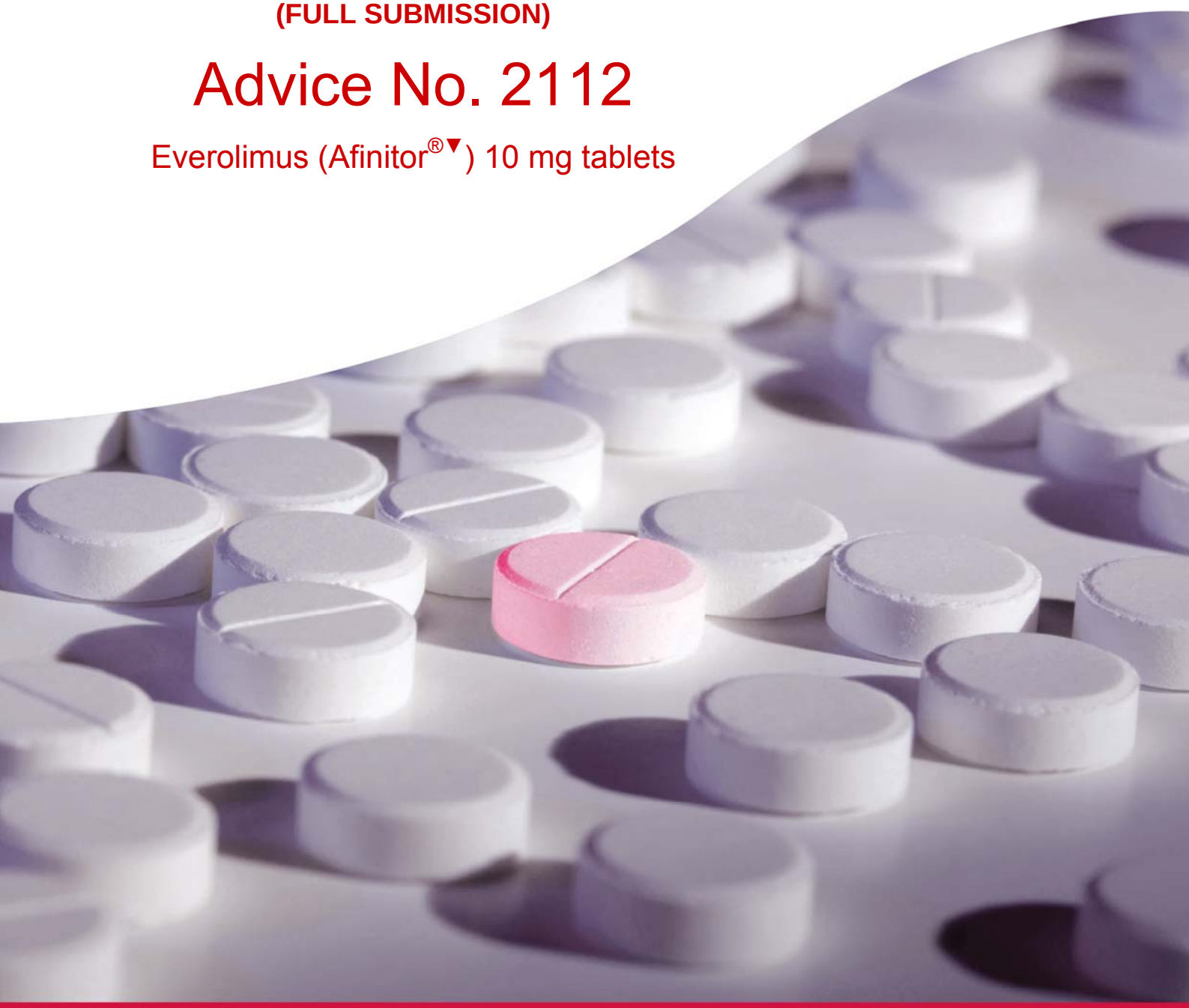
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 2112

Everolimus (Afinitor®▼) 10 mg tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 2112
Everolimus (Afinitor®▼) 10 mg tablets

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd on 29 February 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration[2]	Everolimus (Afinitor®▼) is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.
Dosing[2]	The recommended dose is 10 mg once daily. Treatment should continue as long as benefit is obtained or until unacceptable toxicity occurs. Management of severe and/or intolerable suspected adverse reactions may require dose adjustments. Refer to the Summary of Product Characteristics for recommendations on other groups in which dose adjustments are required.
Marketing authorisation date[3]	Date of licence extension: 24 August 2011 (licensed for the treatment of patients with advanced renal cell carcinoma on 3 August 2009).

2.0 DECISION CONTEXT

2.1 Background

Pancreatic neuroendocrine tumours (pNETs), sometimes referred to as islet cell tumours, arise from pluripotent cells within the exocrine pancreas[4]. These tumours are uncommon: the UKNETwork for neuroendocrine tumours has reported an annual incidence of 0.2–0.4 per 100,000[5].

The majority of pNETs diagnosed are malignant, but are typically slow-growing and have low mitotic activity[6]. pNETs are often described as functional or non-functional: functional pNETs produce excess amounts of a specific hormone and are named accordingly (e.g. insulinomas, gastrinomas, somatostatinomas, glucagonomas or VIPomas [vasoactive intestinal peptide]), whereas non-functional pNETs present with non specific symptoms[6–8]. pNETs are further classified according to their malignancy:

- well-differentiated neuroendocrine tumours (benign or low-grade malignant);
- well-differentiated neuroendocrine carcinomas (low-grade malignant);
- poorly differentiated neuroendocrine carcinomas (high-grade malignant)[7].

Until recently, there has been no well-defined standard of care for pNETs, with surgery the only curative treatment, and patients ineligible for surgery receiving palliative care[5,7]. In November 2010, sunitinib (Sutent®▼) was the first therapy licensed for the treatment of unresectable or metastatic PNETs[9].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership* were:

- Sunitinib (Sutent®▼)
- Best supportive care (BSC).

