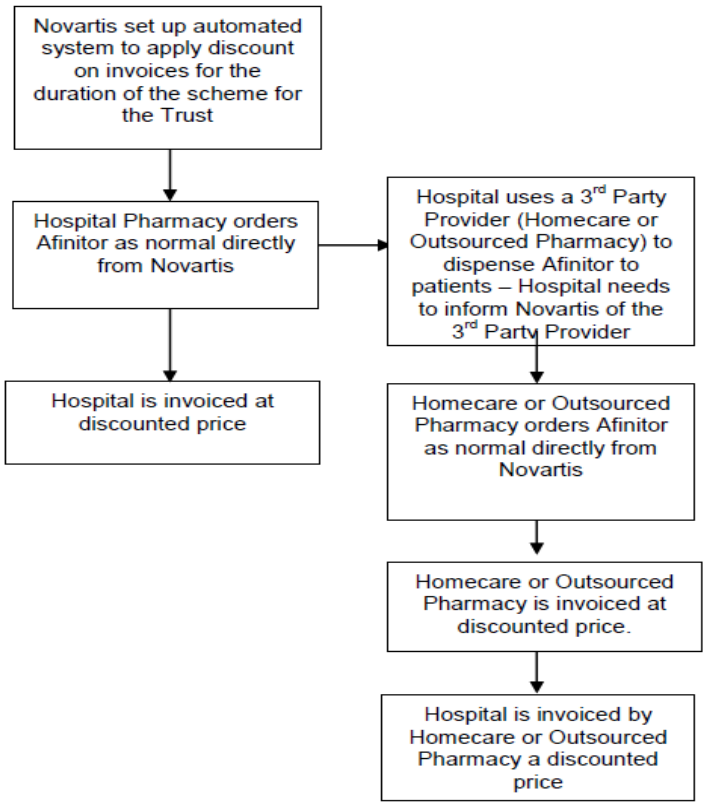
'Commercial in confidence information removed'

3.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional information, further to the standard NHS pharmacy procurement procedure, needs to be collected routinely.

3.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.

Afinitor PAS Process Flow



3.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

'Commercial in confidence information removed'

3.11 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No

3.12 If available, please list any patient access scheme/ commercial access agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

No registration or claim forms are required for this scheme.
Novartis would communicate to Hospital trusts using the attached PAS letter

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

N/A

4 Cost effectiveness

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

Table 1 Assumptions in the economic model

Assumption	Original company model	Appraisal Committee's preferred assumption
Mortality hazard rate multiplier	The hazard ratio (HR) multiplier was incorrectly applied to the transition probabilities in the placebo (i.e. BSC only) arm of the model. This multiplier had been applied directly to the transition probabilities, rather than first converting these probabilities to rates before multiplying and then converting the revised rates back into transition probabilities	The mortality rate multiplier is no longer in use and has been superseded by ERG revisions to transition probabilities.
Mortality hazard rate multiplier	In applying the HR multiplier to mortality probabilities in the BSC only arm, the model fails to account for increased death caused by greater progression in this arm.	The mortality rate multiplier is no longer in use and has been superseded by ERG revisions to transition probabilities.
Discount rates	Discounting after the first year	Discounting applied from the first cycle. Correction on worksheets "Per Patient Model (Afinitor)", "Per Patient Model (BSC)", "PP Afinitor Costs", "PP BSC Cost", Row 11. Correction on all "Markov (BSC)" and "Markov (Afinitor)" worksheets in the discounted values columns.
Adjustment for crossover	Original model used IPCW, and number of cycles increased for transition probabilities	RPSFT based transition probabilities with increased cycles used in line with ERG changes/recommendations. This involved • Removal of sheets • Markov Model (BSC)

		• Markov Model (Afinitor)
		• And replacement with sheets
		  • PP BSC Costs
		  • PP Afinitor Costs
		  • Markov Model (BSC)
		  • Markov Model (Afinitor)

<table>
<tr><td>Converting transition probabilities to rates before applying the multiplier (IPCW method)</td><td>Original model used transition probabilities</td><td>Replacement of original content from ‘transition probabilties’ and ‘TPs’ worksheets with ERG data containining RPSFT transition probabilities as per the ERG changes.</td></tr>
<tr><td>Unit costs</td><td>Original model used unit cost data that is now out of date</td><td>Updates to unit costs as below:

Worksheet “Treatment Costs”

<table>
<tr><th>Item</th><th>Cell</th><th>New input</th><th>Source</th></tr>
<tr><td>Afinitor</td><td>N17</td><td>=2673/30</td><td>BNF 70
10mg/tablet, 30 tablets price of £2673</td></tr>
<tr><td>General Practitioner Visit</td><td>D73, D80, D86, D93</td><td>=65</td><td>PenTAG report assumption: 1 GP visit per month; Curtis, 2015 (PSSRU unit costs) – Table 10.8b: Assumes a 17.2 minute clinic consultation.</td></tr>
<tr><td>Computed Tomography Scan</td><td>D74, D87</td><td>=124.31</td><td>PenTAG report assumption: 1 CT scan every 6 months; Sp. Code RD25Z, RD26Z and RD27Z (CT scan, three or more areas): 2014/15 NHS reference costs</td></tr>
<tr><td>Blood tests</td><td>D75, D81, D88</td><td>=3.01</td><td>PenTAG report assumption: 1 blood test on a monthly basis; Sp. Code DAPS05 (Haematology). 2014/15 NHS reference costs</td></tr>
<tr><td>Community Nurse Visit</td><td>D94</td><td>=78.67</td><td>PenTAG report assumption: 1.5 community nurse visits per month; Sp. Code N21AF- Specialist Nursing, Palliative/respite care: adult face-to-face; 2014/15 NHS reference costs</td></tr>
<tr><td>Pain killers: Morphine Sulphate</td><td>D95</td><td>=15</td><td>PenTAG report assumption: 1 dose per day (1 mg/ml, net price 10-ml vial prefilled syringe £30 per pack(10 ampoule))</td></tr>
</table>
</td></tr>
</table>

injections			
Death: Palliative care	D101	=3923*293.1/267	Coyle D et al. Costs of palliative care in the community, in hospitals and in hospices in the UK. Crit Rev in Oncol: haematology 32, 71-85, 1999 (inflated to 2008 of £3923 as per PenTAG report in the original model, and further inflated to 2014/15 of £4306.84 based on HCHS index from 2015 PSSRU)

Worksheet "AE Costs"

AE	Cell	New input	Source
Anaemia	E4, E14	=(2494*0.785)/267*293.1	Mickisch G. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib. ASCO 2008 Poster: 5110. And inflated to 2014/15 of £2149.47 based on HCHS index from 2015 PSSRU)
Nausea / Vomiting	E8, E18	=(2803*0.785)*267/293.1	Mickisch G. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib. ASCO 2008 Poster: 5110. And inflated to 2014/15 of £2004.42 based on HCHS index from 2015 PSSRU)
Enrich Plus	J63	=3	http://www.chemistdirect.co.uk/ensure-plus-fibre-chocolate/prd-1cg
Metoclopramide, tablet	J67	0.37	BNF 70 28 tablets price £0.37
Metoclopramide, Injection	J69	=1.31/5	BNF 70 5 ampoule price £1.31, converted to per ampoule price
Dexamethasone, tablet	J73, J126	0.93	BNF 70 10mg/tablet, 28 tablets net price of £0.93

		Dexamethasone, injection	J75, J128	=1.31/5	BNF 70 5mg/ml, 2ml-amposule: 5 ampoule price £1.31, converted to per ampoule price
		Megastrol Acetate	J82	=19.52	http://www.evidence.nhs.uk/formulary/bnf/current/8-malignant-disease-and-immunosuppression/83-sex-hormones-and-hormone-antagonists-in-malignant-disease/832-progestogens/megestrol-acetate Megace® (Swedish Orphan) 160mg/tablet, 30 tablets net price of £19.52
		Hospitalizations (for the treatment of Anorexia/Cachexia)	J95	=402.19	FCE-weighted average unit cost per day of FZ49E and FZ49H (NHS reference cost 2014/2015), Non-elective long-stay.
		Morphine soln (Oramorph)	J106	=8.5	BNF 70
		Lorazepam, tablet	J110	=2.65	BNF 70
		Lorazepam, injection	J111	=3.54/10	BNF 70 4mg/ml, 1ml/amp 10 ampoule price £3.54
		Hospitalizations (for the treatment of Dyspnea, Pneumonitis)	J115, J139	=417.98	Unit cost per day of NHS reference cost 2014/2015 DZ19L (Other Respiratory Disorders without Interventions, with CC Score 11+), Non-elective long-stay
		Temporary Ventilary Support (for the treatment of Dyspnea, Pneumonitis)	J116, J140	=20.82	Unit cost per hour of NHS reference cost 2014/2015 DZ37A, Non-Invasive Ventilation Support Assessment, 19 years and over
		O2 Therapy	J117	=0.76	"Domiciliary Oxygen Therapy." Regional Drug and Therapeutics Centre, June 2004; inflated to 2014/15 GBP using HCHS index from PSSRU
		Prednisolone	J131, J132	=1.48	BNF 70

Ceftazidime	J149	7.9	BNF 70
Meropenem	J150	=206.28/10	BNF 70: 10 vial price £206.28, converted to per vial price
Piperacillin/Tazobactam (Tazocin)	J151	=15.17	BNF 70
Fluconazale	J161	=29.28	BNF 70
Valacyclovir	J176	=86.3	BNF 70
Famciclovir, 250 mg/tablet	J179	=151.6	BNF 70
Famciclovir, 500 mg/tablet	J180	=207.86	BNF 70
Ganciclovir	J183	=148.83	BNF 70

Worksheet "Post-trial Costs"

Item	Cell	New input	Source
Xeloda (capecitabine)	C10	=20.58	BNF 70
Mobic (meloxicam)	C11	=1.11/30	BNF 70
Dexamethasone	C12	=49.56/50*5	BNF 70
Prednisolone	C13	=0.12	BNF 70
Thoracotomy	C14	=4964.49	NHS HRG Code DZ63C Major Thoracic Procedures, 19 years and over, with CC Score 0-2. 2014/15 NHS reference costs
Palliative Radiation Therapy	C15	=109.41	Barton 2000. Special Techniques in Palliative Radiotherapy. External beam radiation therapy given in 5 fractions over two weeks. NHS HRG Code SC22Z: Deliver a fraction of therapy on a megavoltage machine. 2014/15 NHS reference costs

Access scheme	Initial cycles at zero cost of everolimus had been hard-coded and were removed, replaced with full costs of treatment.	In the 'Markov Afinitor' and 'Markov BSC' sheets this affects cells Q8 and U8 which were set to zero everolimus costs; these are now replaced with the formulas from the cells below, calculated everolimus costs and total costs based on all patients in PFS receiving everolimus at cost.
Calculation of everolimus cost	Correction to calculation of everolimus cost on the 'Treatment cost' sheet.	Everolimus price and total costs were hard-coded in the 'Treatment costs' sheet in cells H6 and E12 (now in different cell references in the new model, but still on 'Treatment costs' sheet, in cells N17 and D69).

4.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

The population to whom the patient access scheme/ commercial access agreement applies is the same as that in the published technology appraisal

4.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

'Commercial in confidence information removed'

4.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to

section 6.5 of the 'Specification for company submission of evidence'.

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4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Table 2 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)/ commercial access agreement (CAA)

	Everolimus without PAS/ CAA		**Everolimus with PAS/ CAA**		**Reference source**
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Intervention	2,673*	20,525 per patient	*'Commercial in confidence information removed'*	*'Commercial in confidence information removed'* per patient	Economic model
Total treatment-related costs		37,291 per patient		*'Commercial in confidence information removed'* per patient	Economic model

*Note that the Afinitor list price has decreased from £2,970 to £2,673 since the original submission.

NB: Please note that all costs presented in the Table 2 above are not incremental costs but treatment related costs for everolimus only. The total incremental treatment related costs for everolimus compared with BSC is £19,797 with no PAS *'Commercial in confidence information removed'* with PAS.

Summary results

New base-case analysis

4.6 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

A suggested format is shown below (table 4).

Table 4a New base-case cost-effectiveness results using the price as in the published technology appraisal

	Everolimus	**BSC**
Intervention cost (£)	19,714	N/A
Other costs (£)	16,766	17,494
Total costs (£)	36,480	17,494
Difference in total costs (£)	N/A	18,986
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326
ICER (£)	N/A	58,316 per QALY

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Note that the results presented in Table4a use the previous list price of Afinitor, as presented in the original submission (£2,970) as well as the original PAS. As mentioned in Table 1, the original PAS *'Commercial in confidence information removed'.*

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Note also that the model includes updated unit costs (as described in Table1), this explains why the individual total costs of Everolimus and BSC are not the same as those presented in the original model, whereas the Incremental cost is the same (£18,986).

Table 4b Base-case cost-effectiveness results using the new list price, and original PAS

	Everolimus	**BSC**
Intervention cost (£)	17,743	N/A
Other costs (£)	16,765	17,494
Total costs (£)	34,508	17,494
Difference in total costs (£)	N/A	17,014
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326
ICER (£)	N/A	52,261 per QALY

As mentioned in Table 1, Afinitor list price has decreased from £2,970 to £2,673 since the original submission. The ICER presented in Table 4b above is based on the new list price (£2,673) and the original PAS.

