# AWMSG Secretariat Assessment Report – Advice no. 1111
# Sunitinib (Sutent®) for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults

This assessment report is based on evidence submitted by Pfizer Ltd on 28 February 2011.

## 1.0 PRODUCT DETAILS

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| **Licensed indication** | Sunitinib (Sutent®) is indicated 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[1].<br><br>Please refer to the Summary of Product Characteristics (SPC) for licensed indications not covered in this submission[1]. |
| **Dosing** | For pNETs, the recommended dose of sunitinib is 37.5 mg taken orally once daily without a scheduled rest period[1]. |
| **Marketing authorisation date** | 29 November 2010 (initially licensed for gastrointestinal stromal tumours [GIST] 19 July 2006)[1,2]. |

## 2.0 DECISION CONTEXT

### 2.1 Background

pNETs, sometimes referred to as islet cell tumours, arise from pluripotent cells within the exocrine pancreas[4]. These tumours are uncommon and are consistently stated to occur at an incidence of < 1 per 100,000 in the available literature[4–13]; in particular, the UKNETwork for neuroendocrine tumours reported an annual incidence of 0.2–0.4 per 100,000[13].

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 non-specific symptoms[14–16]. 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)[13,14].

The majority of pNETs diagnosed are malignant but are typically slow-growing and have low mitotic activity[15]. Surgery is currently the only curative treatment, and for unresectable pNETs there is no well-defined standard of care[3,13,14]. For patients ineligible for surgery, guidelines recommend various palliative treatments (such as somatostatin analogues or proton pump inhibitors) and sometimes local ablative therapy, chemoembolisation or systemic chemotherapy (possibly by entering a clinical trial) for improving or maintaining quality of life (QoL). However, to date, such treatments have shown limited impact[13,15,17]. Patients with unresectable, locally advanced or metastatic pNETs with recent disease progression have an expected

survival of 1–3 years; each individual's prognosis is dependent on various factors including age, stage at diagnosis and functionality of pNET[14].

Sunitinib has been identified as an inhibitor of several receptor tyrosine kinases implicated in tumour growth, neoangiogenesis and metastasis of cancer cells[1,14]. Due to its anti-tumour properties, and in the absence of a licensed treatment for unresectable pNETs, sunitinib has been trialled for patients with metastatic, well-differentiated pNETs with disease progression[3].

The applicant company suggests that the use of sunitinib in the given population meets end of life (EOL) criteria; however the Welsh Medicines Partnership (WMP) is of the view that sunitinib does not meet EOL criteria.

The All Wales Medicines Strategy Group (AWMSG) did not recommend sunitinib for the treatment of advanced and/or metastatic renal cell carcinoma[18]; however this advice has been superseded by guidance produced by the National Institute for Clinical Excellence (NICE) which recommends its use[19]. Sunitinib has also been recommended by NICE for the treatment of unresectable and/or metastatic malignant GIST[20].

### 2.2 Comparators

WMP has identified best supportive care (BSC) as the most appropriate comparator for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

### 2.3 Guidance and related advice

- Ramage JK et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (2005)[13].
- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Neuroendocrine tumors (2010)[15].
- European Neuroendocrine Tumor Society (ENETS). Rare functioning pancreatic endocrine tumors (2006)[21].
- ENETS. Well-differentiated pancreatic non-functioning tumors/carcinoma (2006)[17].
- North America Neuroendocrine Tumor Society (NANETS). NANETS Treatment Guidelines: Well-differentiated neuroendocrine tumors of the stomach and pancreas (2010)[12].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission describes a phase III, multi-national, randomised, double-blind clinical trial comparing sunitinib and BSC with placebo and BSC for 171 adult patients (≥ 18 years) with unresectable, well-differentiated pNETs with disease progression[3,22]. Study A6181111 was designed to detect a 50% improvement in progression-free survival (PFS) as the primary endpoint. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response and changes in QoL. Systemic treatment-naive and treatment-refractory patients were included in the study, and somatostatin analogues were prescribed concomitantly at the discretion of the investigator. Patients receiving chemotherapy, chemoembolisation therapy or any other investigational anticancer agent were excluded. Patients were randomised (1:1) to two treatment arms. In addition to BSC, each arm received 37.5 mg sunitinib or equivalent placebo once daily as a starting dose. Treatment interruptions and dose reduction to 25 mg per day were permitted to manage adverse

events (AEs), and doses could be increased to 50 mg per day if there was no evidence of disease response. Patients were to be treated until occurrence of Response Evaluation Criteria in Solid Tumours (RECIST) defined progression, unacceptable AEs or death; however, an independent Data Monitoring Committee (DMC) recommended the study be closed ahead of all patients reaching these endpoints due to the difference in PFS and OS observed between the two groups. The DMC deemed that the study had met its primary endpoint at the time of termination (22 months post enrolment and after 81 events from both arms [75 patients with disease progression and 6 deaths without disease progression]) and recommended that patients on placebo be offered sunitinib as part of two open-label ongoing studies (A6181078[23] and A6181114[24]). Currently, no data are available for these studies[3,22]; estimated primary completion dates are August 2012 and May 2014, respectively[23,24].