2.3 Guidance and related advice

- Ramage JK et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (2005)[5].
- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Neuroendocrine tumors (2010)[6].
- European Neuroendocrine Tumor Society (ENETS). Rare functioning pancreatic endocrine tumors (2006)[10].
- ENETS. Well-differentiated pancreatic non-functioning tumors/carcinoma (2006)[11].
- North America Neuroendocrine Tumor Society (NANETS). NANETS Treatment Guidelines: Well-differentiated neuroendocrine tumors of the stomach and pancreas (2010)[12].
- All Wales Guidelines for the treatment of patients with neuroendocrine tumours (2009)[13].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of sunitinib:

- Sunitinib (Sutent®) is recommended for use within NHS Wales for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults. Experience with sunitinib as a first-line treatment is limited[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of the RADIANT-3 trial[15], which compared everolimus with placebo in pNET patients. To provide information on the comparative effectiveness of everolimus and sunitinib, an indirect comparison was also submitted; this compared the two treatments using data from RADIANT-3 and A6181111, a phase III trial comparing sunitinib with placebo[16]. The salient results are discussed briefly in Sections 3.1 and 3.2, with further details provided in Table A1, Appendix 1.

The company submission included reference to other trials. RADIANT-1 was a non-randomised open-label phase II trial that had two strata[17]: stratum 1 consisted of patients treated with everolimus (10 mg/day), while patients in stratum 2 were treated with everolimus (10 mg/day) and a long-acting octreotide preparation. RADIANT-2 was a randomised phase III trial of everolimus plus octreotide versus placebo plus octreotide[18]. In addition, a small (n = 60) single centre, phase II trial of everolimus in conjunction with octreotide was also included[19]. Although supportive, these trials are of less relevance to this submission than RADIANT-3, as all included patients or treatment regimens outside of the licensed indication for everolimus; they will therefore not be discussed further.

* In April 2012 the Welsh Medicines Partnership became part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

3.1 RADIANT-3[1,15]

RADIANT-3 was a multicentre, international, phase III, double-blind, placebo controlled trial. Included patients were adults with low or intermediate grade advanced neuroendocrine tumours that were either unresectable or metastatic and had demonstrable disease progression in the previous 12 months. Patients also required a WHO performance score of 2 or less (see Glossary) to be eligible for inclusion in the trial. Tumour measurements were assessed by computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and every 12 weeks during treatment; scans were assessed by the local investigator and centrally reviewed. Patients (n = 410) were randomised in a 1:1 ratio to treatment with everolimus (10 mg/day) or placebo. If disease progression occurred, subjects in the placebo arm were eligible to switch to open-label everolimus treatment.

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from randomisation to first documentation of disease progression or death from any cause, as documented by the local investigator according to RECIST criteria (see Glossary for definition). The efficacy objective was the demonstration that everolimus extended PFS compared with placebo. Secondary efficacy endpoints were overall survival, response rate, objective response rate and tumour shrinkage. Overall survival (OS) was measured from the date of patient randomisation to death. Response rate represents the proportion of patients whose best response was either complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or unknown (UNK), according to RECIST criteria. Tumour response measurements were repeated at 12 week intervals. From these data the following outcomes were also derived:

- Objective Response Rate (ORR): the proportion of patients achieving either CR or PR.
- Tumour shrinkage: the proportion of patients achieving any shrinkage in tumour size.

The median treatment lengths for the treatment and placebo arms were 37.8 and 16.1 weeks respectively. Using assessments from local centres, median PFS values were 11.0 and 4.6 months for everolimus and placebo respectively, with a hazard ratio (HR) of 0.35 (95% confidence intervals [CI]: 0.27, 0.45). Central review of the data gave PFS values for everolimus and placebo of 13.7 and 5.7 months respectively, with HR of 0.38 (95% CI: 0.28, 0.51). In both cases the differences in median PFS between treatment and placebo were significant ($p < 0.0001$).

In the placebo arm, 148 subjects (73%) were switched onto open-label everolimus after disease progression. This confounded the detection of a treatment-related overall survival benefit. The HR for overall survival was 1.05 (95% CI: 0.26, 1.88) at the time of data cut-off for the blinded analysis and 0.89 (95% CI: 0.64, 1.23) after 40 months of follow up. An attempt was made to correct for the confounding introduced by crossover using a rank preserving structural failure time (RPSFT) model (commercial in confidence data removed).

(commercial in confidence data removed)

No new safety signals were revealed during the study. The most common adverse events (AEs) were stomatitis, rash, diarrhoea and infections; in general these were relatively mild (grade 1/2). Serious adverse events included anaemia, hyperglycaemia, stomatitis, thrombocytopaenia and diarrhoea. Pulmonary embolism occurred in 2.5% of everolimus-treated patients (0.5% for the placebo arm). Cardiac

complications were observed in 4.9% of patients receiving everolimus, compared to 1% of the placebo group. In the everolimus treatment arm 68.1% of patients discontinued treatment compared to 87.2% of placebo patients; the major reason for discontinuation was disease progression (44.4% everolimus, 80.3% placebo).

3.2 Indirect sunitinib/everolimus comparison[1]

The company provided an indirect comparison of everolimus and sunitinib using data from A6181111, a phase III randomised double-blind study comparing sunitinib with placebo[16]. In this trial sunitinib was given orally with a starting dose of 37.5 mg/day, but the final dose was adjusted on an individual basis. Inclusion required histologically or cytologically demonstrated well-differentiated pNETs with at least one measurable tumour. Sunitinib gave a median PFS of 11.4 months compared to 5.5 months for placebo (HR = 0.42 [95% CI: 0.26, 0.66], p = 0.0001), representing a 60% reduction in risk of death or disease progression for sunitinib over placebo. ORR were 9.3% for sunitinib and 0% for placebo (p = 0.0066). Almost all subjects experienced adverse events considered to be treatment related; 44.6% of sunitinib adverse events were considered severe and treatment related (compared to 19.5% for placebo patients).

The indirect comparison assessed the comparative effectiveness of everolimus and sunitinib in terms of PFS, OS and grade 3/4 adverse events. Patient data from the RADIANT-3 trial were used along with published data from A6181111. A matched comparison of these data sets was performed according to the method of Signorovitch[20]. In order to match the baseline characteristics of the two patient populations as closely as possible, it was necessary to remove some patient data. For example, subjects from RADIANT-3 with WHO performance scores of 2 were discounted because few patients from A6181111 were of this performance status. To detect residual bias between the groups a comparison was made between the placebo arms of both trials. (commercial in confidence data removed) Any residual bias is in the direction of increased death and disease progression and will not inflate the performance of everolimus. Table 1 shows the HRs determined for PFS using the indirect comparison, both before and after matching the datasets.