Table 4c New base-case cost-effectiveness results using the patient access scheme/ commercial access agreement

	Everolimus	**BSC**
Intervention cost (£)	*'Commercial in confidence information removed'*	N/A
Other costs (£)	16,765	17,494
Total costs (£)	*'Commercial in confidence information removed'*	17,494
Difference in total costs (£)	N/A	*'Commercial in confidence information removed'*
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326
ICER (£)	N/A	*'Commercial in confidence information removed'*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4c uses the new list price and the proposed actualized PAS.

4.7 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 5.

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

The table above contains the only results, as the comparison is Afinitor vs BSC only.

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

No sensitivity or scenario analyses were presented; an alternate HR was used but this applied to the IPCW method and is replaced by the RPSFT transition probabilities.

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

a) Probabilistic results (2000 iterations) – results using the model submitted in March 2016 (PSA errors identified by the ERG not corrected) with the updated PAS [**Novartis - everolimus RCCCE model for NICE - Nov2016]**

	Everolimus	**BSC**
Intervention cost (£)	*Commercial in confidence information removed'*	N/A
Other costs (£)	16,648	17,580
Total costs (£)	*Commercial in confidence information removed'*	17,580
Difference in total costs (£)	N/A	*Commercial in confidence information removed'*
LYG	1.167	0.736
LYG difference	N/A	0.432
QALYs	0.846	0.518
QALY difference	N/A	0.328
ICER (£)	N/A	*Commercial in confidence information removed'*

'Commercial in confidence information removed'

'Commercial in confidence information removed'

Considering a threshold of 50K/QALY, the probability of Everolimus to be cost-effective is *Commercial in confidence information removed'*.

b) Probabilistic results (2000 iterations)– results using the model with the corrected PSA and the updated PAS [**Novartis - everolimus RCCCE model for NICE - Nov2016-PSA corrected**]

The model was updated to correct the errors in the PSA identified by the ERG ['**Novartis - everolimus RCCCE model for NICE - Nov2016-PSA corrected**']:

- Correction of the programming mistake related to the variation of costs
- Increased variability of health state costs (the results presented below for the corrected PSA use SD = 20%)
- Removal of the variation of Afinitor list price and PAS discount
- Variation of the utilities in the analysis

Issue	Change	Sheets/cells
Programming mistake related to the variation of costs	• CostGamma function replaced with GAMMA.INV function • Inclusion of "Cost_SD" parameter	"Cost_SD" parameter in Sheet "Probabilistic Results" cell Z9
The gamma distribution used to vary costs does not allow for much variability	• Generation of random Gamma values with SD expressed as % of mean (parameter "Cost_SD") instead of using the "CostGamma" function calling the "RanGamma" function • No random values are generated for "active drug costs"	Sheet "PP BSC Costs" and "PP Afinitor Costs" cell C3:Q6 "Cost_SD" parameter in Sheet "Probabilistic Results" cell Z9
Therapy costs inappropriately included in PSA	'CostGamma' function removed from the use of Afinitor costs in the PSA costs sheet, leaving just the deterministic means.	PP Afinitor Costs > E3:E6 PP Afinitor Costs > L3:L6
Utilities not appropriately varied	• an existing array called 'current' removed	Per Patient Model (BSC) > AX2:AX6

	• the Beta-distributed PSA calculations added instead	Per Patient Model (Afinitor) > AX2:AX6 Per Patient Model (BSC) > AX2:AX6 Per Patient Model (Afinitor) > AX2:AX6

	Everolimus	**BSC**
Intervention cost (£)	*'Commercial in confidence information removed'*	N/A
Other costs (£)	16,804	17,728
Total costs (£)	*'Commercial in confidence information removed'*	17,728
Difference in total costs (£)	N/A	*'Commercial in confidence information removed'*
LYG	1.166	0.741
LYG difference	N/A	0.425
QALYs	0.846	0.523
QALY difference	N/A	0.324
ICER (£)	N/A	*'Commercial in confidence information removed'*

'Commercial in confidence information removed'

'Commercial in confidence information removed'

Considering a threshold of 50K/QALY, the probability of Everolimus to be cost-effective is *'Commercial in confidence information removed'*.

The results are consistent with those previously submitted.

4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

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5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

N/A

5.3 Details of outcome-based schemes

5.3.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

N/A

5.3.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

N/A

5.3.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

N/A

5.3.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

N/A

5.3.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

N/A

5.3.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

N/A

5.3.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

N/A

5.3.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

N/A

5.3.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

N/A

Additional Considerations

End of life

Everolimus met the end of life criteria and still meets the new end of life criteria. As described section 4.16 of TA 219, everolimus met the end of life criteria for this indication. In TA 219, it is stated that “the Committee was satisfied that everolimus met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.”

Criterion	Data available	Source of evidence
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	"The Committee heard from the clinical specialist that the life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 5 months. The Committee also noted that the evidence from the RPSFT analysis suggested that everolimus increased survival by more than 3 months compared with best supportive care."	Afinitor RCC Technology appraisal guidance 219 Published: 19 April 2011 nice.org.uk/guidance/ta219
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	"The Committee also noted that the evidence from the RPSFT analysis suggested that everolimus increased survival by more than 3 months compared with best supportive care."	Technology appraisal guidance 219 Published: 19 April 2011 nice.org.uk/guidance/ta219

NB:We also conducted summary exploratory analyses of everolimus compared with axitiunib presented in Appendix 1.

NOVARTIS

Appendix 1: Additional Exploratory analysis comparing everolimus with axitinib

Introduction

We recognise that clinical practice has evolved over the years and axitinib is now the standard of care for renal cell carcinoma patients in this setting. After consultations with NICE, it was agreed that we could present exploratory analysis on the cost effectiveness of everolimus compared with axitinib. We recognise that this is only an exploratory analysis and therefore we only cover the key messages and results from our analyses.

Background

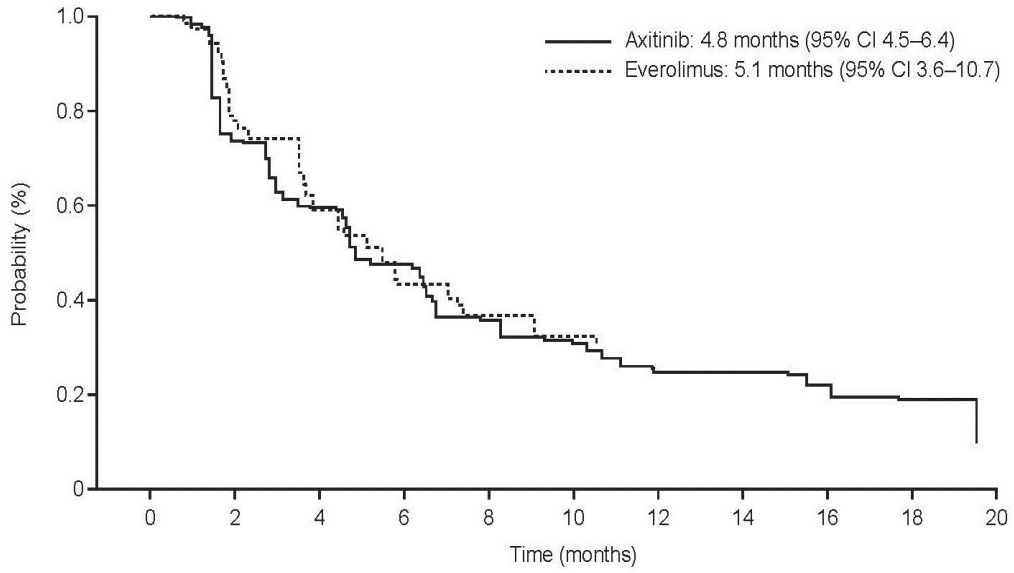
The data that informs the analyses comes from the pivotal RECORD 1 trial (everolimus) and the AXIS trial (axitinib). Because no direct comparative studies were identified in the literature, an indirect comparison was performed to compare PFS between everolimus and axitinib for the treatment of aRCC second-line based on data from the RECORD-1 and AXIS trials. The availability of patient-level data from RECORD-1 meant that it was possible to perform a matched indirect comparison between these two studies (which lack a common reference treatment) by using a weighted-adjusted comparison to align the patient characteristics between the two cohorts. This methodology, recently published by Signorovitch et al. (2012),has been applied in a number of therapeutic areas and is now included in the ISPOR Task Force publication on good practices for indirect comparison.

Both RECORD-1 and AXIS involved patients receiving the treatment of interest second-line but differed in the permitted first-line treatments, although both included patients refractory to sunitinib. As prior treatment may influence the response to second-line therapy, the indirect comparison was performed for the subgroup of patients from each study who had failed on first-line sunitinib therapy (RECORD-1, n = 43; AXIS, n = 194).

Results of the matched indirect analysis

After weighting, the median PFS for weighted everolimus patients was 5.1 months (95% CI: 3.6–10.7) which was similar to that reported for axitinib patients (4.8 months [95% CI: 4.5–6.4];

Figure 1 **Kaplan-Meier progression-free survival curves for axitinib and weighted everolimus patients.**



As can be seen the results, everolimus has slightly better PFS compared with axitinib after the matching. The results of the weighted-adjusted indirect comparison provide a more robust estimation of the relative efficacy between everolimus and axitinib than a naïve comparison. The indirect comparison provides an estimate of the relative PFS for everolimus or axitinib in patients refractory to sunitinib based on the approved indication for everolimus and axitinib. This approach was adopted in order to ensure statistical rigour but the analysis could be generalised to overall everolimus population in routine clinical practice as the results are not expected to be significantly different to the results of the current analysis.

Cost effectiveness analysis

An economic evaluation using a Markov model with area under the curve (AUC) analysis was performed to assess the cost-effectiveness of everolimus versus axitinib. The model has three health states.

Model inputs and key features of the analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (12 years)	To capture all relevant health consequences and costs
Cycle length	30.42 days (the average number of days per month)	Appropriate to provide sufficient granularity to capture patient movement between health states
Measurement of health effects	Health effects were measured as incremental cost per LYG as well as per QALY gained	To ensure that both quantity and quality of life were captured

Discounting for costs and efficacy	Costs and efficacy were discounted at 3.5%	To reflect positive time preference in line with NICE reference case
Perspective	NHS/PSS	As per NICE reference case

Model inputs: base case analysis

Parameter	Description	Justification
Treatment efficacy (PFS and OS)	PFS data based on the indirect analysis of the RECORD 1 and AXIS trials. For OS, data from the RECORD 1 (unadjusted for crossover) and AXIS trials could not be indirectly compared and therefore an assumption of equal OS for everolimus and axitinib is applied. The Weibull survival distribution was chosen for both PFS and OS.	The Weibull survival distribution was chosen because the extrapolation was a good fit with the data and its long term survival projection was in line with the survival of patients with aRCC on active treatment in clinical practice.
Utilities	Utilities derived Swinburn et al., (2010)	Most appropriate utilities identified in the systematic review.
Treatment dosing	*Active treatments:* Everolimus: 10 mg once daily Axitinib: 5 mg twice daily *Post-progression treatments:* Treatments were based on those for the everolimus arm in RECORD-1 and the axitinib arm in AXIS (from the ODAC briefing document)	Dosing for everolimus and axitinib was based on the RECORD-1 and AXIS trials, respectively, and corresponds to recommended dosing for each therapy
Dose intensity	*Active treatments:* Everolimus: *Academic in confidence information removed'* (mean dose intensity across all patients calculated using patient-level data for the matched population from the RECORD-1 trial) Axitinib: 102% (mean dose intensity obtained from the axitinib ODAC briefing document)	Based on data from large randomised studies for the interventions of interest
Duration of active treatment	Everolimus: *'Academic in confidence information removed'* (calculated from the RECORD-1 trial) Axitinib: 6.67 months (obtained from the axitinib ODAC Briefing Document	Based on data from large randomised studies for the interventions of interest
Resource utilisation	Per-patient-month resource utilisation rates (aside from AEs and post-progression treatments) were derived from the PenTAG Report and RECORD-1 publication.	Model resource utilisation assumptions were based on the medical management of patients with RCC treated with sunitinib, sorafenib, temsirolimus and bevacizumab, as described in the PenTAG report

Survival analysis

Survival functions for PFS for everolimus were based on the indirect comparison using patient-level data from RECORD-1 among patients who failed prior sunitinib therapy. Survival functions for PFS for axitinib were derived from the AXIS trial. Six distributions were tested to determine

the best fit for the survival functions for PFS and OS: Weibull, log-normal, exponential, log-logistic, Gompertz, and piecewise exponential. Visual fits as well as goodness-of-fit statistics were generated to determine the best fit to the efficacy data.

Clinical validation was also sought from published literature to determine the survival distribution that most closely resembled the survival of this patient group in clinical practice. Weibull was considered to be the best survival distribution for both PFS and OS.

Data informing OS for both everolimus and axitinib in the base case analysis were based on the RECORD-1 OS data. OS data from the RECORD-1 and AXIS trials could not be indirectly compared because both trials did not show a statistically significant result and thus any results from an indirect analysis would be misleading. In addition patients in both trials received varied therapies on progression until death, making it impossible to match for these treatments. Because of these limitations, OS for the everolimus arm was assumed to be equivalent to that of the axitinib arm; this was a reasonable assumption given that the independent trials (RECORD-1 and AXIS) showed a median OS of 19.77 months for everolimus after adjusting for crossover and 20.1 months for axitinib.
The utility values were based on Swinburn et al and were 0.795 for stable disease and 0.355 for disease progression.