At the point of study termination, patients had received sunitinib for a median duration of 4.6 months or placebo for a median duration of 3.7 months. Twenty-seven patients in the sunitinib arm had confirmed disease progression, compared with 48 in the placebo arm. An improvement in PFS was reported: a median of 11.4 months PFS for the sunitinib arm, compared with 5.5 months for the placebo arm. Kaplan-Meier analyses estimated a 71.3% probability of being event-free at six months for the sunitinib arm and a 43.2% probability for the placebo arm. With respect to OS, 9 deaths were reported in the sunitinib group compared with 21 in the placebo group, indicating a significant difference ($p = 0.02$). The hazard ratio for death, based on 30 events was 0.41 (95% confidence interval: 0.19, 0.89) in favour of sunitinib. Kaplan-Meier estimates of the probability of survival at six months were 92.6% and 85.2%, for the sunitinib and placebo groups, respectively. A significant proportion of patients (118/171; 69%) crossed over from placebo to sunitinib. The rank preserving structural failure time (RPSFT) model which corrects for substantial and early crossover was used and resulted in OS hazard ratios of 0.245 (0.080, 1.074) and 0.181 (0.057, 0.683) for the extension and blinded phases, respectively. Eight patients in the sunitinib arm had confirmed tumour response, compared with none in the placebo arm (ORR $p = 0.007$), and duration of response for these eight patients ranged from 0.9 to over 15.0 months. The European Organisation for Research and Treatment of Cancer Quality of Life (EORTC) questionnaire QLQ-C30 was used to measure patients' QoL over the first ten cycles of treatment. Data were available for 74/86 patients in the sunitinib arm and 71/85 patients in the placebo arm. No significant differences were determined between the two arms for any QoL measure with the exception of diarrhoea which is a known sunitinib toxicity[3,22].

The company submission included results from a supportive open-label, non-randomised phase II study (RTKC-0511-015); however this study was not specific to patients with pNETs and did not use a relevant comparator or primary endpoint. As suitable phase III data are available, this study will not be discussed further[3].

## 4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

During study A6181111, AEs were reported in 82/83 (98.8%) patients in the sunitinib arm and 78/82 (95.1%) patients in the placebo arm[3,14,22]. The most common treatment-related AEs in the sunitinib arm included diarrhoea, nausea, asthenia, neutropenia, leucopenia, hypertension and palmar-plantar erythrodysaesthesia syndrome. Serious AEs (SAEs) were experienced more frequently in the sunitinib arm compared with the placebo arm (11/83 [13.3%] versus 6/82 [7.3%], respectively). The AE profile of sunitinib was generally tolerable and manageable by dose adjustment and/or standard medical therapy. Discontinuation due to AEs occurred in 18 patients in the sunitinib arm and 14 patients in the placebo arm; however only four in the sunitinib

arm and one in the placebo arm were deemed treatment-related. The death rate was higher in the placebo arm (21/82 [25.6%]) than in the sunitinib arm (9/83 [10.8%]) and most were due to the underlying disease. One death in the sunitinib arm (cardiac failure) was deemed attributable to sunitinib[14,22].

Long-term safety data are not available as study A6181111 was terminated early; however the safety profile of sunitinib has been well documented for other indications and no new adverse events have been reported in this population[14].