Table 1: (commercial in confidence data removed)

In common with RADIANT-3, A6181111 allowed patients with disease progression in the placebo arm to cross over to treatment with open-label sunitinib. However, the company state that no data are available from A6181111 that either correct for crossover, or allow a correction to be modelled using RPSFT. Therefore to estimate OS, non-adjusted data were used from both studies. Differences in treatment provided as part of the placebo arm of the two studies, and the higher rates of crossover in RADIANT-3 compared to A6181111, prevented the use of both placebo groups as a common anchor. Thus both sunitinib and everolimus were compared to the sunitinib placebo group. The results, both pre- and post-matching, are summarised in Table 2.

Table 2: (commercial in confidence data removed)

Comparative safety data were also supplied for the indirect comparison: details are provided in Appendix 1, Table A2. None of the differences between treatment groups reached statistical significance for any adverse event with the exception of neutropaenia, which occurred more frequently with sunitinib than everolimus with borderline statistical significance (p = 0.0495).

3.3 AWTTC critique

- RADIANT-3, the pivotal study, was a large double-blinded trial that shown an improved efficacy for everolimus over placebo. Everolimus gave a median increase in PFS of 6.4 months with a hazard ratio of 0.35 (suggesting a 65% reduction in risk of disease progression or death over placebo).
- Although the confounding caused by placebo-treated patients crossing over to everolimus upon disease progression is a limitation of RADIANT-3, this is acknowledged as ethically unavoidable and common to many studies of cancer treatments. Patient crossover is the likely reason that no significant difference in OS was observed between the sunitinib and placebo arms. However, it should be noted that whilst the results of an analysis undertaken by the company to correct for patient crossover give a HR that favours everolimus over placebo in terms of OS, this difference remains not statistically significant. As highlighted by the company, the uncertainty around OS may also be partly due to immaturity of the dataset from RADIANT-3, and later analyses of survival outcomes may prove more robust.
- There is no evidence available to allow a direct head-to-head comparison of the clinical effectiveness of everolimus and sunitinib, but the indirect comparison provided follows established paradigms and is credible. Hazard ratios derived from the indirect comparison marginally favour everolimus over sunitinib in terms of both PFS and OS, but no statistically significant difference between the two treatments was found.
- Pharmacovigilance and risk management strategies are included for everolimus that cover commonly-occurring adverse events, in addition to some rarer serious adverse events (such as pulmonary embolism and cardiac events).
- Greater than 75% of the participants in RADIANT-3 were Caucasian. While this is lower than the Caucasian representation in Wales, it is higher than the Caucasian representation in A6181111, where this group accounted for approximately 55% of the trial population.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence[1]

4.1.1 Context

The company submission describes a cost utility analysis (CUA) of everolimus in its licensed indication for the treatment of unresectable or metastatic, well- or moderately-differentiated pNETs in adults with progressive disease (i.e. advanced pNETs)[1]. Two comparators are used: sunitinib (primary comparator) and best supportive care (secondary comparator). The analysis utilises a Markov model with four health states: stable disease without adverse events (SD), stable disease with adverse events (SD with AEs), progressive disease (PD) and death. Transition allowed between the health states is unidirectional, except for the transition between SD and SD with AEs, which is allowed in both directions. Cycle length is one month and the base case model assumes a 20-year time horizon to represent lifetime in the base case.

For the primary comparison with sunitinib a matched indirect comparison is used to derive comparative effectiveness data, due to the lack of head-to-head trials. The indirect comparison provides the hazard ratios for the risk of PFS and OS and the odds ratio for the AEs that could be matched between the two pivotal studies

(RADIANT-3 for everolimus and A6181111 for sunitinib). For the secondary comparison with BSC alone, the effectiveness estimates are taken directly from the RADIANT-3 trial in which everolimus plus BSC is compared to placebo plus BSC in the target population.

Drug acquisition costs are calculated taking into account the duration of treatment and adjusted average doses based on the RADIANT-3 and A6181111 trials for everolimus and sunitinib, respectively. A discounted acquisition cost is assumed for sunitinib to reflect the fact that sunitinib is recommended for use in NHS Wales under a confidential patient access scheme (PAS). Non-drug resource use and cost estimates are based on a survey of UK clinicians and relate to the treatment of 13 patients with advanced pNETs. Health utilities used in the model were derived from a direct measurement study[21] using vignettes for the health state description and the time trade-off (TTO) method for preference elicitation from a sample (n = 100) of the UK general public.

4.1.2 Results of the company base case analysis

Results of the base case analyses are presented in Table 3. The results show that treatment with everolimus is estimated to be both more costly and more effective when compared with both sunitinib and BSC. The key driver of costs is the difference in drug costs. For the primary comparison, quality-adjusted life year (QALY) gains in the progressive disease state contribute most to overall QALY gains: everolimus is estimated to generate an additional 0.186 QALYs over sunitinib in the progressive disease state, compared with 0.123 QALYs in the stable disease states.

Table 3. Company reported results of the base case cost utility analysis.

	Primary comparison			Secondary comparison		
	Everolimus	Sunitinib	Difference	Everolimus	BSC	Difference
Drug costs*	£24,347	£20,190	£4,157	£24,347	£0	£24,347
Symptomatic care costs	£1,339	£1,154	£185	£1,764	£3,045	-£1,281
Resource use costs: doctor visits	£3,332	£2,906	£426	£4,146	£2,814	£1,332
Resource use costs: procedures/tests	£1,024	£886	£138	£1,248	£790	£458
Resource use costs: hospitalisation	£802	£691	£111	£1,057	£744	£313
Adverse event costs	£923	£1,657	-£734	£1,689	£528	£1,161
Post disease progression drug and non-drug costs	£6,129	£6,343	-£214	£6,090	£6,790	-£700
Palliative care costs: end of life terminal care	£4,758	£4,837	-£79	£4,613	£4,892	-£279
Total discounted costs	£42,654	£38, 665	£3,990	£44,954	£19,602	£25,352
Total discounted life years	3.355	2.902	0.453	4.083	2.578	1.505
Total discounted QALYs	2.227	1.918	0.309	2.673	1.659	1.014
Incremental cost per LYG	£8,812			£16,884		
ICER (£/QALY gained)	**£12,894**			**£24,999**		

BSC: best supportive care; ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life-year
*Based on doses, treatment duration and intensities in the pivotal trials; sunitinib drug costs includes a discount to reflect the patient access scheme under which sunitinib is made available to NHS Wales.