Various data sources for health care resource use and cost estimates for the stable and progressive disease states were used. Post-progression treatments and rates of were derived from patient-level data from RECORD 1 trial for everolimus and from the ODAC briefing document for axitinib. Data used to calculate the rate of treatment-related grade 3-4 AEs for the everolimus and axitinib arms were taken from the pivotal everolimus RECORD-1 and AXIS trials, respectively.

Base case analysis: Everolimus vs axitinib: list prices

	Everolimus	**Axitinib**
Total costs (£)	23,576	42,533
Difference in costs (£)	-18,956	
Total LYG	1.132	1.132
LYG difference	0	
Total QALYs	0.649	0.631
QALY difference	0.017	
ICER (£)	Everolimus dominant (-1,095,808)	

Scenario analysis

Parameter	**Base case value**	**Explored value**	**Incremental costs**	**Incremental QALYs**	**ICER (£)**
Base case			**–18,956**	**0.017**	Dominant
Method of extrapolating PFS	Weibull	Log normal	–21,196	0.093	Dominant
		Gompertz	–19,666	0.055	Dominant
		Exponential	–19,679	0.056	Dominant
		Piecewise exponential	–20,992	0.087	Dominant
		Log logistic	–21,241	0.092	Dominant

Parameter	Base case value	Explored value	Incremental costs	Incremental QALYs	ICER (£)
Scenarios applying a discount for everolimus and variable discounts for axitinib (Eve vs Axit)					
Vary axitinib discount	0%	*'Commercial in confidence information removed'*	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*
		'Commercial in confidence information removed'	*'Commercial in confidence information removed'*	0.017	*'Commercial in confidence information removed'*

Interpretation of the results

As shown in the table, at full list price for both treatments everolimus dominates axitinib in all survival extrapolation scenarios. *'Commercial in confidence information removed'*. The key drivers (treatment costs and total care costs) are mainly influenced by the following factors:

- Axitinib costs more per month (£3,820) compared with everolimus (£2,673).
- The treatment duration for axitinib is almost 1.6 times longer than that of everolimus based on RECORD 1 and AXIS trial data. This is because unlike everolimus, patients in the AXIS trial received a higher dose than planned dose thus resulting in a dose intensity of 102%. The SmPC for axitinib states that for patients who tolerate axitinib the dose can be escalated to a maximum of 10 mg twice daily. This means that over the treatment duration, a proportion of patients will end up on 20mg per day (twice the recommended dose at the beginning of treatment). In the AXIS trial at least 37% of patients were dose escalated to higher doses per day. This has significant implications on the treatment costs associated with axitinib over the course of treatment. The impact of dose

escalation is not captured in our analysis but it is expected that the analysis would favour everolimus if dose escalation was included.

It could be argued that there is no difference in efficacy between the two treatments and therefore assuming the same PFS and OS will be more plausible. This reduces the analysis to cost minimisation implying that we can ignore the QALY gains and ICERs reported in the table and focus on costs alone. *'Commercial in confidence information removed'*

Conclusions

'Commercial in confidence information removed' .It is worth reiterating that as per the SmPC for axitinib, a proportion of patients will dose escalate to a maximum of 10 mg twice daily (twice the recommended dose at the beginning of treatment). This has the potential to increase the treatment costs of axitinib in the long term. On the other hand, in addition to covering a broader licensed population, everolimus confers similar survival benefits to axitinib, but these are achieved with lower overall costs as demonstrated by the cost effectiveness/minimization analysis. By adopting everolimus the NHS will realise significant savings for the same benefit in this patient population. We recognise that this is only an exploratory analysis we have demonstrated that compared with the standard of care (axitinib), everolimus is either cost effective or cost saving.

Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219) [ID1015]

Response to Clarification questions – November 18th 2016

1- Two analyses are mentioned in the *Appendix 1 Exploratory analyses* document, a cost-minimisation analysis and a cost-utility analysis. Of the two, please specify what your preferred company approach is?

The preferred company approach is the **cost-minimisation analysis**.

Novartis agree with the ERG that assuming that PFS and OS are equal for both axitinib and everolimus is a plausible simplification (*ERG report page 25*) . This assumption of similar efficacy was recently confirmed by NICE in the Final Appraisal Determination document for nivolumab in RCC (published October 21st 2016), in which the Committee concluded that axitinib and everolimus were likely to have similar effectiveness.

Novartis therefore believe that the 2 drugs should be assumed of having the same efficacy and that the cost-minimisation analysis is the most relevant approach.

2- In addition, it is not clear how the cost of treatment was calculated for the cost-minimisation analysis. Please provide an explanation?

In the Appendix 1, the costs considered for the cost-minimisation analysis are the Total costs for everolimus and axitinib based on the Cost effectiveness analysis. We ignored the QALY gains and ICERs and focused on the Costs alone when applying the Patient Access Scheme for everolimus and variable discounts for axitinib) (*see Table 'Scenario analysis', Appendix 1*). In that case, cost parity can be achieved at '*Commercial in confidence information removed*'

The Total costs compared in that case are Total care costs and are therefore broader than treatment costs because also consider the costs of post progression, adverse events, palliative care… , even if the overall difference observed is largely attributable to higher drug costs of axitinib.

We acknowledge that these costs are not replicable without using the Cost-effectiveness model. As agreed with NICE, this model was not provided considering that the submission versus axitinib was only an addendum.

Therefore since the cost-minimisation is Novartis's preferred approach, we replicated the ERG's scenario analysis as part of this clarification response:

- As suggested by the ERG, we assumed the same treatment duration for both drugs (5 months), despite the fact that treatment duration was almost 1.6 times longer for axitinib than that of everolimus based on RECORD-1 and AXIS trial data.

- Similarly, we used a dose intensity of 91.8% for everolimus, as per TA219, despite the fact that the mean dose intensity across all patients calculated using patient-level data for the matched population from the RECORD-1 trial (as per the matched-ITC) was 88%. Novartis does not agree with a scenario where the dose intensity would be 100%, since it is not consistent with real-life clinical practice.

- The dose intensity for axitinib is 102% as per TA333

In that case, as per ERG's assumptions, axitinib becomes less expensive than everolimus at a *'Commercial in confidence information removed'* **level of discount (break-even point** *'Commercial in confidence information removed',* **figure 1).**

Table 1. Axitinib cost for different discount levels

Axitinib discount	Axitinib cost
10%	£17,585
15%	£16,608
20%	£15,631
25%	£14,654
30%	£13,677
35%	£12,700
40%	£11,723
45%	£10,746
50%	£9,769
55%	£8,792
60%	£7,815
65%	£6,839
70%	£5,862
75%	£4,885
80%	£3,908
85%	£2,931
90%	£1,954

Table 2. Everolimus cost with PAS applied

'Commercial in confidence information removed'	Everolimus dose intensity
'Commercial in confidence information	91.8%

'Commercial in confidence information removed'	**Everolimus dose intensity**
removed'	

Figure 1. Cost comparison for axitinib and everolimus with PAS applied

'Commercial in confidence information removed'

The cost-minimisation is mainly dependent on the assumptions for treatment duration, dose intensity and treatment costs (PASes applied). Therefore, we can expect that in practice the discount required for axitinib to be cost saving versus everolimus would be even higher, considering :

- the potential dose escalation for axitinib : the SmPC for axitinib states that for patients who tolerate axitinib the dose can be escalated to a maximum of 10 mg twice daily ; in the AXIS trial at least 37% of patients were dose escalated to higher doses per day. As mentioned by the ERG in their report, if the dose for axitinib increases up to 20mg per day, then the discount levels needed for axitinib to be cost saving in comparison with everolimus would increase;

- the expected longer treatment duration for axinitib based on the data from the clinical trials : treatment duration was almost 1.6 times longer for axitinib than that of everolimus based on RECORD-1 and AXIS trial data;

- the potential reduced dose intensity for Afinitor (88% dose intensity calculated using patient-level data for the matched population from the RECORD-1 trial).

Nota bene: Novartis would like to take this opportunity to correct a factual inaccuracy: p5 of Appendix 1, it is said that the monthly cost for axitinib is £3820, compared with ***£2673*** *for everolimus. The monthly cost for everolimus* ***is £2710*** *using the same assumption as for axitinib (1 month = 30,42 days).*

3- Finally, please explain why the LYG changed from 1.17 to 1.132 in the submission with the new everolimus *'Commercial in confidence information removed'* **PAS?**

The change from 1.17 to 1.132 in the total LYG is independent from the updated PAS. It was a formatting error when copying the results from the Cost-effectiveness model that we identified when updating the Appendix in November.

All the results presented in Appendix 1 always used 1.132 for the LYG and this change was only a factual error that we corrected since we had the opportunity of submitting the Appendix 1 with updated PAS.
We apologize for the confusion and acknowledge that we should have made that clear when submitting the updated Appendix 1 on November 9th.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Kidney Cancer Support Network
Your position in the organisation: [redacted]
Brief description of the organisation:

Kidney Cancer Support Network (KCSN) was founded in 2006 by two cancer patients/survivors, who started by offering bespoke, practical support and representation to individual renal cancer patients who were being denied NHS funding for life-extending cancer drugs to treat metastatic renal cancer.

Empowering patients to take an active role in their own health care and, more generally, in decisions affecting the choice, provision and quality of cancer services throughout the UK, remains the top priority for the Kidney Cancer Support Network.

Over the years the Network has grown considerably; the online patient resources forum now has a membership of over 800 members with a further 530+ active and committed renal cancer patients and carers on its confidential social networking sites, all resident in the UK. Kidney Cancer Support Network is unique; it has always been totally patient-led and managed by the patients and carers it represents.

Kidney Cancer Support Network was registered with the Charities Commission in November 2015 (charity number 1164238).

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic renal cancer is a devastating terminal disease, and the impact of any terminal disease is very complex. Patient's lives are impacted in a number of ways too complicated to go into detail here, and patients and families need to deal with a multitude of physical, practical and emotional issues. Dealing with these issues is central to a patient's overall care and impacts their quality of life.

For most people, metastatic renal cancer cannot be cured. After surgery to remove the tumour, they may be offered systemic treatments with the aim to prevent recurrence of the cancer, or to try to slow down its growth and spread. These treatments can control the cancer for a number of months or years, in some cases. However, in the case of metastatic renal cancer, the disease never goes away completely, and patients live with the constant threat of recurrence or spread.

When diagnosed with metastatic renal cancer, patients and their families go through a whole range of emotions, such as, shock, fear, sadness, anger, and disbelief. These emotions can lead to anxiety, stress and depression, sometimes requiring professional psychological support and treatment. The majority of patients are forced to give up work, and current treatments are very debilitating. This brings with it enormous financial pressures for the patient and their family (and additional costs to

the State) and can precipitate psychological problems, such as depression and loss of confidence and self-worth. These emotions are exacerbated, for both patients and their families, when access to treatments becomes an issue, as highlighted in this statement from a metastatic renal cancer patient:

> *"Sutent has worked well for me with minimal side effects which is fantastic for the short term but the distress this issue* [has caused and] *the preliminary refusal not to provide funding for NHS patients like me, has caused both me and my wife huge stress. Coupled with the point made about depression and not being able to have future responsibility for my family's financial security if I cannot continue to work, has caused my wife and I unprecedented on-going clinical depression. Add to this the severe anxiety about our future as a family and you can see how cancer and potential lack of effective treatment invades every part of our life. To have the certainty of clinically effective drugs being made available to me when this TKI fails is priceless to me and my family and must be taken into account."*

Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental as well as physical clinical situation. Sexual function is affected for both male and female patients, and family life suffers as a result.

Kidney cancer patients often have to deal with the physical effects of the cancer and/or its treatment, the main effects being fatigue, pain and nausea. Patients may suffer constant pain from metastatic tumours in the brain, bones, lungs, liver, and other more rare sites. Patients with bone metastases are at risk of bone breaks and spinal compression. Kidney function is often compromised and patients find daily living difficult, often needing periods of rest during the day.

One of the most distressing side effects of cancer is fatigue, which can significantly impact quality of life. Fatigue may be caused by many factors, including depression, insomnia, anaemia, cancer treatment, and metabolic disturbances caused by the cancer itself. Treatment-related fatigue is quite common:

> *"I started to get very bad mouth ulcers which took a few weeks to clear up, fatigue and tiredness. Also experienced anaemia and had 2 blood transfusions (on ferrous sulphate 200 mg daily and bloods seem to be holding). I suffered from nose bleeds, mainly when blowing my nose!"*

Currently, there are three systemic treatments available for metastatic renal cancer: sunitinib and pazopanib in the first-line setting, and axitinib in the second-line setting. These are all VEGF tyrosine kinase inhibitors (TKIs), with very similar modes of action and side-effect profiles. Side effects to TKIs can be very debilitating, and can severely impact quality of life and the patient's ability to contribute socially and economically to their community. This is highlighted in the following statement from the wife of a metastatic renal cancer patient:

> *"He was firstly treated with Pazopanib, which caused several side effects such as hypertension, nausea and loss of appetite. In September 2015 my husband started on Axitinib. We had hoped this drug would work well but the treatment was stopped in February 2016 when my husband developed severe sepsis. Axitinib caused severe side effects for my husband and at times he was unable to eat or walk. Axitinib caused diarrohea, severe blistering to feet and mouth and we had to seek help from a chiropodist to try and enable him to walk but even she couldn't help him. In all my husband lost*

5 stone in weight during his time on TKIs. My husband has a very strong character but even he struggled with the side effects of Axitinib."