## 5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Considering the unmet need for treatment of pNETs, a significant improvement in PFS with no deterioration of QoL is an important clinical benefit. An improvement in PFS was seen independent of baseline histology, Ki-67 (an antigen and cellular marker for proliferation) index, disease burden, prior therapy and time from diagnosis. In addition, improvements for the secondary endpoints of ORR (9% versus 0%, p = 0.007) and OS (hazard ratio 0.41, 95% confidence interval: 0.19, 0.89 , p = 0.02) in the sunitinib arm were observed[3,14].
- Concerns were raised by the Committee for Medicinal Products for Human Use (CHMP) regarding the overestimation of the clinical benefit of sunitinib due to the early termination of the study[14]. The calculated p-value for the PFS endpoint was deemed statistically significant by the company (p = 0.0001); however the trial was terminated after three data observations, which were not taken into account in the 'headline' statistical analyses. From the results of subsequent sensitivity analyses, CHMP acknowledged that whilst the true benefit may be more modest than initially presented it was unlikely to have been a dramatic overestimation[14].
- A blinded independent central review (BICR) provided by the company supported the efficacy findings (p < 0.001) and reported a hazard ratio value consistent with previous results[3,14].
- CHMP highlighted that the number of treatment-naive patients included was low (53/171 [31%]; 29 in the sunitinib arm and 24 in the placebo arm) and stated a need for further evidence in support of the efficacy of sunitinib in this population[14]. It is for this reason that the licensed indication states that experience with sunitinib as a first-line treatment is limited[1].
- After study termination there were 21 additional deaths reported among patients who withdrew or enrolled in one of the open-label sunitinib extension studies. Overall, 21 deaths occurred in the sunitinib arm and 30 occurred in the placebo arm[3]. The updated Kaplan-Meier six-month survival probabilities were 91.6% and 84.0%, respectively. The crossover to sunitinib of some patients who had previously received placebo would, however, confound the OS results, hence PFS was chosen as the primary endpoint[3].
- The characteristics of the cohort may not be representative of the population of Wales as only 59% were white; however 27% were categorised as 'other or unspecified'[22].
- A Good Clinical Practice (GCP) investigation determined several critical and major deviations from protocol including discrepancies between site and inspector assessment of the PFS criteria (e.g. status of the disease and date of progression); therefore quality control of the study by the applicant company has been questioned by CHMP[14].
- CHMP raised concerns regarding the high rate of (and inconsistencies in) censoring; 56/86 (65.1%) patients in the sunitinib arm and 34/85 (40%) patients in the placebo arm were censored[14]. These concerns were however addressed

by the applicant company and accepted by CHMP. Sensitivity analyses confirmed that the effects of certain censored events did not alter the interpretation of the results[14].

- The treatment effect of sunitinib (improvement in PFS) was statistically significant regardless of age, race, gender, Eastern Cooperative Oncology Group (ECOG) performance status, number of disease sites and time from diagnosis to study enrolment[3]. The treatment effect of sunitinib showed a trend towards increased benefit in functioning (as opposed to non-functioning) tumours. The efficacy of sunitinib appeared similar regardless of the number of prior treatments or previous exposure to somatostatin analogues. Sunitinib appeared to favour the few patients (n = 29) with Ki-67 index > 5%[3].

## 6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

### 6.1 Cost-effectiveness evidence

#### 6.1.1 Context

The company submission describes a cost-utility analysis (CUA) of sunitinib with BSC compared with BSC alone in the treatment of unresectable or metastatic, well-differentiated pNETs with disease progression in adults[3]. The analysis takes into account sunitinib being supplied via a patient access scheme (PAS)[3]. Details of the PAS are commercial in confidence. The analysis is based on a Markov state transition model, which employs PFS data derived from A6181111[25], and OS data derived from a post-hoc analysis of these trial data. Patients enter the model in a progression-free state, where they may remain or from which they may progress to a progressive disease state and/or to a death state over a ten-year time horizon. Sensitivity analyses include variation in survival rates, time horizon, sunitinib acquisition costs, treatment discontinuation rates and use of somatostatin analogues. Uncertainty surrounding the cost effectiveness estimates is considered using probabilistic analysis. See Appendix 1 for further details.

#### 6.1.2. Results

When the PAS is not incorporated into the analysis (i.e. NHS Wales is assumed to meet the full cost of sunitinib treatment), the ICER increases to £24,098 per QALY gained[3].

The table containing information on the CUA of sunitinib versus BSC has been removed as it contains commercial in confidence data.

All sensitivity analyses relate to the company supplying sunitinib via a PAS. These analyses included variation in the time horizon (5–15 years), dose intensity (70–100%), discontinuation rate (0–3.22%), proportion of patients receiving somatostatin analogues (0–28%), cost of palliative care (£0–£4,490) and different methods of extrapolating survival over time.

#### 6.1.3 WMP critique

Strengths of the economic evidence include:

- The major costs and consequences associated with treatment are incorporated into the model.
- A wide range of sensitivity analyses have been conducted to explore the impact of different modelling approaches to PFS and OS data extrapolation.