The company reports a wide range of one way sensitivity analysis. These indicate that the ICERs for the primary comparison against sunitinib are most sensitive to the assumption regarding the everolimus dose intensity (100% dose intensity increases the ICER to £25,800/QALY gained) and the duration of treatment with sunitinib (increasing or decreasing by one month results in an ICER of £20,600 or £5,500/QALY gained, respectively). Assuming 100% dose intensity for both everolimus and sunitinib increases the ICER to £19,500/QALY, assuming use of somatostatin analogues alongside everolimus and sunitinib as per the clinical trials produces an ICER of £15,500/QALY. Varying the survival outcome for everolimus according to the upper and lower bounds of the Weibull curve results in an ICER range of £10,700 to £16,000/QALY gained. Using the log-normal function rather than Weibull reduces the ICER to £8,300/QALY gained. Varying post progression costs by ±20% results in an ICER range of £8,900 to £16,900/QALY gained. The ICER is not sensitive to variations and alternative scenarios regarding utilities, time horizon, relative PFS efficacy, disease progression or AE costs, palliative care costs or the discount rate.

Supplementary analyses provided by the company indicate that the ICER increases to £28,700 per QALY gained when OS is assumed to be equivalent for everolimus and sunitinib. When both PFS and OS are assumed equivalent, there are no differences in QALYs, and everolimus is estimated to cost an additional £155 per patient per year over the 20 year time horizon.

Probabilistic sensitivity analysis (PSA) indicates that the probability of everolimus being cost effective compared with sunitinib at a cost effectiveness threshold of £20,000 to £30,000 per QALY gained is around 63% to 71%.

The ICER for the secondary comparison against BSC is most sensitive to the survival outcome for everolimus. Using the upper and lower bounds of the Weibull curve generates an ICER range of £17,000 to £41,000/QALY gained. Using the log normal function fitted to the PFS and OS data from RADIANT-3 produces an ICER of £30,800/QALY gained. Assuming 100% dose intensity for everolimus increases the ICER to £28,900/QALY gained. The ICER is not particularly sensitive to other variables.

4.1.3 AWTTC critique

Strengths of economic evidence include:

- In the absence of direct comparative data, the company has attempted an indirect comparison of everolimus and sunitinib using data from the pivotal trials.
- A wide range of sensitivity analysis is provided to explore the impact of assumptions and uncertainty in key parameter values.

Limitations of the economic evidence include:

- There is a lack of direct comparative data to inform the most relevant comparison of everolimus, and there appears to be significant uncertainty in the relative effectiveness estimates derived from the indirect comparison. Although some baseline characteristics of subjects in the everolimus and the sunitinib trials have been matched, there is no adjustment for any potential residual baseline differences in prognostic factors, and OS estimates are not adjusted for crossover.
- The survival function adopted for extrapolation of PFS with sunitinib treatment appears to fit the sunitinib data poorly, which may bias the estimates in favour of everolimus.
- Resource use estimates used in the model are based on a small survey conducted by the company in which resource use data were collected for 13 patients. In the absence of alternative sources this is appropriate but would still seem to be a source of uncertainty.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost effectiveness of everolimus in the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin (pNETs) in adults with progressive disease.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

NOT FOR NMG TO CONSIDER; PLEASE MOVE TO SECTION 6.0

5.1 Budget impact evidence[1]

5.1.1 Context and methods

The company reports that only the incidence of pNETs will be relevant (commercial in confidence data removed). Hence, neither prevalence nor mortality estimates are taken into account. The company reports that the incidence of pNETs is 0.32 per 100,000 population, based on Surveillance Epidemiology and End Results (SEER) data from the US[22]. Applying this incidence rate to Welsh population estimates, and assuming no material change in incidence or population estimates, the number of incident pNETs cases is estimated to be 10 per year over the next five years. Based on company market research, 76% of these 10 patients are estimated to have well- or moderately-differentiated histology, of which 35% have experienced progression in the last 12 months. Therefore, approximately three patients are expected to be

eligible for treatment with either everolimus or sunitinib. The company anticipates two of these three patients will receive everolimus rather than sunitinib each year.

5.1.2 Results of company's budget impact analysis

Based on the mean duration of treatment (commercial in confidence data removed) and a dose intensity of 85.9% as observed in the RADIANT-3 trial, the company anticipates acquisition costs of everolimus to be £24,347 per patient. Based on the mean duration of treatment of 9.6 months (approximately 292 days) and a dose intensity of 91.3% (as observed in the AWMSG Secretariat Assessment Report for sunitinib), and including the PAS discount for sunitinib, the company anticipates acquisition costs of sunitinib to be £20,190 per patient. Assuming that everolimus will displace sunitinib in two patients each year, a net increase in cost of £8,314 per year is estimated in each of the next five years.

Sensitivity analyses provided by the company explore the impact of varying the number of eligible patients (one to four patients), duration of treatment and dose intensity. Results of the sensitivity analysis show that the net drug cost per year varies within a range of a decrease of £1,431 and an increase of £18,128 in the various scenarios explored.

5.1.3 AWTTC critique of the budget impact analysis

- The company utilises an estimate for the incidence of pNETs derived from a USA dataset, which is consistent with that based on the UKNETwork for neuroendocrine tumours, which reported an annual incidence of 0.2–0.4 per 100,000.
- The company assumes that prevalence and mortality need not be considered in the budget impact analysis, (commercial in confidence data removed). However, it should be noted that the range of treatment durations reported in the RADIANT-3 trial is 1.1 to 118.1 weeks and as the anticipated number of patients eligible for everolimus treatment is small, there is potential for the duration of treatment in practice, and hence the net budget impact, to differ from the trial-based mean estimates.
- The analysis assumes 0% discontinuation on everolimus treatment and does not take into account the possibility of discontinuing treatment, which has been reported in 13% of patients receiving everolimus treatment in the RADIANT-3 trial[15].

5.2 Table of comparative unit costs

Only everolimus and sunitinib are currently licensed for the treatment of pNETs in the UK, although other treatments may be used off-label in practice. Recommended doses and unit costs for both licensed treatments are presented in Table 4

Table 4: Acquisition costs for licensed pNETs treatments

Regimen	Estimate of daily dose	Approximate average daily cost
Everolimus (Afinitor®▼) 10 mg oral tablets	10 mg once daily	£99
Sunitinib (Sutent®▼) 12.5mg, 25 mg oral capsules	37.5 mg once daily	£84.08
Costs based on MIMS list prices as of March 2012[23]. This table does not imply therapeutic equivalence of the stated drugs and doses. See all relevant Summaries of Product Characteristics for full dosing details.		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that everolimus is suitable for specialist only prescribing within NHS Wales for the stated indication.