Metastatic renal cancer is an incurable cancer with limited treatment options. Treatments currently available can keep the disease under control for a few months, sometimes years, but patients eventually stop responding to treatment and viable alternative second/third-line treatments are needed to keep the cancer at bay. Difficulty accessing treatments can lead to anxiety, stress and depression in patients and families dealing with the distress caused by living with a terminal diagnosis. Patients with hereditary forms of renal cancer or very rare subtypes of renal cancer currently have limited treatment options.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

From our discussions with patients, the most important treatment outcome for metastatic renal cancer patients and their families is improved overall survival, but not at the expense of good quality of life. Patients want to live as near normal a life as possible for as long as possible. They want to continue to be active participants in society, continue to work and contribute to the economy, spend quality time with their loved ones and, if the cancer cannot be cured, live for many years with minimal side effects from treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Standard practice for the treatment of metastatic renal cancer is surgery followed by first-line treatment with sunitinib or pazopanib. These treatments have given patients hope, but at the cost of severe side effects and limited progression free survival.

Sunitinib and pazopanib can both keep the disease at bay and extend life by, on average, about 11 months. Side effects to these drugs can be debilitating and severely impact quality of life. Those patients who are unable to tolerate the side effects to these first-line drugs, or those for whom their disease no longer responds to treatment, can be prescribed second-line treatment with axitinib via NHS England. However, sunitinib, pazopanib and axitinib are all VEGF TKIs; if a patient is intolerant or unresponsive to VEGF TKIs, there are no second-line alternatives available through NHS England.

Second-line alternatives to TKIs, such as the mammalian target of rapamycin (mTOR) inhibitor, everolimus, or the immunotherapy drug, nivolumab, are currently available through participation in clinical trials, which requires a high degree of commitment from patients in terms of clinic visits and patient monitoring. Clinical trials for these drugs have strict entry criteria, and are few and far between in the UK, requiring patients to travel long distances for treatment.

Without viable treatment alternatives in the second-line, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second-line therapy to continue managing their disease, and to maintain quality of life. Otherwise, the only treatment available to these patients is palliative care to make their last months of life as

comfortable as possible.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

1. Choice of an alternative treatment with a different mode of action for non-responders to VEGF TKIs or patients unable to tolerate TKIs. Clinicians in England should have the ability to choose the most effective treatments for individual patients from those available. Without everolimus, the clinician's choice of treatment is compromised. Having a choice in second-line treatment would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.

2. Ease of use, e.g. a tablet that can be taken at home, rather than an injection or infusion that requires a hospital visit.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

See answer above.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The main concern about current NHS treatments in England is the lack of choice of drug with a different mode of action in both the second and third-line setting for those patients who do not respond to VEGF TKIs. The only non-VEGF TKI treatments available are everolimus and interleukin 2 (IL2). IL2 is not suitable for many patients due to its extreme toxicity limiting its use for a select group of patients in otherwise good health.

Please list any concerns patients or carers have about the treatment being appraised.

The main concerns patients and carers have about everolimus are:

1. Failure to respond to the drug, i.e. the drug doesn't stop the cancer from growing/spreading.

"…… the scans were showing that perhaps pazopanib had stopped working. Lymph nodes in my diaphragm and abdomen had increased."

2. Side effects impacting quality of life and preventing them from living as near a normal life as possible:

"At that point I was advised that Everolimus was to be made available to me. I had a 10 day period between coming off pazopanib and going onto everolimus. In that period I suffered fluid on my left pleura leading to a collapsed left lung. I was then prescribed 10mg of everolimus to be taken daily in tablet form. Initially side effects were minimal, however about a month I started to get very bad mouth ulcers which took a few weeks to clear up, fatigue and tiredness. Lung condition didn't help and was experiencing dry cough and breathlessness as well.

Experienced lots of indigestion also had mild doses of feeling shaky and shivery. Ct scan showed that everolimus was struggling….'

3. Financial impact on the family if unable to work due to side effects:

"Further, I know for a fact I would not have been able to undertake any work whilst on TKI's…"

"……not being able to have future responsibility for my family's financial security if I cannot continue to work….."

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who are not responsive to VEGF TKIs, or who are unable to tolerate the side effects to VEGF TKIs, might benefit more from treatment with an mTOR inhibitor, such as everolimus.

Clinicians in England should have the ability to choose the most effective treatments for individual patients from those available. Biomarkers for the treatment of renal cancer are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without viable treatment alternatives in the second-line, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second-line therapy to continue managing their disease, and to maintain quality of life.

Choice in the second-line, and access to new innovative treatments remains paramount to managing the progression of this disease. Having a choice in second-line treatment would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

No

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;

- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes x No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Everolimus has been proven to be an effective second-line treatment for metastatic renal cancer and is a viable alternative to current treatments for those patients unable to tolerate VEGF TKIs or who no longer respond to treatment with VEGF TKIs
- Renal cancer is difficult to treat; it does not respond to chemotherapy or radiotherapy, and a one size fits all VEGF TKI approach does not work for all patients
- Without biomarkers for renal cancer, clinicians need to be able to choose between drugs with different modes of action to treat individual patients and provide equity of care to all renal cancer patients
- There is a huge unmet need for a clinically effective drug in the second/third-line setting that has been proven to improve overall survival
- English patients, carers and families want the best possible treatment at this stage of disease to improve quality of life, overall survival and family life, and to enable them to continue to contribute socially and economically to their communities.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

Your name: [redacted], submitting on behalf of:

Name of your organisation:
NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
No links

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219)

What is the expected place of the technology in current practice?

Palliative treatment of metastatic Renal Cell Carcinoma (mRCC) is evolving rapidly with novel agents showing activity through a number of different molecular pathways including inhibition of the mTOR (mammalian target of rapamycin) pathway. Everolimus is an orally administered mTOR inhibitor which demonstrated activity in the setting of mRCC following first-line VEGF-targeted therapy in the Phase III randomised, placebo-controlled RECORD-1 clinical trial[1]. This study met its primary endpoint of improved progression free survival (PFS) for Everolimus of 4.9 months compared to 1.9 months for placebo (hazard ration 0.33 P<0.01). It has been widely accepted that the high degree of cross-over from placebo to Everolimus on disease progression (81% of eligible patients) accounts for the apparent lack of Overall Survival (OS) advantage for Everolimus in the RECORD-1 trial.

The evidence from RECORD-1 has supported Everolimus being adopted into international guidelines for the treatment of mRCC including the European Society of Medical Oncology (ESMO)[2] Clinical Practice Guidelines and European Association of Urology (EAU)[3] as a second or subsequent line of therapy for mRCC.

Following the RECORD-1 trial Everolimus was considered by NICE in 2011 (ta219). Whilst the results of the trial were considered to be robust and the toxicities (including stomatitis, fatigue, pneumonitis and immunosuppression) were felt to manageable in the context of metastatic cancer, Everolimus was not recommended for the second-line treatment of advanced renal cell carcinoma.

In the UK Axitinib is currently the only NICE approved (ta333) agent available for treatment of patients with mRCC following failure of first line VEGF-targeted therapy. For a subset of patients who fulfil the criteria set out by the Cancer Drug Fund (EVE3_v2.2), Everolimus may be considered, but only where Axtinib is contraindicated or where there has been excessive toxicity with Axitinib necessitating discontinuation of Axitinib within 3 months of starting therapy and at which time there is no evidence of disease progression.

Recent publications have now demonstrated clinical benefit for Everolimus following first-line VEGF-targeted therapy in the 'real-world' setting of routine clinical care. The CHANGE study was a non-interventional study of 334 patients treated in Germany with Everolimus. Median time to progression (TTP) was 7.1 months with an acceptable safety profile that was consistent with previous reports[4]. The French retrospective SECTOR study assessed outcomes of second or third-line Everolimus in 144 patients and found median duration of treatment with Everolimus to be 4.0 months and both this and the toxicity profile were in line with RECORD-1. Therefore evidence supports the use of Everolimus as an active agent with an acceptable toxicity profile following failure of first-line VEGF-targeted therapy in clinical practice.

In a meta-analysis of 937 patients based on 4 retrospective studies in the second-line setting, support was found for Everolimus having greater efficacy than another mTOR inhibitor, Temsirolimus, with a reduction in risk of death by 26% (HR, 0.74;

95% confidence interval [CI], 0.59-0.93; *P* = .008) and reduction of risk of treatment failure by 30% (HR, 0.70; 95% CI, 0.56-0.88; *P* = .002)[5].

There are, however, two recent pivotal prospective, randomised phase III studies, both of which used Everolimus as the comparator arm and both of which found a survival advantage for the experimental arm. The first of these was the CHECKMATE 025 study which demonstrated improved tolerability and an improved median OS for Nivolumab of 25.0 months (95% CI 21.8 to not estimable) compared to 19.6 months for Everolimus (95% CI 17.6 to 23.1)[6]. The second trial was the METEOR study in which median OS was 21.4 months (95% CI 18.7 to not estimable) with Cabozantinib and 16.5 months (95% CI, 14.7–18.8) with Everolimus in vascular endothelial growth factor (VEGF)–resistant RCC[7].

Although internationally Nivolumab and Cabozantinib are being recommended as standard of care in the post-VEGF failure setting in mRCC, Everolimus is still considered appropriate therapy if the other drugs are not safe, tolerable or not available[3]. In the UK neither Nivolumab nor Cabozantinib are currently available through NICE approval or (in England) the Cancer Drug Fund. Therefore, in the context of mRCC following failure of first-line VEGF targeted therapy Everolimus remains an active agent that continues to have a place in therapy algorithms and access to this drug is considered important to optimise palliative management of these patients and to ensure that the UK is aligned to international norms.
.

The advantages and disadvantages of the technology
Everolimus is an oral agent which can be administered as an outpatient. It was previously widely available in England through the Cancer Drug Fund as second-line therapy post VEGF-targeted treatment failure. Although access to it is now more restricted, knowledge of its specific toxicities relative to alternative second-line therapies are recognised and considered manageable. This is particularly relevant to patients who are intolerant of VEGF-targeted therapies or where checkpoint inhibitors (such as Nivolumab, should it become available) are contraindicated such as in the context of autoimmune disease.

Any additional sources of evidence
Please see references below, in particular Evidence based guidelines (references 2 and 3).

Implementation issues
Everolimus has previously been widely used within Oncology setting in the NHS. As such barriers to implementation are not envisaged to be a significant issue.

Equality
No issues identified.

References
1 Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. 2008. Motzer *et al* Lancet 372 449-456.
2 Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2014. Escudier et al Annals of Oncology 25(supp3)

3 European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor–Targeted Therapy. 2016. Powles T, et al. Eur Urol 69 4-6 http://dx.doi.org/10.1016/ j.eururo.2016.06.009

4 Everolimus in metastatic renal cell carcinoma after failure of initial anti-VEGF therapy: final results of a noninterventional study. 2015. Bergmann et al BMC Cancer 15:303

5 Everolimus and temsirolimus are not the same second-line in metastatic renal cell carcinoma. A systematic review and meta-analyisisof literature data. 2015 Clin Genitourin Cancer 13, 137-41

6 Nivolumab Versus Everolimus in Advanced Renal-Cell Carcinoma. 2015. Motzer et al NEJM 373 19 1803-1813

7 Cabozantinib Versus Everolimus in advanced renal cell carcinoma (METEOR): Final results from a randomised, open-label Phase III trial. 2016. Choueiri et al Lancet Oncol 17(7) 917-27

NHS England submission on the re-appraisal of everolimus in metastatic renal cell cancer

1. The CDF previously re-considered in August 2015 the case for everolimus to remain in the CDF as treatment for patients with metastatic renal cell carcinoma who had previously received and progressed on treatment with one vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI).
2. There was one randomised trial (the RECORD-1 study) considered as the main evidence base related to this indication. This study randomised 416 patients with metastatic and previously treated renal cell carcinoma who had received prior sunitinib (44%) or sorafenib (14%) or both (26%) to receive everolimus plus best supportive care vs placebo plus best supportive care (BSC). The primary end point was progression free survival (PFS) as assessed by central review. The study was stratified as to whether one or two previous TKIs had been used. Updated analysis on an intention to treat basis demonstrated that PFS was significantly greater in the everolimus arm (4.9 vs 1.9 mo, Δ 3.0 mo, hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.25-0.43, p<0.001) and overall survival (OS) was not significantly different (14.8 vs 14.4 mo), respectively. The study was halted early. The CDF noted that 80% of placebo patients had crossed over to receive everolimus.
3. Toxicity was increased in the everolimus arm, the most common side-effects being infections, dyspnoea, stomatitis, rash, fatigue and diarrhoea. The CDF noted uncommon but serious pulmonary toxicity of everolimus.
4. There was no difference in general quality of life (QOL) scores between the two arms and thus QOL was maintained. QOL was assessed with the EORTC QLQ-C30 and FACT Kidney Symptom Index.
5. The median duration of treatment in the everolimus plus BSC arm was 20.1 weeks (4.7 mo).
6. The CDF examined the pre-planned subgroup analyses which examined PFS according to whether patients had been previously treated with sunitinib or one or two previous TKIs. For the 44% who had previously received sunitinib, the PFS was significantly different (3.9 vs 1.8 mo, Δ 2.1 mo, HR 0.34, 95% CI 0.23-0.51, p<0.001) respectively. For those patients treated with only one previous TKI (74%), the PFS was significantly superior with everolimus (5.4 vs 1.9 mo, Δ 3.5 mo, HR 0.32, 95% CI 0.24-0.43, p<0.001). For those patients treated with two previous TKIs (26%), the PFS was significantly superior with everolimus (4.0 vs 1.8 mo, Δ 2.2 mo, HR 0.32, 95% CI 0.19-0.54, p<0.001).
7. The manufacturer submitted survival data from the Motzer paper which had used the Rank Preserving Structural Failure Time model to allow for cross-over and which estimated the OS gain for everolimus to be 4.8 mo (14.8 vs 10.0 mo). The CDF noted the uncertainty in all methods which attempt to allow for cross-over and noted that the manufacturer had originally used a different method (the Inverse Probability of Censoring Weight method) in its first submission to NICE in order to allow for the effect of crossover.