Limitations of the economic evidence include:

- The trial providing the main efficacy data was terminated prematurely at the recommendation of an independent DMC. This results in uncertainty associated with the post-hoc estimation of OS which includes data from the open-label extension in which a significant proportion of patients crossed over to the sunitinib arm.
- The use of alternative approaches to model treatment effect (hazard ratio) and extrapolation of PFS and OS results in higher ICERs, although these are more likely to be influenced by the confounding effect of crossover.
- It is not clear that all relevant sunitinib-related AEs and associated costs over time have been incorporated into the model; however, these are likely to be small compared to the acquisition costs of sunitinib and are not likely to have a substantial impact on the magnitude of the ICER estimates.
- Combined uncertainty in parameter values has been explored via probabilistic sensitivity analysis, but this is still based on the base case approach to survival data extrapolation. Alternative extrapolation approaches yield lower probabilities of sunitinib being cost effective at any given threshold of cost effectiveness.

### 6.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of sunitinib treatment in pNET patients.

## 7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 7.1 Budget impact evidence

#### 7.1.1 Context and methods

The company estimates that there are five patients newly diagnosed with pNET each year based on a range of published studies for non-Welsh populations[3]. When considering an estimated five-year survival of 33% (in the absence of sunitinib), the company expects there to be eight prevalent cases, resulting in an estimated total of 13 cases in year 1. Assuming the economic model-derived survival rates of 83%, 66%, 52% and 40% after years 1, 2, 3 and 4 post-diagnosis, respectively, the net number of eligible patients is expected to increase from 13 at year 1 to 20 at year 5. The company anticipates an uptake rate of 60% for sunitinib; therefore, the estimated number of patients prescribed sunitinib would be 8 at year 1, rising to 12 in year 5.

Reportedly based on the economic model, it is assumed that patients would receive an average of 293 days treatment per year. The estimated number of patients treated with sunitinib and the associated costs over the five-year period are shown in Table 2.

A scenario analysis is provided in which it is assumed there are no discontinuations (i.e. continuous treatment for 12 months per year).

**Table 2. Company-reported costs associated with sunitinib treatment.**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Number of eligible patients | 13 | 16 | 18 | 19 | 20 |
| Uptake (%) | 60% | 60% | 60% | 60% | 60% |
| Number of treated patients | 8 | 10 | 11 | 11 | 12 |

| | | | | | |
|---|---|---|---|---|---|
| Sunitinib drug costs | **CIC | **CIC | **CIC | **CIC | **CIC |
| Medical management | £16,348 | £20,435 | £22,478 | £22,478 | £24,522 |
| Somatostatin analogues | £31,004 | £38,755 | £42,631 | £42,631 | £46,506 |
| Adverse event costs | £727 | £909 | £1,000 | £1,000 | £1,091 |
| **Overall net costs*** | **CIC | **CIC | **CIC | **CIC | **CIC |

* Taking into account discontinuation rate of 2.5944% per 4-week cycle according to A6181111 trial[25].

** CIC-commercial in confidence

### 7.1.2 WMP critique of the company's budget impact estimates

The budget impact analysis is based on costs derived from the economic model. The limitations of the economic model would therefore apply to the budget impact. The assumption is that a PAS is in operation. The company's estimates of the number of eligible patients for sunitinib treatment in Wales are based on a range of non-Welsh sources. Welsh cancer statistics data[26,27] suggest there are around 450 patients diagnosed with pancreatic cancer each year, but the proportion with pNET is not certain. There would therefore appear to be a degree of uncertainty in the estimated budget impact.

### 7.2 Comparative unit costs

There are currently no other licensed treatments for pNETs in the UK. Somatostatin analogues may be used as a component of BSC in pNETs patients, but are not direct comparators. The 28-day cost of sunitinib at the recommended dose of 37.5 mg once daily would be £2,354.10[28].

## 8.0 ADDITIONAL INFORMATION

### 8.1 Shared care arrangements

WMP is of the opinion that sunitinib is not suitable for shared care within NHS Wales.

### 8.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

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## Appendix 1. Additional health economic information