6.2 Ongoing studies

Follow-up on the RADIANT-3 trial is still ongoing; a more mature dataset is expected in 12–18 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 22 March 2012
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

RECIST (Response Evaluation Criteria In Solid Tumours)[24]: a set of criteria that allow classification of patient response to treatment into:

- Complete response (CR): absence of all target lesions, confirmed after 4 weeks;
- Partial response (PR): ≥ 30% reduction of the longest diameter of the target lesion taking as reference the baseline value, confirmed at 4 weeks, with no appearance of new tumours;
- Stable disease (SD): neither PR or PD criteria met;
- Progressive disease (PD): ≥ 20% increase in the sum of the longest diameter of target lesions taking as reference the smallest sum of the longest diameter recorded sicne treatment started, or the appearance of new tumours.

Version 1.0 was published in 2000. The current version is 1.1, published in 2009.

WHO (World Health Organisation) performance status[25]: also known as the ECOG (Eastern Cooperative Oncology Group) performance score, this is.a graded scale for assessing general health in clinical trial patients:

0: fully active
1: ambulatory; capable of light work
2: ambulatory; capable of self-care; unable to work but up and about more than 50% of waking hours
3: capable of limited self-care; in bed/chair more than 50% of working hours
4: completely disabled
5: dead

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Appendix 1. Additional clinical information

Table A1. Summary of studies RADIANT-3 and A6181111

Study: RADIANT-3[1,15]

Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
International (n = 18) multicentre (n = 81) double-blinded random placebo-controlled phase III trial. Dose: everolimus 10 mg/day at same time immediately after meal, or placebo. Dose could be delayed or reduced to 5 mg/day (and then 5 mg every other day) if serious adverse effects noted. Day 1 of cycle 1 is first day of treatment: each cycle 28 days. Treatment until disease progression/death/unacceptable toxicity. Double-blinded up to point of documented radiological (CT/MRI) disease progression (assessed by RECIST criteria). At this point treatment arm revealed and cross-over from placebo to open-label everolimus allowed. After further disease progression patients discontinued everolimus and enter 28 day scheduled follow up to assess adverse events and monthly survival assessment. Best supportive care available to both arms of trial consisting of medicine/non-medicine treatment including	Inclusion criteria: • ≥ 18 years. • Low/intermediate grade advanced unresectable or metastatic pNET. • Radiologically documented disease progression in last year. • WHO performance status 0–2. • Adequate liver, renal and bone marrow function. • Prior antineoplastic treatment acceptable if stopped ≥ 4 weeks before enrolment. Exclusion criteria • Poorly differentiated neuroendocrine tumour. • High grade neuroendocrine tumour. • Cytotoxic chemotherapy, immunotherapy or radiotherapy within 4 weeks of randomisation. • Hepatic artery embolism in previous 6 months. • Cryoablation/radio-frequency ablation of hepatic metastasis in 2 months prior to enrolment. • Prior treatment with mTOR inhibitor (everolimus, sirolimus, temsirolimus etc). • Glucose > 1. 5 x ULN. • Severe/uncontrolled conditions such as unstable angina pectoris, acute infection, cirrhosis. • Chronic treatment with corticosteroids or other	n = 410 Everolimus (E): n = 207 Placebo (P): n = 203 Median age (range), years E; 58 (23-87) P: 57 (20-82) Males: E: 53% P: 58% Caucasian E: 75.4% P 81.8% WHO performance status: 0 – E: 67%, P: 66% 1 – E: 30%, P: 32% 2 – E: 3%, P: 3% Patients stratified by: • Previous use (or not) of cytotoxic chemotherapy. • WHO performance status 0 vs. 1,2.	Primary efficacy endpoint: • Progression free survival Secondary efficacy endpoints: • Tumour response • Overall survival **Results** (commercial in confidence data removed) Everolimus group treated for median 37.8 weeks (range 1.1-118.1). Placebo group treated for 16.1 weeks (0.4-132.4). **PFS (months)** Analysis / E / P / HR [95% CI] / p value Local review / 11.0 / 4.6 / 0.35 [0.27, 0.45] / < 0.001 Central review / 13.7 / 5.7 / 0.38 [0.28, 0.51] / <.0.001 Central adjudicated review / 11.4 / 5.4 / 0.34 [0.26, 0.44] / < 0.001

Table A1. Summary of studies RADIANT-3 and A6181111

Study: RADIANT-3[1,15]

Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
• Somatostatin analogues • Proton pump inhibitor (gastrinoma) • Diazoxide +/- feeding tube (insulinoma) • Pancreatic lipase (exocrine pancreatic insufficiency) • Loperamide (anti-diarrhoeal) • Opiates No other commercial/IND anti-cancer agents allowed. (commercial in confidence data removed).	immunosuppressant. • HIV positive.	Histological status of tumour: Well differentiated E: 82% P: 84% Moderately differentiated E: 17% P: 15% Unknown E: 1% P: 1% Sites of metastases: Liver E: 92%, P: 92% Pancreas E: 44%, P: 41% Lymph node E: 33%, P:76% Lung E: 14%, 15% Bone E: 6%, P: 14%	**Subgroup analysis** Subgroup / n / HR [95% CI] / p value Local investigator 410 0.35 [0.27, 0.45] <0.0001 Central adjudicated 410 0.34 [0.26, 0.44] <0.0001 *Previous chemotherapy?* Yes 189 0.34 [0.24,0.49] <0.0001 No 221 0.41 [0.29, 0.58] <0.0001 *WHO performance score* 0 279 0.39 [0.28, 0.53] <0.0001 1,2 131 0.30 [0.20, 0.47] <0.0001 *Age* ≤ 65 years 299 0.39 [0.29,0.53] <0.0001 > 65 years 111 0.36 [0.22, 0.58] <0.0001 *Gender* M 227 0.41 [0.30, 0.58] <0.0001 F 183 0.33 [[0.23, 0.48] <0.0001 *Ethnicity* White 322 0.41 [0.31, 0.53] <0.0001 Asian 74 0.29 [0.15, 0.56] <0.0001 *Tumour differentiation* Well differentiated 341 0.41 [0.31, 0.53] <0.0001 Moderately differentiated 65 0.21 [0.11,0.42] <0.0001 *Any SSA use* Y 221 0.40 [0.29, 0.56] N 189 0.35 [0.24, 0.50] *Concomitant SSA use* Y 163 0.43 [0.29, 0.64] N 247 0.34 [0.25, 0.46] *Previous SSA use* Y 203 0.40 [0.28, 0.57] <0.0001 N 207 0.29 [0.25, 0.51] <0.0001 *Previous and concomitant SSA use* Y 145 0.43 [0.28, 0.66] N 265 0.34 [0.25, 0.47]