8. The manufacturer also submitted a review which had examined the relationship between PFS and OS in renal cell cancer and had concluded that one month of incremental PFS translates to a 1.17 month gain in OS. The CDF noted that 48% of these studies were published before 2006; 45% of these studies were in previously treated patients; 23% of studies had allowed cross over to active treatment after disease progression; and in some of these, results were used from the various statistical methods applied to estimate the results of the trial had cross over not taken place. The CDF was therefore very unsure as to the robustness of this analysis and how the result of this review was applicable to 2nd line therapies.
9. The CDF was also aware that NICE had issued guidance with a positive recommendation for the use of axitinib in patients previously treated with a 1st line TKI as per axitinib's licensed indication which restricts use of axitinib to just the post-sunitinib population (ie the post pazopanib patients would not have received axitinib as a consequence of the licensed indication). NHS England has issued a treatment policy which extended the statutory funding direction to ensure that this recommendation covered patients previously treated with sunitinib or pazopanib. The CDF also then noted that both the NICE approval for 2nd line axitinib post 1st line sunitinib and the extension of this by NHS England to approve the use of axitinib post pazopanib trump 2nd line CDF everolimus as axitinib carries NICE approval in this setting whereas everolimus does not.
10. Thus, the CDF concluded in August 2015 that everolimus could not be used 2nd line after sunitinib or pazopanib and had previously considered the clinical impact of 3rd line after either sunitinib/pazopanib to be insufficient to merit retention within the CDF in January 2015.
11. The manufacturer submitted an abstract of a phase 2 study of 2nd line everolimus (the RECORD-4 trial). The CDF noted the results but did not consider that this trial offered a better assessment of the clinical impact of 2nd line everolimus. The manufacturer also submitted an abstract of a randomised controlled trial of 1st line everolimus followed by sunitinib vs 1st line sunitinib followed by everolimus (the RECORD-3 study). The trial was primarily designed to determine if 1st line everolimus is non-inferior to 1st line sunitinib. At the time only an abstract of the results of the trial was available and in terms of detail the CDF noted the observations by the Scottish Medicines Consortium that everolimus did not meet the predefined non-inferiority margin and so the primary outcome was not met. In addition, the SMC noted that a large number of cross over patients did not receive the planned therapy which made further analysis underpowered. The CDF did not consider that either of these above two studies described here contributed to its overall assessment of 2nd line everolimus.
12. The CDF recognised that there were other systemic therapies available in renal cancer and two of these were approved by NICE. It did not regard the benefits of everolimus in this indication to be a step change in the management of renal cancer when

considering the absence of proven survival benefit and the absence of any differential tail in the PFS curve over time.

13. In the light of the above considerations and rather exceptional circumstances, the CDF panel chose to use the subgroup analysis relating to whether patients had received one previous TKI. It noted that the degree of impact of everolimus on PFS was less according to the intention to treat analysis. The CDF noted the high degree of crossover and the fact that there were no approved therapies beyond second line therapy in renal cancer and was therefore prepared to assume that there was OS benefit of a similar degree to that observed for PFS.
14. The CDF (as has been stated above) recalled that axitinib had been approved by NICE as 2nd line treatment after 1st line therapy with a TKI and that in NHS practice this is likely to trump any CDF option as axitinib had been shown to be cost effective according to NICE's usual standards and everolimus had not. Clinicians are expected to take account of NICE guidance and to depart from it only for a sufficient reason. The CDF was also concerned that the CDF should not disrupt existing treatment pathways in the NHS, particularly where these result from the detailed evidence assessment which informs NICE guidance. As a consequence, the CDF did not approve the retention of everolimus in the CDF as 2nd line therapy for those patients who were eligible for axitinib. The CDF had previously removed the use of everolimus as 3rd line therapy and this remained the CDF's position.
15. The CDF also considered the clinical scenario in which a patient with renal cancer would not tolerate a 2nd line TKI as a consequence of previous hypertension, hand foot syndrome and bleeding with 1st line therapy. The panel considered that its assessment of 2nd line everolimus as set out above still applied to this situation and thus for those patients in which 2nd line axitinib is contra-indicated, use of everolimus as 2nd line therapy was retained in the CDF. The CDF also recognised that there would be some patients treated with 2nd line axitinib who would develop toxicities which would necessitate discontinuation of axitinib within 3 months of commencing the drug. In these patients, the CDF agreed to allow everolimus use provided that there was no evidence of disease progression in that 3 month treatment period with axitinib.
16. NHS England now notes that the treatment pathway for patients with advanced and previously TKI-treated renal cance may become more complicated with the potential inclusion of nivolumab for the TKI 1-prior and 2-prior populations, this being dependent on the currently running NICE appraisal. NHSE notes that the main evidence base for the benefit of nivolumab in renal cancer lies in a trial which compared nivolumab with everolimus. NHSE considers that any NICE recommendation for nivolumab within its licensed indication is likely to result in considerable use of nivolumab either as 2nd line treatment with axitinib being used 3rd line (as there is as yet no biological reason shown why axitinib should not work as well post-nivolumab as pre-nivolumab) or nivolumab used as 3rd line post-axitinib. Either

of these scenarios would displace any potential availability of everolimus to 4th line therapy.

17. NHS England notes that the relevance and importance of everolimus in the treatment of renal cancer has reduced, noting that the clinical expert input into the nivolumab appraisal clearly stated that there was clinical preference for the use of axitinib 2nd line rather than everolimus 2nd line. At present, the potential position of everolimus would be as 3rd line in the treatment pathway. This assessment may further change if nivolumab is recommended by NICE within its licensed indication and in which case everolimus would be positioned as a potential 4th line of treatment.
18. NHS England notes that everolimus is also being re-appraised by NICE within its licensed indication in breast cancer when it is used in combination with exemestane.
19. In summary, NHSE notes the modest clinical impact on PFS of everolimus at the expense of increasing toxicity but without impairing quality of life in patients with previously treated renal cancer. The key question remains as to its cost effectiveness, particularly in patients treated with several lines of systemic therapy.

[redacted]

[redacted]

September 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **NCRI-ACP-RCP-RCR** and consequently I will not be submitting a personal statement.

Name: .... [redacted]

Signed: .. [redacted]

Date: ..... [redacted]

Everolimus for the second-line treatment of advanced renal cell carcinoma

Rapid review

This report was commissioned by the NIHR HTA Programme as project number 16/51/01

BMJ Technology Assessment Group

Everolimus for the second-line treatment of advanced renal cell carcinoma – rapid review

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Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Contributions of authors:

Steve Edwards	Read and commented on draft versions of the ERG report. Guarantor of the report
Mariana Bacelar	Critical appraisal of the company's re-submission; critical appraisal of the economic model; critical appraisal of the economic and clinical evidence; carried out the economic analyses; and wrote the report.
Andrea Berardi	Read and commented on draft versions of the ERG report. Carried out the economic analyses.

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1 BACKGROUND

According to the submission template for the reconsideration of current Cancer Drugs Fund (CDF) technologies (hereafter referred to as the company submission) all cancer drugs that were previously appraised by NICE and are currently funded through the CDF will be reconsidered by NICE in line with the Guidance to the Methods of Technology Appraisal (2013) and the proposed new CDF criteria outlined in the CFD consultation paper.

The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance and the company evidence submission should focus on cost-effectiveness analyses using a new patient access scheme (PAS) or an amendment of a PAS previously used, which must be agreed with the Department of Health (DoH) or with NHS England. (CS).

The cost-effectiveness analysis submitted by the company must use the assumptions that determined the most plausible ICER(s) identified by the Appraisal Committee and presented in the published guidance (CS).

This rapid review re-assesses everolimus (Afinitor®, Novartis Pharmaceuticals), which currently does not have a recommendation for the second-line treatment of advanced renal cell carcinoma (RCC) in the UK,[1] and is funded through the CDF. Novartis has proposed a new PAS for everolimus (for all its current and future indications) and has also undertaken additional exploratory analysis comparing everolimus with axitinib, as agreed with NICE. In this report, the Evidence Review Group (ERG) looks at the new PAS submitted by the company as well as the exploratory analysis, providing a critique of the new evidence submitted to NICE.

2 DETAILS OF THE PATIENT ACESS SCHEME AND COMMERCIAL ACCESS AGREMENT

2.1 Technology

Everolimus is an active inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. Everolimus has a UK marketing authorisation for the treatment of patients with advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.

2.2 Patient access scheme

The PAS is a financially-based scheme, a simple discount to list price (fixed price which will not vary with any change to the UK list price). The PAS will apply to all supplies and preparations of Afinitor, applicable to all patients.

The PAS will be in place until a NICE review of the guidance for Afinitor. The PAS might be stopped if Novartis Pharmaceuticals UK Ltd decides to adjust the UK list price for Afinitor, so that the list price is the same as or less than that under this proposed patient access scheme. Any changes or termination of the scheme would be subject to agreement with the DoH.

The final PAS was agreed between Novartis and the Patient Access Scheme Liaison Unit (PASLU) and was set as a [redacted] simple discount.

The list price of everolimus during the development of TA219 was £2,970.(1) The original PAS consisted on [redacted]. The list price for everolimus has since then decreased and it is now £2,673. Therefore, the final price of everolimus with the new PAS applied corresponds to [redacted].

3 COST-EFFECTIVENESS

The company presented the changes made to the original base case model to align with the underlying assumptions in the most plausible ICER as determined by the Appraisal Committee and presented in published guidance.[1] These are reported in Table 1 below.

The population to whom the PAS applies is the same as that in the published TA219.[1] Furthermore, given that only the final price of everolimus is changed by the PAS, only drug acquisition costs for everolimus changed in the new base case results using the updated list price and updated PAS.

The ERG undertook a rapid assessment of the changes made in the company's updated model. However, given time and resource constraints and the complexity of some of the changes undertaken, such as using the Rank Preserving Structural Failure Time Model (RPSFTM) instead of Inverse Probability of Censoring Weight (IPCW) method to estimate effectiveness in the model, the ERG focused its efforts on assessing the plausibility of any model amendments and their impact on the final results. Given that the company's new base case ICER incorporating the Appraisal Committee changes is similar to the original ERG's proposed ICER in TA219[1] (Section 4 of this report), further and more detailed investigation of the economic model was not undertaken.

The ERG points out that some of the new sources for costs, such as adverse event costs, were not reported or justified in a systematic way. Nonetheless, given the proximity of the new base case ICER with the previous ERG ICER in TA219,[1] the impact of using the new sources for costs is unlikely to be of concern.