### Table 1A. Health economic model detail.

| | Base case model | Appropriate? |
|---|---|---|
| **Comparator(s)** | BSC (including use of somatostatin analogues where relevant). | Yes, as requested by WMP. Currently there are no other licensed products for treatment of pNETs in the UK. |
| **Population** | Adults with unresectable or metastatic, well-differentiated pNETs with disease progression. | Yes, in line with the licensed indication[1]. |
| **Analysis type** | CUA of sunitinib versus BSC with or without use of somatostatin analogues. Patients enter the model in a progression-free state, where they may remain or from which they may advance to a progressive disease state and/or to a death state. | CUA is the preferred type of analysis. The modelled clinical pathway would seem appropriate. |
| **Perspective** | Considers direct medical costs only, from the perspective of NHS Wales. | Yes. |
| **Time horizon** | The base case analysis assumes a ten-year time horizon. Sensitivity analysis includes projections over 5 and 15 years. | Yes, justified based on the life expectancy for pNET patients. |
| **Discount rate** | For base case analysis a 3.5% p.a. discount rate is applied to both costs and outcomes. Sensitivity analysis includes 0% and 6% discount rates. | Yes. |
| **Efficacy** | PFS data are derived directly from the pivotal phase III randomised, double-blind trial (A6181111)[25]. OS data are derived from post hoc analyses of the trial data, undertaken to account for the significant degree of crossover of patients from the placebo arm to the sunitinib arm at the point of disease progression. Survival data were fitted with three statistical distributions to select the most appropriate model. Two extrapolation methods (stratified modelling versus common shape modelling) were explored to estimate PFS and OS in sensitivity analyses. | The pivotal trial was terminated very early due to reported increases in median PFS with sunitinib treatment at interim analyses. The company has conducted post hoc analyses of the OS data to account for the fact that a significant proportion of patients in the placebo arm crossed over to the sunitinib arm at the point of progression. A variety of methods have been explored to extrapolate patient-level PFS and OS data, and it is not possible to verify these data with published sources. The methods used in the base case analyses are stated to be conservative in terms of their impact upon modelled PFS and OS, although ICER estimates are generally lower using the base case methods compared with the other methods that have been explored. |
| **Adverse effects** | Costs associated with AEs included treatment of hypertension, diarrhoea, hypoglycaemia, hypothyroidism and palmar-plantar erythrodysaesthesia for sunitinib patients, and abdominal and back pain for patients receiving BSC. Management costs are based on company sought expert opinion on trial data. | The model presented by the company includes probabilities of various AEs based on the trial follow-up period, but the model assumes ongoing treatment that extends beyond this period, and data from ongoing extension studies indicate increased rates of some grade three or four adverse events[14], e.g. neutropenia incidence of 12% is assumed in the model for sunitinib treatment based on rates observed in the published A6181111 trial[22]; however, ongoing extension studies in pNET patients have reported rates of 21% for grade three or four neutropenia. In addition, treatment costs for neutropenia are not included. |

**Table 1A continued.**

| | Base case model | Appropriate? |
|---|---|---|
| **Utility values** | Utility values were derived by mapping data from the EORTC QLQ-C30 questionnaire collected during the A6181111 trial[25] into the EQ-5D instrument using a published mapping algorithm[29]. The mean baseline utility value for both sunitinib and placebo groups was 0.73. For post-progression patients a utility value of 0.596 was assumed. | The company has used the mapped utility derived from the phase III A6181111 trial in the base case analysis. Sensitivity analysis includes the use of directly obtained utility values from a phase II trial, which demonstrate that the approach used in base case analysis is more conservative. Sensitivity analysis demonstrated that post-progression utility was the most sensitive parameter affecting ICER. |
| **Resource use and costs** | The maximum number of treatment cycles is curtailed at 22. Other treatment costs include somatostatin analogues, consultations, CT scans, biochemistry and blood count tests, and palliative care costs. | The major resource utilisation costs associated with sunitinib treatment are addressed although it is not clear that all sunitinib AE costs (e.g. neutropenia) have been captured. The end-of-life care costs are based on a study published in 1999[30] and other costs are based on reference costs from 2008 to 2009, rather than more recent sources[31], though sensitivity analyses indicate that the modelled ICER is relatively insensitive to most non-drug cost components. |
| **Uncertainty and scenario analyses** | Uncertainty associated with structural assumptions in the model was assessed by varying sunitinib dose intensity (70–100%), discontinuation rate (0–3.22%), time horizon (5–15 years), discounting rate (0–6%), costs of palliative care (£0–£4,490) use of somatostatins, and PFS and OS estimated using different modelling methods. Uncertainty associated with model parameters was assessed using one-way sensitivity analyses varying all model parameters by ±20%. Probabilistic analysis was conducted to produce CEACs for threshold values of cost per life-year and cost per QALY. Scenario analysis addressed the impact of alternative methods of extrapolating survival data. | A wide range of sensitivity analyses were performed based on Sunitinib being supplied via a PAS. |
| **Model provided?** | Yes. | Yes. |

AEs = adverse events; BSC = best supportive care; CEAC = cost effectiveness acceptability curve; CUA = cost utility analysis; EORTC = European Organisation for Research and Treatment of Cancer; ICER = incremental cost per QALY gained; OS = overall survival; p.a. = per annum; PAS = patient access scheme; PFS = progression-free survival; pNETs = pancreatic neuroendocrine tumours