Table A1. Summary of studies RADIANT-3 and A6181111

Study: RADIANT-3[1,15]			
Study information	**Main inclusion/exclusion criteria**	**Patient characteristics**	**Outcomes**
			OS After 40 months follow up, OS unadjusted for confounding effects of patient cross-over showed 11% reduction in progression of disease or death for everolimus over placebo (HR = 0.89 [0.64, 1.23]). (commercial in confidence data removed) RESPONSE RATE (commercial in confidence data removed) CR, PR, SD, PD, UNK, ORR – see Section 3.1 for definitions.

Best response	Local review		Central review		Adjudicated central review	
	E	**P**	**E**	**P**	**E**	**P**
n =	*207*	*203*	*207*	*203*	*207*	*203*
CR	0%	0%	0%	0%	0%	0%
PR	4.8%	2.0%	2.4%	0.5%	2.9%	0.5%
SD	72.9%	50.7%	80.7%	66.5%	78.7%	59.1%
PD	14.0%	41.9%	9.7%	27.6%	11.1%	35.5%
UNK	8.2%	5.4%	7.2%	5.4%	7.2%	4.9%
ORR	4.8%	2.0%	2.4%	0.5%	2.9%	0.5%

Table A1. Summary of studies RADIANT-3 and A6181111

Study: RADIANT-3[1,15]			
Study information	**Main inclusion/exclusion criteria**	**Patient characteristics**	**Outcomes**
			SAFETY Most AEs were grade 1 or 2. Commonest AEs (all grades) AE — Everolimus (%) — Placebo (%) Stomatitis — 64 — 17 Rash — 49 — 10 Diarrhoea — 34 — 10 Infection — 23 — 6 Commonest SAE (grade 3/4) Anaemia — 6 — 0 Hyperglycaemia — 5 — 2 Stomatitis — 7 — 0 Thrombocytopaenia — 4 — 0 Diarrhoea — 3 — 0 Deaths — 6 — 2 *Due to cancer — 2.5 — 1.5* *Due to AE — 3.5 — 0.5* *Due to drug — 0.5 — 0*

Table A1. Summary of studies RADIANT-3 and A6181111

Study: A6181111[16]

Study information	Main inclusion/exclusion criteria	Patient characteristics	Outcomes
Phase III international (n = 11) multicentre (n = 42) randomised double-blind study of sunitinib versus placebo. Oral sunitinib 37. 5 mg/day continuous daily dosing therapy or placebo. Dose of sunitinib adjusted individually on basis of tolerance. Planned interim analysis at 130 events and final analysis after 260 events. Study terminated early on advice of independent data management committee after 73 events as primary end point met.	Inclusion criteria: • Histologically/cytologically proven well differentiated pancreatic islet cell tumour • ≥ 1 measureable target lesion. Exclusion criteria • Any chemotherapy, chemoembolisation therapy, immunotherapy, investigational anticancer drug agent other than SSA. • Prior treatment with tyrosine kinase inhibitor or anti vascular endothelial growth factor angiogenesis inhibitors.	n = 340 required for power to detect 50% improvement in PFS. 171 patients randomised and 165 treated. Sunitinib (S): n = 86 Placebo (P): n = 85 Males: S: n = 42 P: n = 40 Mean age (SD) (y) S: 55.4 (13.6) P: 55.9 (12.7) Caucasian S: 55. 8% P: 62. 4% ECOG grades 0: S 61.6%, P 48.2% 1: S 38.4%, P 50.6% 2: S 0%, P 1.2%	Primary endpoint: • Comparison PFS of sunitinib (starting at 37. 5 mg/d) with that of placebo Secondary efficacy endpoints • Compare TTR, OS, OR, DR between sunitinib and placebo **Results** Median Endpoint / S / P / HR [95% CI] / p-value PFS (months) / 11.4 / 5.5 / 0. 418 [0.263,0.662] / 0.0001 OS (months) / 20. 6 / NR / 0. 409 [0.187,0.894] / 0.0204 OR (%) / 9.3 / 0 / / 0.0066 Median Endpoint / S / P / HR [95% CI] / p-value CR (%) / 2.3 / 0 PR (%) / 7.0 / 0 SD (%) / 62.8 / 60.0 PD (%) / 14 / 27.1 Indeterminate(%) / 14 / 12.9 TTR (months) (range) / 3.1 (0.8-11.1) / NA DR / NR / NA

AE: adverse event; **CR**: complete response; **DR**: duration of response; **LVEF**: left ventricular ejection volume; **ECG**: electrocardiogram; **ECOG**: Eastern Cooperative Oncology Group; **EORTC-QLQ**: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; **HR**: hazard ratio; **IND**: investigational new drug; **OR**: objective response = CR + PR; **OS**: overall survival; **PFS**: progression-free survival; **pNET**: pancreatic neuroendocrine tumour; **NR**: not reached; **PD**: disease progression; **PR**: partial resposnse; **RECIST**: response evaluation criteria in solid tumours; **SAE**: serious adverse event; **SD**: stable disease; **SSA**: somastatin analogue; **TTR**: time to response; **Tx**: treatment; **ULN**: upper limit of normality

Table A2: Incidence rates and odds ratios for the indirect comparison of most frequent grade 3/4 adverse events with everolimus and sunitinib[1].