Table 1. Assumptions in the company's original and updated model

Assumption	Original company model	Appraisal Committee's preferred assumption
Mortality hazard rate multiplier	The hazard ratio (HR) multiplier was incorrectly applied to the transition probabilities in the placebo (i.e. BSC only) arm of the model. This multiplier had been applied directly to the transition probabilities, rather than first converting these probabilities to rates before multiplying and then converting the revised rates back into transition probabilities	The mortality rate multiplier is no longer in use and has been superseded by ERG revisions to transition probabilities.
Mortality hazard rate multiplier	In applying the HR multiplier to mortality probabilities in the BSC only arm, the model fails to account for increased death caused by greater progression in this arm.	The mortality rate multiplier is no longer in use and has been superseded by ERG revisions to transition probabilities.
Discount rates	Discounting after the first year	Discounting applied from the first cycle. Correction on worksheets "Per Patient Model (Afinitor)", "Per Patient Model (BSC)", "PP Afinitor Costs", "PP BSC Cost", Row 11. Correction on all "Markov (BSC)" and "Markov (Afinitor)" worksheets in the discounted values columns.
Adjustment for crossover	Original model used IPCW, and number of cycles increased for transition probabilities	RPSFT based transition probabilities with increased cycles used in line with ERG changes/recommendations. This involved Removal of sheets Markov Model (BSC) Markov Model (Afinitor) And replacement with sheets PP BSC Costs PP Afinitor Costs Markov Model (BSC) Markov Model (Afinitor)

<table>
<tr><td>Converting transition probabilities to rates before applying the multiplier (IPCW method)</td><td>Original model used transition probabilities</td><td>Replacement of original content from ‘transition probabilities’ and ‘TPs’ worksheets with ERG data containing RPSFT transition probabilities as per the ERG changes.</td></tr>
<tr><td>Unit costs</td><td>Original model used unit cost data that is now out of date</td><td>Updates to unit costs as below:

Worksheet “Treatment Costs”

<table>
<tr><th>Item</th><th>Cell</th><th>New input</th><th>Source</th></tr>
<tr><td>Afinitor</td><td>N17</td><td>=2673/30</td><td>BNF 70
10mg/tablet, 30 tablets price of £2673</td></tr>
<tr><td>General Practitioner Visit</td><td>D73, D80, D86, D93</td><td>=65</td><td>PenTAG report assumption: 1 GP visit per month; Curtis, 2015 (PSSRU unit costs) – Table 10.8b: Assumes a 17.2 minute clinic consultation.</td></tr>
<tr><td>Computed Tomography Scan</td><td>D74, D87</td><td>=124.31</td><td>PenTAG report assumption: 1 CT scan every 6 months; Sp. Code RD25Z, RD26Z and RD27Z (CT scan, three or more areas): 2014/15 NHS reference costs</td></tr>
<tr><td>Blood tests</td><td>D75, D81, D88</td><td>=3.01</td><td>PenTAG report assumption: 1 blood test on a monthly basis; Sp. Code DAPS05 (Haematology). 2014/15 NHS reference costs</td></tr>
<tr><td>Community Nurse Visit</td><td>D94</td><td>=78.67</td><td>PenTAG report assumption: 1.5 community nurse visits per month; Sp. Code N21AF- Specialist Nursing, Palliative/respite care: adult face-to-face; 2014/15 NHS reference costs</td></tr>
<tr><td>Pain killers: Morphine Sulphate injections</td><td>D95</td><td>=15</td><td>PenTAG report assumption: 1 dose per day (1 mg/ml, net price 10-ml vial prefilled syringe £30 per pack(10 ampoule))</td></tr>
</table>
</td></tr>
</table>

Death: Palliative care	D101	=3923*293.1/267	Coyle D et al. Costs of palliative care in the community, in hospitals and in hospices in the UK. Crit Rev in Oncol: haematology 32, 71-85, 1999 (inflated to 2008 of £3923 as per PenTAG report in the original model, and further inflated to 2014/15 of £4306.84 based on HCHS index from 2015 PSSRU)		

Worksheet "AE Costs"

AE	Cell	New input	Source
Anaemia	E4, E14	=(2494*0.785)/267*293.1	Mickisch G. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib. ASCO 2008 Poster: 5110. And inflated to 2014/15 of £2149.47 based on HCHS index from 2015 PSSRU)
Nausea / Vomiting	E8, E18	=(2803*0.785)*267/293.1	Mickisch G. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib. ASCO 2008 Poster: 5110. And inflated to 2014/15 of £2004.42 based on HCHS index from 2015 PSSRU)
Enrich Plus	J63	=3	http://www.chemistdirect.co.uk/ensure-plus-fibre-chocolate/prd-1cg
Metoclopramide, tablet	J67	0.37	BNF 70 28 tablets price £0.37
Metoclopramide, Injection	J69	=1.31/5	BNF 70 5 ampoule price £1.31, converted to per ampoule price
Dexamethasone, tablet	J73, J126	0.93	BNF 70 10mg/tablet, 28 tablets net price of £0.93
Dexamethasone, injection	J75, J128	=1.31/5	BNF 70 5mg/ml, 2ml-amposule: 5 ampoule price £1.31, converted to per ampoule price

		Megastrol Acetate	J82	=19.52	http://www.evidence.nhs.uk/formulary/bnf/current/8-malignant-disease-and-immunosuppression/83-sex-hormones-and-hormone-antagonists-in-malignant-disease/832-progestogens/megestrol-acetate Megace® (Swedish Orphan) 160mg/tablet, 30 tablets net price of £19.52
		Hospitalizations (for the treatment of Anorexia/Cachexia)	J95	=402.19	FCE-weighted average unit cost per day of FZ49E and FZ49H (NHS reference cost 2014/2015), Non-elective long-stay.
		Morphine soln (Oramorph)	J106	=8.5	BNF 70
		Lorazepam, tablet	J110	=2.65	BNF 70
		Lorazepam, injection	J111	=3.54/10	BNF 70 4mg/ml, 1ml/amp 10 ampoule price £3.54
		Hospitalizations (for the treatment of Dyspnea, Pneumonitis)	J115, J139	=417.98	Unit cost per day of NHS reference cost 2014/2015 DZ19L (Other Respiratory Disorders without Interventions, with CC Score 11+), Non-elective long-stay
		Temporary Ventilary Support (for the treatment of Dyspnea, Pneumonitis)	J116, J140	=20.82	Unit cost per hour of NHS reference cost 2014/2015 DZ37A, Non-Invasive Ventilation Support Assessment, 19 years and over
		O2 Therapy	J117	=0.76	"Domiciliary Oxygen Therapy." Regional Drug and Therapeutics Centre, June 2004; inflated to 2014/15 GBP using HCHS index from PSSRU
		Prednisolone	J131, J132	=1.48	BNF 70
		Ceftazidime	J149	7.9	BNF 70
		Meropenem	J150	=206.28/10	BNF 70: 10 vial price £206.28, converted to per vial price

Piperacillin/Tazobactam (Tazocin)	J151	=15.17	BNF 70
Fluconazale	J161	=29.28	BNF 70
Valacyclovir	J176	=86.3	BNF 70
Famciclovir, 250 mg/tablet	J179	=151.6	BNF 70
Famciclovir, 500 mg/tablet	J180	=207.86	BNF 70
Ganciclovir	J183	=148.83	BNF 70

Worksheet “Post-trial Costs”

Item	Cell	New input	Source
Xeloda (capecitabine)	C10	=20.58	BNF 70
Mobic (meloxicam)	C11	=1.11/30	BNF 70
Dexamethasone	C12	=49.56/50*5	BNF 70
Prednisolone	C13	=0.12	BNF 70
Thoracotomy	C14	=4964.49	NHS HRG Code DZ63C Major Thoracic Procedures, 19 years and over, with CC Score 0-2. 2014/15 NHS reference costs
Palliative Radiation Therapy	C15	=109.41	Barton 2000. Special Techniques in Palliative Radiotherapy. External beam radiation therapy given in 5 fractions over two weeks. NHS HRG Code SC22Z: Deliver a fraction of therapy on a megavoltage machine. 2014/15 NHS reference costs

Access scheme	Initial cycles at zero cost of everolimus had been hard-coded and were removed, replaced with full costs of treatment.	In the 'Markov Afinitor' and 'Markov BSC' sheets this affects cells Q8 and U8 which were set to zero everolimus costs; these are now replaced with the formulas from the cells below, calculated everolimus costs and total costs based on all patients in PFS receiving everolimus at cost.
Calculation of everolimus cost	Correction to calculation of everolimus cost on the 'Treatment cost' sheet.	Everolimus price and total costs were hard-coded in the 'Treatment costs' sheet in cells H6 and E12 (now in different cell references in the new model, but still on 'Treatment costs' sheet, in cells N17 and D69).

4 RESULTS

In this Section, the ERG reports the results for everolimus with the original PAS (Table 2), the results for everolimus with the original PAS and the updated everolimus list price (Table 3) and finally the results with the new PAS (Table 4). All model results are based on the updated model submitted by the company and are reflective of the Appraisal Committee preferred assumptions in TA219.[1]

In Table 2, the results for the updated model and the original PAS (equivalent to a [redacted]) present an ICER of £58,316 QALY gained, which compares to the ICER of £58,300 per QALY gained concluded to be the most plausible ICER by the Committee in TA219.[1]

Table 3 reports a lower ICER, which is expected given the decrease in the list price of everolimus from £2,970 to £2,673.

Table 4 presents the updated ICER, with the new [redacted] PAS incorporated. The resulting ICER is considerably lower than the ICERs reported in Table 2 and Table 3 which reflects the drop in price for everolimus from £2,673 to [redacted].

Table 2. New base case results and original PAS

	Everolimus	BSC
Intervention cost (£)	19,714	N/A
Other costs (£)	16,766	17,494
Total costs (£)	36,480	17,494
Difference in total costs (£)	N/A	18,986
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326
ICER (£/QALY)	N/A	58,316
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years.		

Table 3. New base case results using updated list price and original PAS

	Everolimus	BSC
Intervention cost (£)	17,743	N/A
Other costs (£)	16,765	17,494
Total costs (£)	34,508	17,494
Difference in total costs (£)	N/A	17,014
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326

	Everolimus	BSC
ICER (£/QALY)	N/A	52,261
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years.		

Table 4. New base case results using updated list price and updated PAS

	Everolimus	BSC
Intervention cost (£)	[redacted]	N/A
Other costs (£)	16,765	17,494
Total costs (£)	[redacted]	17,494
Difference in total costs (£)	N/A	[redacted]
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326
ICER (£/QALY)	N/A	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years.		

4.1 Sensitivity analysis

The company did not provide any details on how the probabilistic sensitivity analysis (PSA) was conducted (other than reporting that 2,000 iterations were ran). The probabilistic ICER along with the scatter plot for the ICERs and the cost-effectiveness acceptability curve (CEAC) graphs were also provided.

The ERG inspected the PSA in the Excel model and concluded that the company appears to have ran a patient simulation model to vary how patients move through the model in each simulation, through the variation of effectiveness estimates. The ERG has some doubts on the reliability of the PSA reported by the company. When examining the procedure, the ERG noted an issue with the implementation in the PSA as costs were not varied in the analysis because of a programming mistake. However, once the ERG corrected this problem, the results were very similar to those reported by the company.

It would also appear that the Gamma distribution used to vary costs does not allow for much variability of health state costs (once the programming mistake was corrected by the ERG). The ERG produced Table 6, showing the costs that were varied in the company's analysis, together with the standard deviation, the median and the maximum and minimum costs used in the PSA. It can be observed (as also noted in Figure 1) that the variation allowed was very limited (with no justification provided), therefore potentially underestimating the amount of uncertainty related with costs in the model. Furthermore, everolimus' list price and the PAS discount seem to vary in the PSA. This should not

happen as the drug price and its discount are not uncertain parameters. It would also appears that the utility values were not varied in the analysis.

Finally, it can also be noted from Figure 2 that at a [redacted].

The company submitted an updated model with an updated PSA, which the ERG did not have time to review. The updated probabilistic ICER is [redacted] per QALY gained.

Figure 1. Incremental cost-effectiveness ratios

[redacted]

Figure 2. Cost-effectiveness acceptability curve

Table 5. Probabilistic results

	Everolimus	BSC
Intervention cost (£)	[redacted]	N/A
Other costs (£)	16,755	17,732
Total costs (£)	[redacted]	17,732
Difference in total costs (£)	N/A	[redacted]
LYG	1.166	0.741
LYG difference	N/A	0.425
QALYs	0.845	0.522
QALY difference	N/A	0.323
ICER (£/QALY)	N/A	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years.

Table 6. Variation in costs in company's PSA

	AE costs (everolimus)	Nurse and GP costs (pre-progression)	Nurse and GP costs (post-progression)	Palliative care	Terminal care	Tests (pre-progression)	Post-trial Rx	AE costs (BSC)
Minimum	£675.19	£120.79	£352.21	£877.57	£4,256.14	£4.20	£2,421.74	£225.28
Maximum	£720.19	£138.65	£380.67	£924.28	£4,360.24	£8.14	£2,512.02	£251.22
Median	£700.66	£130.19	£366.36	£899.79	£4,305.96	£6.01	£2,460.38	£237.39
Mean	£700.68	£130.17	£366.21	£899.99	£4,306.17	£6.01	£2,460.22	£237.32
Standard deviation	£6.53	£2.75	£4.62	£7.33	£15.67	£0.60	£12.32	£3.78

5 ADDITIONAL EXPLORATORY ANALYSIS UNDERTAKEN BY THE COMPANY

In their re-submission the company acknowledged that, given the evolution of clinical practice in the UK, BSC is no longer the standard of care for advanced RCC but instead axitinib should be considered as such. The company states that the additional analysis presented is only exploratory and therefore only key results were presented. The ERG notes that no electronic models were provided alongside the additional exploratory analysis. In this Section, the ERG presents the company's analysis and interpretation alongside with the ERG's critique to the submitted evidence.

5.1 Clinical effectiveness

The data used to inform the exploratory analysis came from the RECORD-1 and the AXIS trials. The company found no head-to-head comparison studies for everolimus and axitinib, which is consistent with the ERG's experience in the RCC evidence base. Table 7 reports the treatment regimens in the AXIS and RECORD-1 trials.

5.1.1 Progression-free survival data

The company undertook a matched indirect comparison analysis to compare PFS between everolimus and axitinib for the second-line treatment of advanced RCC by using a weighted-adjusted comparison to align patient's characteristics between the two cohorts. Individual patient-level data (IPD) from RECORD-1 were used to perform a matched indirect comparison with the AXIS cohort, for which only summary outcome measures are available. The company stated that this methodology had been published by Signorovitch *et al.* (2012) and by the ISPOR Task Force. The company decided to use the subgroup of patients from each trial who had previously received sunitinib, as it was believed that prior treatment could influence the response to second-line therapy. This resulted in 43 patients being selected from the RECORD-1 (n=277) trial and 194 patients from the AXIS trial (n=361). The company stated that this approach was adopted in order to ensure statistical rigour but that the analysis could be generalised to the overall everolimus population in routine clinical practice, as the results were not expected to be significantly different to the results of the current analysis.