Adverse event	Post matched RADIANT-3		A6181111 trial		Placebo-adjusted everolimus vs placebo-adjusted sunitinib	
	Everolimus (n=200)	Placebo (n=194)	Sunitinib (n=86)	Placebo (n=85)	Odds ratio	P value
Anaemia	7.1%	1.3%	1.2%	1.2%	6.00	0.257
Stomatitis	7.1%	0.0%	3.6%	0.0%	3.90	0.374
Thrombocytopaenia	4.8%	0.0%	3.6%	0.0%	2.64	0.537
Diarrhoea	6.3%	1.7%	4.8%	2.4%	1.93	0.541
Neutropaenia	3.9%	3.7%	12.0%	0.0%	0.08	0.049
Fatigue	2.7%	2.5%	4.8%	8.5%	2.05	0.458
Abdominal pain	3.1%	6.9%	4.8%	9.8%	0.91	0.916
Upper abdominal pain	2.7%	1.9%	1.2%	0.0%	0.66	0.799
Asthenia	2.9%	3.0%	4.8%	3.7%	0.73	0.761
Hand-foot syndrome	0.9%	0.0%	6.0%	0.0%	0.44	0.607
Hypertension	0.6%	0.4%	9.6%	1.2%	0.20	0.328
Hyperglycaemia	7.4%	3.9%	4.9%	< 5%	-	-
Pneumonitis	3.1%	0.0%	< 5%	< 5%	-	-
Pruritis	0%	0%	< 5%	< 5%	-	-
Infections	5.7%	3.1%	NA	NA	-	-
Peripheral oedema	1.0%	1.1%	0.0%	1.2%	1.83	0.700
Pyrexia	0.8%	1.3%	1.2%	0.0%	0.37	0.531
Rash	0.4%	0.0%	0.0%	0.0%	1.71	0.774

Appendix 2. Additional health economic information

Table A3. Health economic model detail

	Base Case Model	Appropriate?
Comparator(s)	Everolimus (Afinitor®▼) oral tablets is compared against sunitinib (Sutent®) and best supportive care (BSC), which includes symptomatic treatment with a long acting somatostatin analogue (SSA).	Yes. Sunitinib was requested as the comparator by AWTTC and was recently recommended by AWMSG as a first line treatment in advanced pNETs. Before that, treatment options were limited to best supportive care (BSC), which is considered as a secondary comparator in the company submission.
Population	Adult patients (≥ 18 years) with unresectable or metastatic pancreatic neuroendocrine tumours (pNETs) with well- or moderately differentiated histology who have experienced disease progression in the previous 12 months.	Yes. This population reflects the licensed indication for everolimus covered by this submission.
Model type and description	Cost utility analysis (CUA) is used. It utilises a Markov model with area under the curve (AUC) analysis. The model consists of four health states: stable disease (SD), stable disease with adverse events (SD with AEs), progressive disease (PD) and death. Area under the curve analysis is used to derive the monthly transition probabilities. A cumulative distribution function is calculated using the parameters of the progression free survival (PFS) and the overall survival (OS) parametric Weibull functions. A monthly cycle length is assumed.	Yes. CUA is the preferred type of analysis with QALYs gained as the primary outcome measure. The model structure appears reasonably reflective of the current treatment pathway.
Perspective	NHS Wales.	Yes. The company submission states that no personal social services costs were included but the end of life care cost estimate in the model appears to include some such costs[26].
Time Horizon	A lifetime horizon set at 20 years in the base case. In sensitivity analysis (SA), a 10 year time horizon is also explored.	A lifetime horizon is appropriate given the terminal nature of the disease. At 10 years around 99% of the modelled cohort has died. The model is relatively insensitive to the time horizon explored at 10 years.
Discount rate	3.5% discount rate for costs and outcomes, with 0% and 6% explored in sensitivity analyses.	Yes, appropriate.
Efficacy	The main source of efficacy data for everolimus is a double-blind, placebo controlled, phase III RCT (RADIANT-3) in which everolimus plus BSC is compared with placebo plus BSC. The HRs for the risk of progression or death (PFS and OS) obtained from the trial are used to calculate the transition probabilities from the SD and SD with AEs states to PD and Death for the secondary comparison (everolimus vs. BSC alone).	In the absence of direct comparative trial data for everolimus and sunitinib, the company has conducted an indirect comparison using trial data from the pivotal placebo-controlled trials of these agents. However there are a number of limitations and uncertainties associated with the indirect relative efficacy estimates. The A6181111 trial was terminated early and may have resulted in an overestimation of treatment benefit. In both the RADIANT-3

Table A3. Health economic model detail

	Base Case Model	Appropriate?
	For the primary comparison (everolimus vs. sunitinib), a matched indirect comparison of everolimus and sunitinib is used as the source for comparative efficacy estimates, using individual patient level data from the RADIANT-3 trial, for everolimus, and aggregated data from the A6181111 trial, for sunitinib. Extrapolation of the efficacy estimates beyond the trials' time horizon is done using a parametric Weibull survival function. A log-normal survival function is also used in a sensitivity analysis.	and the A6181111 trials a high proportion of patients switched over from the placebo arms to the active treatment arms. The company states that, due to differences in the types of treatment provided as part of placebo/BSC across the trials, and the higher rates of cross-over in the latest follow-up datasets for overall survival in the RADIANT-3 study compared to the A6181111 study, the placebo arms in these studies could not serve as a common reference arm for an anchor-based indirect comparison of OS for everolimus and sunitinib. Therefore, OS with everolimus has been compared with the sunitinib and the placebo arm population of the sunitinib trial, with no adjustment of any residual baseline differences in prognostic factors. (commercial in confidence data removed). A scenario of equal PFS benefit is explored in sensitivity analysis, and the model is not sensitive to the change, reportedly showing only a small increase in the ICER for everolimus versus sunitinib. In response to requests from AWTTC, the company has provided additional analyses in which no differences in OS between everolimus and sunitinib are assumed, The ICER increases to £28,700 per QALY gained (from a base case estimate of £12,900 per QALY gained). When no differences in either PFS or OS are assumed, the modelled QALY gains are identical and everolimus is estimated to cost £3,200 more than sunitinib over the 20 year time horizon (which the company notes is an additional cost of £155 per year). , In the everolimus versus sunitinib comparative analysis, the Weibull survival function used to extrapolate PFS over the longer term does not have a good fit for the sunitinib data. The company suggests that this is due to the small number of data points populating the right hand side of Kalpan-Meier curve; however, irrespective of this, the approach adopted by the company may introduce bias in favour of everolimus.

Table A3. Health economic model detail

	Base Case Model	Appropriate?
Adverse effects	AEs are incorporated in the model in a distinct health state (SD with AEs). Transition to this state is based on the probability of occurrence of common grade 3 and 4 AEs derived directly from the RADIANT-3 trial (for the secondary comparison vs. BSC) or indirectly using matched indirect comparison (for the primary comparison vs. sunitinib).	Some common grade 3 and 4 adverse events related to everolimus (e.g. infections, pneumonitis) are not included in the primary comparison with sunitinib, as they were not possible to be matched in the indirect comparison between the two trials (RADIANT-3 and A6181111). It is therefore possible that not all relevant AEs are included in the model. However, the model appears relatively insensitive to adverse event costs when explored in the range +/-20%. Discontinuation due to adverse events, which occurred in 19.1% of patients receiving everolimus in the RADIANT-3 trial, and dose reductions due to AEs are reflected in the resource use estimates.
Utility values	Utilities applied to the health states in the model are taken from a direct measurement study[21] conducted with 100 participants from the UK public. The health states "vignettes" used are based on review of the literature and in-depth discussions with pNET patients and clinicians. The method used for preference elicitation is time trade off (TTO) supplemented by a visual analogue scale (VAS) rating exercise.	There are limitations to the method used for deriving the utilities used in the model. The vignettes used to describe the health states are difficult to validate and are usually concise, hence may not fully describe the health state. Given the availability of EQ-5D utilities derived by the manufacturer of sunitinib, (using mapping from HRQoL data collected directly from pNET patients) these utilities may be more appropriate; however, the model was not very sensitive to the actual utility values used.

Table A3. Health economic model detail

	Base Case Model	Appropriate?
Resource use and costs	Drug acquisition cost for everolimus is based on the BNF 62 list price, which is applied to the dose, duration and intensity of treatment observed in the RADIANT-3 trial. For sunitinib, the acquisition cost in the base case analysis is assumed to include a discount (commercial in confidence data removed), to reflect the fact that sunitinib is recommended for use in NHS Wales under a confidential patient access scheme. The dose, duration and intensity of treatment observed in the A6181111 trial of sunitinib are assumed in the model. The impact of incorporating potential additional costs associated with administration of the sunitinib PAS is explored in sensitivity analysis. SSA costs are not included in the primary base case analysis, on the basis that in practice SSAs would not be administered alongside either everolimus or sunitinib. However, SSAs are included as part of BSC in the secondary analysis. Non-drug resource use is based on a survey of 32 UK clinicians involved in the treatment of pNETs. The survey collected data for 13 patients with advanced pNETs. End of life care costs are taken from a published study[5].	Resource use data are based on a small survey including 13 patients and it is not possible to assess whether the resource use estimates are representative of current treatment patterns in Wales. None of the patients whose resource use is reported in the survey were in the second progression state, which represents the PD state in the model. Resource use estimates for this state are, thus, based on hypothetical scenarios presented to the physicians resulting in uncertainty around these estimates. Sensitivity analyses indicate the model is moderately sensitive to these costs. Assumptions relating to time spent in model states (used to derive an average per month cost) were based on physician estimates. No monitoring test costs are included in the model, as the company submission reports that monitoring tests are considered routine practice in this patient population. The use of SSAs is assumed to be zero in the base case analysis, in contrast to their use in the everolimus and sunitinib arms of the RADIANT-3 and A6181111 trials, based on the assumption that in practice SSAs would not be administered alongside either everolimus or sunitinib. Inclusion of SSA costs alongside everolimus or sunitinib (as per the clinical trials) increases the ICER to £15,500/QALY gained. The company has explored the impact of incorporating an additional one-off £3,000 into the sunitinib costs to account for administration of the PAS. This reduces the ICER for everolimus vs. sunitinib to £3,200/QALY gained. Whilst PAS administration will attract costs (which if taken into account would potentially reduce the ICER for everolimus versus sunitinib), it should be noted that an additional £3,000 PAS administration cost per patient (commercial in confidence data removed) would seem an untenable scenario.

Table A3. Health economic model detail

	Base Case Model	Appropriate?
Uncertainty	A range of one-way sensitivity and scenario analyses is provided. Sensitivity analyses explored the impact of variation in mean treatment duration, dose intensity, utilities, time horizon, relative PFS efficacy, disease progression and AE costs, palliative care costs and the discount rate. Probabilistic sensitivity analysis (PSA) results are reported for the everolimus versus sunitinib comparison only.	All sensitivity analyses provided indicate that everolimus is more effective and more costly than both sunitinib and BSC alone. One way sensitivity analyses for the comparison with sunitinib (the most relevant comparator) indicate that the ICER is most sensitive to everolimus dose intensity - assuming 100% dose intensity increases the ICER to £25,800/QALY gained. The PSA results show that the probability of everolimus being more cost effective than sinitunib is 64% at £20,000 threshold and increases to 71% at £30,000 threshold. The comparison with BSC alone is most sensitive to the survival outcome for everolimus according to the upper and lower bounds of the Weibull curve, producing an ICER range of £17,000–£41,000/QALY gained. No PSA has been conducted by the company for this comparison, but running the PSA for the base case analysis using £30,000 threshold resulted in a probability of 46.1% that everolimus plus BSC is more cost effective compared with BSC alone. Using £20,000 threshold, the probability falls to 16.9%. The company attributes these low estimates to the skewed distribution assumed around the utility values.
Model provided?	Yes.	Yes.
Other considerations	The company suggests that everolimus should be considered as an ultra-orphan drug, given that the prevalence of advanced pNET is 0.32 per 100,000[1,22]. The company does not consider everolimus to fulfil the criteria for consideration under the AWMSG policy for appraising life-extending, end-of-life medicines.	AWMSG defines ultra-orphan medicines as orphan drugs that are licensed for the treatment of diseases with a prevalence of less than 1 in 50,000 persons in the EU[27]. Everolimus does not have orphan drug status for the treatment of pNETs.

BSC: best supportive care; SSA: somatostatin analogue; pNETs: pancreatic neuroendocrine tumours; AWTTC: All Wales Therapeutics and Toxicology Centre; CUA: cost utility analysis; AUC: area under the curve; AE: adverse event; SD: stable disease; PD: progressive disease; PFS: progression free survival; OS: overall survival; QALYs: quality adjusted life year; ICER: Incremental cost-effectiveness ratio; TTO: time trade off; VAS: visual analogue scale; HRQoL: health-related quality of life; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; CEAC: Cost Effectiveness Acceptability Curve; EMA: European Medicines Agency.