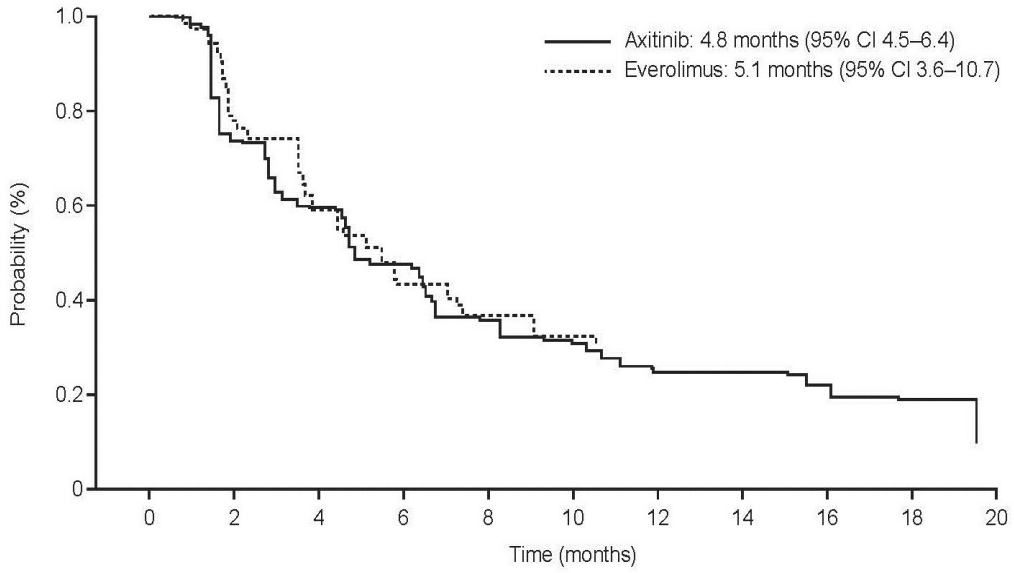
After weighting, the median PFS for weighted everolimus patients was 5.1 months (95% CI: 3.6–10.7), similar to that reported for axitinib patients (4.8 months [95% CI: 4.5–6.4]).

The company reported the Kaplan Meier curve for PFS for the weighted analysis of everolimus and axitinib (**Figure 3**). The company concluded that everolimus had a slightly better PFS compared with axitinib after the matching.

Table 7. AXIS and RECORD-1 trials

Trial name	Treatment arms	Previous treatment	Line of treatment
AXIS[2]	Axitinib vs sorafenib	Sunitinib, cytokines, bevacizumab, temsirolimus	Second-line
RECORD-1[3]	Everolimus plus BSC vs placebo plus BSC	Sunitinib, sorafenib, cytokines interferon, interleukin-2, bevacizumab	Second-line
Abbreviations in table: BSC, best supportive care.			

Figure 3. Kaplan-Meier progression-free survival curves for axitinib and weighted everolimus patients



The ERG notes that no additional details were provided on the matching-adjusted indirect comparison (MAIC) analysis undertaken by the company. This prohibited the ERG from performing a detailed evaluation of the methods employed. Furthermore, the reference made by the company, Signorovitch *et al.* (2012), was not provided as a full reference, therefore the ERG could not be sure which paper it referred to.

At face value, the clinical results obtained by the company suggest that everolimus and axitinib have similar PFS outcomes. The ERG therefore disagrees with the company conclusion that everolimus has slightly better PFS compared with axitinib after the MAIC analysis. The ERG found another source of published evidence funded by Novartis, using the same MAIC method and looking at the comparative effectiveness of everolimus and axitinib (Sherman 2015)[4]. The study reached the conclusion that

everolimus and axitinib have similar efficacy with a median PFS of 4.7 months (95% CI 3.5 to 10.6) for everolimus and 4.8 months (95% CI 4.5-6.4) for axitinib. This compares to 5.1 months (95% CI: 3.6–10.7) for everolimus and to 4.8 months (95% CI: 4.5–6.4) for axitinib in the company's analysis.

The ERG also notes that the company used the MAIC method instead of a network meta-analysis (NMA) without providing any justification for the use of the former. While the ERG can see some of the benefits of using the MAIC method given the available data (as it can make use of richer data such as IPD), it also carries disadvantages. Some of the discussed disadvantages of the MAIC method are for example, the limited possibility of always matching outcome definitions or inclusion/exclusion criteria between studies through the use of IPD and the need for having a sufficient number of patients in trials with IPD. In fact, two limitations acknowledged by Sherman *et al.* 2015[4] in their analysis are the differences in the Memorial Sloan-Kettering Cancer Centre (MSKCC) risk score calculations between the AXIS and the RECORD-1 trials, a baseline prognostic variable used in the weighting algorithm, and the small sample size in the everolimus IPD analysis, which may have adversely affected the ability to obtain exact distributional matches after weighting.

5.1.2 Overall survival data

The company considered that OS data from AXIS and RECORD-1 could not be indirectly compared and therefore OS was assumed to be the same for both drugs. Data informing OS for both everolimus and axitinib in the base case analysis were based on the RECORD-1 OS data. The company considered this to be a reasonable assumption given that the independent trials (RECORD-1 and AXIS) showed a median OS of 19.77 months for everolimus after adjusting for crossover and 20.1 months for axitinib.

The company considered that OS data from the RECORD-1 and AXIS trials could not be indirectly compared because both trials did not show a statistically significant result in OS and thus any results from an indirect analysis would be misleading. In addition, patients in both trials received different subsequent therapies after progression, which would make the matching of these treatments impossible.

The ERG disagrees that the lack of statistically significance in OS outcomes in the AXIS and RECORD-1 trials renders an indirect comparison analysis misleading. However, caution would have to be taken when using the two trials for an indirect comparison, considering the presence of cross-over in RECORD-1 and the difference in subsequent therapies received by progressed patients in the AXIS trial. Nonetheless, the ERG finds that the assumption of similar OS between everolimus and axitinib is not unreasonable and is in line with clinical expert opinion.

5.2 Cost-effectiveness

The company reported using a Markov model with an area under the curve (AUC) approach to assess the cost-effectiveness of everolimus compared with axitinib. It is also stated that the model had three

health states, even though these are not reported. The ERG assumes the health states included are stable disease, progressed diseased and death. The company reported some of the key features of the economic analysis (Table 8) as well as the model inputs used (Table 9).

Table 8. Model key features

Factor	Chosen values	Justification
Time horizon	Lifetime (12 years)	To capture all relevant health consequences and costs
Cycle length	30.42 days (the average number of days per month)	Appropriate to provide sufficient granularity to capture patient movement between health states
Measurement of health effects	Health effects were measured as incremental cost per LYG as well as per QALY gained	To ensure that both quantity and quality of life were captured
Discounting for costs and efficacy	Costs and efficacy were discounted at 3.5%	To reflect positive time preference in line with NICE reference case
Perspective	NHS/PSS	As per NICE reference case
Abbreviations in table: LYG, life years gained; NHS, National Health Service; PSS, Personal Social Services.		

Table 9. Model inputs

Parameter	Description	Justification
Treatment efficacy (PFS and OS)	PFS data based on the indirect analysis of the RECORD-1 and AXIS trials. For OS, data from the RECORD-1 (unadjusted for crossover) and AXIS trials could not be indirectly compared and therefore an assumption of equal OS for everolimus and axitinib is applied. The Weibull survival distribution was chosen for both PFS and OS	The Weibull survival distribution was chosen because the extrapolation was a good fit with the data and its long term survival projection was in line with the survival of patients with advanced RCC on active treatment in clinical practice
Utilities	Utilities derived Swinburn *et al.*, (2010) Stable disease: 0.795 Diseases progression: 0.355	Most appropriate utilities identified in the systematic review
Treatment dosing	Active treatments: Everolimus: 10 mg once daily Axitinib: 5 mg twice daily Post-progression treatments: Treatments were based on those for the everolimus arm in RECORD-1 and the axitinib arm in AXIS (from the ODAC briefing document)	Dosing for everolimus and axitinib was based on the RECORD-1 and AXIS trials, respectively, and corresponds to recommended dosing for each therapy
Dose intensity	Active treatments: Everolimus: 88% (mean dose intensity across all patients calculated using patient-level data for the matched population from the RECORD-1 trial) Axitinib: 102% (mean dose intensity obtained from the axitinib ODAC briefing document)	Based on data from large randomised studies for the interventions of interest
Duration of active treatment	Everolimus: 4.08 months (calculated from the RECORD-1 trial) Axitinib: 6.67 months (obtained from the axitinib ODAC	Based on data from large randomised studies for the interventions of interest

Parameter	Description	Justification
	Briefing Document	
Resource utilisation	Per-patient-month resource utilisation rates (aside from AEs and post-progression treatments) were derived from the PenTAG Report and RECORD-1 publication	Model resource utilisation assumptions were based on the medical management of patients with RCC treated with sunitinib, sorafenib, temsirolimus and bevacizumab, as described in the PenTAG report
Abbreviations in table: AE, adverse event; ODAC, Oncologic Drug Advisory Committee; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.		

The company explained that survival functions for PFS for everolimus were based on the indirect comparison using patient-level data from RECORD-1 among patients who failed prior sunitinib therapy. Survival functions for PFS for axitinib were derived from the AXIS trial. The company reports that six distributions were tested to determine the best fit for the survival functions for PFS and OS: Weibull, log-normal, exponential, log-logistic, Gompertz, and piecewise exponential. It is also reported that visual fits as well as goodness-of-fit statistics were generated to determine the best fit to the efficacy data even though none of these were presented in the company's exploratory analysis.

The company reported that clinical validation to determine the survival distribution that most closely resembled the survival of this patient group in clinical practice was sought from published literature and that the Weibull was considered to be the best survival distribution for both PFS and OS.

Without having access to any of the fitted curves and the goodness-of-fit statistics, the ERG cannot assess the appropriateness of the Weibull distribution. Even though the Appraisal Committee for TA219[1] considered Weibull to be the most appropriate distribution for modelling survival outcomes, this offers little (if any) validation to the use of the Weibull in this analysis given the difference in data used.

A quick review of TA219[1] and TA333[5] showed that, while the utility value chosen for the stable disease state is in line with previously used values, the utility score associated to the progressed disease state (0.36) was considerably lower than the utilities used in previous TAs for everolimus (0.68) and axitinib (0.61).

Treatment regimens of 10 mg orally every day for everolimus and 5 mg orally twice a day for axitinib are in line with the trial data and with recommended doses. The ERG notes that in the UK there are no NICE-approved subsequent treatment line for advanced RCC after second-line treatment, therefore any analysis including post-progression treatments (such as the analysis submitted by the company) needs to be interpreted with caution.

A mean dose intensity of 88% was assumed for everolimus patients and 102% for axitinib patients (same as in TA333[5]). The ERG is not clear why 88% was the chosen value given that the mean dose intensity for everolimus was 91.8% in TA219[1] (based on RECORD-1). Assuming an 88% dose intensity for everolimus and 102% for axitinib will have a direct (and likely considerable) impact in the estimation of drug costs and consequently in potential cost savings. Therefore the company should have used the 91.8% dose intensity regimen and conducted sensitivity analysis assuming 100% of dose intensity for everolimus.[1]

5.2.1 Cost-effectiveness results

The company reported the cost-effectiveness analysis results, replicated in Table 10. Table 11 presents the company's analysis using different distributions to fit PFS data and also a scenario analysis applying [redacted].

Table 10. Base case analysis: everolimus vs axitinib: list prices

	Everolimus	Axitinib
Total costs (£)	23,576	42,533
Difference in costs (£)	18,956	
Total LYG	1.170	1.170
LYG difference	0	
Total QALYs	0.649	0.631
QALY difference	0.017	
ICER (£)	Everolimus dominant (-1,095,808)	
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.		

Table 11. Scenario analysis

Parameter	Base case value	Explored value	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case			**–18,956**	**0.017**	Dominant
Method of extrapolating PFS	Weibull	Log normal	–21,196	0.093	Dominant
		Gompertz	–19,666	0.055	Dominant
		Exponential	–19,679	0.056	Dominant
		Piecewise exponential	–20,992	0.087	Dominant
		Log logistic	–21,241	0.092	Dominant
Scenarios applying a discount for everolimus and variable discounts for axitinib (everolimus vs axitinib)					
Vary axitinib discount	[redacted]	[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]

Parameter	Base case value	Explored value	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
		[redacted]	[redacted]	0.017	[redacted]
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PFS, progression-free survival; QALY, quality-adjusted life year.					

The company concluded that, at full list price for both treatments, everolimus dominated axitinib in all survival extrapolation scenarios. [redacted] The company considered that the key drivers of the analysis were:

- Axitinib costs compared with everolimus,
- The fact that treatment duration for axitinib was almost 1.6 times longer than that of everolimus based on RECORD 1 and AXIS trial data. This was because patients in the AXIS trial received a higher than planned dose of axitinib thus resulting in a dose intensity of 102%. The SmPC for axitinib states that, for patients who tolerate axitinib, the dose can be escalated to a maximum of 10 mg twice daily.[6] This means that over the treatment duration, a proportion of patients may receive 20mg per day. The company reported that in the AXIS trial, at least 37% of patients were dose escalated to higher doses per day. The company also added that this has significant implications on the treatment costs associated with axitinib over the course of treatment but that the impact of dose escalation was not captured in the company analysis.

The ERG considers that there are too many "black boxes" in the company's analysis of cost-effectiveness. Therefore, assuming that PFS and OS are equal for both axitinib and everolimus is a plausible simplification that can potentially aid the Appraisal Committee in their decision making. The company undertook a cost-minimisation analysis, reproduced in Section 5.2.2 by the ERG. The ERG also conducted a cost-minimisation analysis to overcome some of the uncertainty in the company's analysis.

5.2.2 Cost minimisation

Table 12 shows the list prices for axitinib and everolimus. In their analysis, the company reported that the monthly cost for axitinib is £3,820, compared with £2,673 for everolimus. When the company assumed equal effectiveness for OS and PFS for axitinib and everolimus, it was concluded that [redacted]

[redacted] (Appendix A of CS).

The ERG is not clear on how the company reached these values and notes that the cost minimisation analysis was mainly dependant on the assumptions for treatment duration, dose intensity and the PASs applied. The dose of axitinib is also a relevant point, given that patients could receive up to 20mg per day.

Table 12. List price of axitinib and everolimus

Drug	Formulation (mg)	Vials/tabs per pack	Price per vial/pack	Price per tab	Price per day	Source for price
Everolimus	10	30	£2,673.00	£89.1	£89.1	BNF 2016[7]
Axitinib	5	56	£3,517.00	£62.804	£125.61	BNF 2016[7]
Abbreviations in table: mg, milligram; tabs, tablets.						

Given that there are no NICE-approved third and further lines of treatment in the UK, and assuming similar PFS for everolimus and axitinib, it could be assumed that patients are on treatment for the same period of time with both drugs, discontinuing the drug after disease progression. Therefore, the ERG ran a scenario analysis where treatment duration for axitinib and everolimus is assumed to be the same.

Dose intensity is also a key factor in determining the incremental cost for everolimus compared with axitinib. The ERG does not agree with the use of 88% dose intensity given that the mean dose intensity for everolimus was 91.8% in TA219[1] (based on RECORD-1). Therefore, the ERG ran a scenario analysis using a dose intensity for everolimus of 91.8% and of 100% to reflect a scenario where all patients receive everolimus. The dose intensity for axitinib is 102% as per TA333.[5]

Table 13 and Table 14 present the ERG's scenario analysis, which compares the cost of 5 months treatment with everolimus and axitinib.

If the dose for axitinib increases up to 20mg per day, then the discount levels needed for axitinib to be cost saving in comparison with everolimus would increase.

Table 13. Axitinib cost for different discount levels

Axitinib discount	Axitinib cost
10%	£17,585
15%	£16,608
20%	£15,631
25%	£14,654
30%	£13,677

Axitinib discount	Axitinib cost
35%	£12,700
40%	£11,723
45%	£10,746
50%	£9,769
55%	£8,792
60%	£7,815
65%	£6,839
70%	£5,862
75%	£4,885
80%	£3,908
85%	£2,931
90%	£1,954

Table 14. Everolimus cost with PAS applied for different dose intensity

[redacted]	Everolimus dose intensity
[redacted]	100%
[redacted]	91.8%

6 END OF LIFE

Second-line treatment with everolimus was considered to meet the end-of-life criteria for advanced RCC in TA219.[1] The Appraisal Committee noted that the total number of people in England and Wales who would be eligible for treatment with everolimus was less than 4,000. The Committee also noted that the life expectancy for people with advanced RCC receiving BSC alone was unlikely to be greater than 24 months and was potentially as low as 5 months, according to clinical specialist comments. The evidence from the RPSFTM OS analysis suggested that everolimus increased survival by more than 3 months compared with BSC (Appendix A of CS).

With regards to the updated economic analysis re-submitted by the company, the ERG believes that the end-of-life criteria should still be met by second-line everolimus when compared with BSC.

However, survival was assumed the same for everolimus and axitinib in the company's exploratory analysis comparing the two drugs. Therefore when everolimus is compared with axitinib, there is no expected survival benefit for patients with advanced RCC receiving everolimus thus the end-of-life criteria is no longer met by everolimus when compared with axitinib.

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Everolimus for the second-line treatment of advanced renal cell carcinoma - CDF reconsideration of TA219

Confidential appendix 2

This report was commissioned by the NIHR HTA Programme as project number 16/51/01

BMJ Technology Assessment Group

Summary of the document

The ERG produced this confidential appendix to provide the Technology Appraisal Committee with the results of the ERG's cost comparison analysis for everolimus vs. axitinib applying the confidential patient access scheme (PAS) for everolimus and the list price for axitinib. The official PAS discount applied is reported in Table 1 while the list price for axitinib is reported in Table 2.

Table 1. Official PASs applied in the economic model

Technology	PAS	
	Type	Amount
Everolimus	Discount	[redacted]
Abbreviations in table: PAS, patient access scheme.		

Table 2. List price of axitinib and everolimus

Drug	Formulation (mg)	Vials/tabs per pack	Price per vial/pack	Price per tab	Price per day	Source for price
Axitinib	5	56	£3,517.00	£62.804	£125.61	BNF 2016
Abbreviations in table: mg, milligram; tabs, tablets.						

Given that there are no NICE-approved third and further lines of treatment in the UK, and assuming similar PFS for everolimus and axitinib, it was assumed that patients are on treatment for the same period of time with both drugs, discontinuing the drug after disease progression. Based on the Sherman 2015[4] paper results (PFS of 4.7 months [95% CI 3.5 to 10.6] for everolimus and 4.8 months [95% CI 4.5-6.4] for axitinib) and the company's cost-effectiveness analysis (PFS 5.1 months [95% CI: 3.6–10.7] for everolimus and 4.8 months [95% CI: 4.5–6.4] for axitinib, the ERG has used 5 months as an estimate for treatment duration.

Table 2 presents the total costs for everolimus and axitinib, assuming 5 months of treatment with both treatments. Results are presented assuming a dose intensity for everolimus of 91.8% (as per TA219) and of 100% to reflect a scenario where all patients receive everolimus. The dose intensity for axitinib is 102% as per TA333.

Table 3. Total cost for everolimus and axitinib with PAS included for everolimus

Technology	**Total cost (with PAS for everolimus)**
Everolimus (100% dose intensity)	[redacted]
Everolimus (91.8% dose intensity)	[redacted]
Axitinib	£19,539
Abbreviations in table: PAS, patient access scheme.	

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Everolimus for the second-line treatment of advanced renal cell carcinoma

You are asked to check the ERG report from BMJ Technology Assessment Group (BMJ-TAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Wednesday 10 August 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Level of PAS discount

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Patient Access Scheme Liaison Unit (PASLU) PAS proposal template submitted by the company, the proposed discount was not specified. Novartis states that the estimated discount is between [redacted], depending on the results of the cost-effectiveness analysis presented to NICE. Nonetheless, the results of the economic analysis submitted by the company (and presented in Section 3 of this report) are based on a [redacted] PAS discount on the new list price of everolimus	[redacted].	[redacted].	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.

Issue 2 PAS price

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The list price of everolimus during the development of TA219 was £2,970.(1) The original PAS consisted on [redacted]. The list price for everolimus has	[redacted].	[redacted]	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.

since then decreased and it is now £2,673. Therefore, the final price of everolimus with the new PAS applied corresponds to [redacted].		[redacted].	

Issue 3 Level of PAS discount

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 4 presents the updated ICER, with the new [redacted] PAS incorporated. The resulting ICER is considerably lower than the ICERs reported in Table 2 and Table 3 which reflects the drop in price for everolimus from £2,673 to [redacted]. **Table 4. New base case results using updated list price and updated PAS** [redacted] Abbreviations in table: BSC, best supportive care; ICER,	[redacted].	[redacted].	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.

	Everolimus	BSC
Intervention cost (£)	[redacted]	N/A
Other costs (£)	16,765	17,494
Total costs (£)	[redacted]	17,494
Difference in total costs (£)	N/A	[redacted]
LYG	1.169	0.738
LYG difference	N/A	0.431
QALYs	0.843	0.517
QALY difference	N/A	0.326
ICER (£/QALY)	N/A	[redacted]

incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years.			

Issue 4: Sensitivity analyses (section 4.1)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It would also appear that the Gamma distribution used to vary costs does not allow for much variability of health state costs (once the programming mistake was corrected by the ERG). The ERG produced Table 6, showing the costs that were varied in the company's analysis, together with the standard deviation, the median and the maximum and minimum costs used in the PSA.	See additions/edits in bold and italics below: It would also appear that the Gamma distribution used to vary costs does not allow for much variability of health state costs (once the programming mistake was corrected by the ERG). The ERG produced Table 6, showing the costs that were varied in the company's ***replication of the original ERG's analysis***, together with the standard deviation, the median and the maximum and minimum costs used in the PSA. It can be observed (as also noted in Figure 1) that the variation allowed was very limited (with no justification provided), therefore potentially underestimating the amount of uncertainty related with costs in the model. Furthermore, everolimus' list price and the PAS discount seem to vary in the PSA.	Novartis suggests that the ERG revise this paragraph with the proposed amendments. This is because the PSA was implemented as per the previous ERG's recommendations. The previous ERG updated the PSA in the model and because of the nature of the rapid review process, Novartis had to replicate the original ERG updates to the PSA. Thus it is inaccurate for the current ERG to lay blame on Novartis when the rapid review process only allowed replication of the original analysis.	Not a factual error.

Issue 5: Interpretation of the results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Finally, it can also be noted from Figure 2 that the CEAC is not very informative in this case. At a [redacted].	Finally, ***the CEAC***~~it can also be noted from~~ ***in*** Figure 2 ~~that the CEAC is not very informative in this case.~~ ***shows that*** at a [redacted].	The proposed amendment accurately reflects the results from the CEAC. It also makes sense to use an upper WTP threshold of £50K per QALY given that this is the level for EOL medicines (the ERG has acknowledged that everolimus meets EOL). The £40K threshold used by the ERG seems arbitrary and will not be useful for decision making.	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis. The CEAC curve has been updated and the respective changes in text requested by the company have been made.

Issue 6: With PAS results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Tables 5,6, 11,14 and figure 4	[redacted]	See earlier justification on this issue. All current results and figures that include the new PAS are inaccurate. Please note that Novartis shared an updated submission package with NICE [redacted].	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.

Issue 7: Description of the with PAS results/analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The company reported the cost-effectiveness analysis results, replicated in Table 10. Table 11 presents the company's analysis using different distributions to fit PFS data and also a scenario analysis applying [redacted].	[redacted].	See earlier justification under level of PAS discount. Please note that Novartis shared an updated submission package with NICE [redacted].	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.
Table 12 shows the list prices for axitinib and everolimus. In their analysis, the company reported that the monthly cost for axitinib is £3,820, compared with £2,673 for everolimus. When the company assumed equal effectiveness for OS and PFS for axitinib and everolimus, it was concluded that [redacted] (Appendix A of CS).	[redacted].	See earlier justification under level of PAS discount. Please note that Novartis shared an updated submission package with NICE [redacted].	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.
Table 13 and Table 14 present the ERG's scenario analysis, which compares the cost of 5 months treatment with everolimus and axitinib. If we assume a dose intensity of 100% for everolimus, then axitinib becomes less expensive than everolimus at a [redacted] discount level [redacted]. If we assume a dose intensity of 91.8%, then axitinib becomes cost saving at a discount level of [redacted] ([redacted]).	[redacted]. Please remove the scenario analysis using 100% dose intensity	See earlier justification under level of PAS discount. Please note that Novartis shared an updated submission package with NICE [redacted]. Novartis does not agree with the use of 100% dose intensity. The	The ERG acknowledges the change in the PAS agreed between the company and the Department of Health and has replaced the previous PAS discount of [redacted] by the updated PAS of [redacted] in the report and economic analysis.

		pivotal trial dose intensity was 91.8% and this is the average dose that underpins the efficacy results of this indication. The use of 100% dose intensity is subjective and only serves to artificially inflate the treatment costs of everolimus.	Regarding the scenario analysis using 100% dose intensity for everolimus, the ERG points to the fact that this is an exploratory analysis and it is not factually incorrect.

Issue 8: Description of cost effectiveness analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG considers that there are too many "black boxes" in the company's analysis of cost-effectiveness. Therefore, assuming that PFS and OS are equal for both axitinib and everolimus is a plausible simplification that can potentially aid the Appraisal Committee in their decision making.	~~The ERG considers that there are too many "black boxes" in the company's analysis of cost-effectiveness.~~ Therefore, assuming that PFS and OS are equal for both axitinib and everolimus is a plausible simplification that can potentially aid the Appraisal Committee in their decision making.	Novartis believes it is misleading and factually inaccurate for the ERG to allege "black boxes" in the company's analysis of cost effectiveness. The analysis for everolimus vs BSC is solely based on the Committee's preferred assumptions and the changes made by the original ERG. The second exploratory analysis is based on an assumption of equal OS for both everolimus and axitinib and a small QALY gain for everolimus in the pre-progressed state of the model with the main driver of cost effectiveness being treatment costs. Novartis believes the analyses conducted were either in line with the rapid review process requirements or straightforward and therefore suggest the ERG removes the "black box" statement from the ERG report.	Not a factual error.