

Sunitinib and everolimus for the treatment of pancreatic neuroendocrine tumours: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

September 2017

Abstract

Purpose

To compare the predicted and actual utilisation of sunitinib and everolimus for the treatment of pancreatic neuroendocrine tumour (pNET) since these medicines were PBS listed for this indication in December 2013 and April 2015 respectively.

Current PBS restriction for pNET

Sunitinib (Sutent®) 12.5 mg, 25 mg and 50 mg capsules were PBS listed for pNET on 1 December 2013. The 37.5 mg strength was added on 1 September 2015. Everolimus (Afinitor®) 5 mg and 10 mg capsules were listed for pNET on 1 April 2015.

Eligible patients must have metastatic or unresectable, well-differentiated malignant pNET. Patients must be symptomatic (despite somatostatin analogues); or patients must have disease progression.

Patients who have developed progressive disease on everolimus are not eligible to receive PBS-subsidised sunitinib for this condition. Disease progression must be documented in the patient's medical records. Patients who have developed intolerance to sunitinib or everolimus that is sufficiently severe to necessitate permanent treatment withdrawal are eligible to receive PBS-subsidised treatment with the other listed medicine.

Key Findings

- The actual prescription utilisation and R/PBS expenditure was less than predicted for both sunitinib and everolimus.
- The number of patients treated was more than expected for both drugs ([REDACTED] and [REDACTED]).
- The number of prescriptions per patient per year and the overall length of treatment per patient for both drugs were much less than predicted.

Purpose of analysis

To compare the predicted and actual utilisation of sunitinib and everolimus for the treatment of pNET since they were PBS listed for this indication in December 2013 and September 2014 respectively. To review the pattern of utilisation as requested by the PBAC at its August 2013 meeting.

Background

Clinical situation

pNET is a rare cancer with a poor prognosis for many patients. This tumour is often diagnosed at an advanced stage and metastases are often present. Surgical removal of the tumour is not always practical for many patients with pNET.

Sunitinib and everolimus provide a therapeutic option for patients who have metastatic disease and where surgery is not an option.

PBAC considered at its March 2012 meeting there was a high clinical need for treatment in this rare type of cancer.

Pharmacology

Sunitinib is a small molecule that simultaneously inhibits multiple receptor tyrosine kinases that are implicated in tumour growth, pathologic angiogenesis and metastatic progression of cancer.

Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival.

Therapeutic Goods Administration (TGA) approved indications

Sunitinib (Sutent®) is TGA registered for

- Unresectable well-differentiated pNET, 2 March 2011.
- Advanced renal cell carcinoma.
- Gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance.

Everolimus (Afinitor®) is TGA registered for the following indications:

- For the treatment of postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

- For the treatment of patients with progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin.
- For the treatment of patients with advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.
- For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), who require therapeutic intervention but are not candidates for curative surgical resection.
- For the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

Dosage and administration

Sunitinib does not usually require dose adjustments based on age, body weight, race, gender or progression of disease.

Sunitinib and everolimus are metabolised by CYP3A4 enzymes. Coadministration of potent inhibitors will increase serum levels and dose adjustment may be required.

Absorption of food affects serum levels of everolimus.

Relevant aspects of consideration by the PBAC (abridged)

The PBAC considered four submissions for sunitinib in pNET (PBAC meetings July 2011, March and July 2012 and August 2013) and two submissions for everolimus in pNET (PBAC meetings November 2012 and March 2014).

Comparative Clinical Effectiveness

Sunitinib

The PBAC considered evidence from a randomised clinical trial (A618-1111) and a 36-month follow-up analysis. The primary outcome of the trial was progression free survival. Overall survival was measured in the trial and in follow-up analyses; however the trial allowed early cross over of patients from the placebo arm and, as a result, the PBAC considered that the magnitude of the overall survival measured is likely to be overestimated. The trial was also terminated early and there were multiple interim analyses that lead to greater uncertainty about the magnitude of benefit in progression free survival.

The progression free survival reported for the clinical trial was 11.4 months (sunitinib) compared to 5.5 months (placebo) [HR 0.418, 95% CI 0.263, 0.662, p=0.000118].

The PBAC considered that sunitinib was likely to have some survival benefit but the size of the effect is unknown and likely to be less than claimed.

Everolimus

PBAC considered two submissions for everolimus in pNET. The submissions presented an indirect comparison of everolimus (RADIANT-3) and sunitinib (A618-1111). There was some uncertainty in the exchangeability and remaining concern in the likely overestimation of progression free survival in the A618-111 study (noted above).

Economic evaluation

Sunitinib

The economic model used overall survival measured in the clinical trial [HR=0.409, 95% CI 0.187, 0.894, p=0.0204]. The model then extrapolated the trial values (using the rank preserving structural failure time method) to adjust the overall survival values for use in the model. The resulting values for overall survival were 30.5 months on sunitinib compared to 17.5 months on placebo or best supportive care in a 10 year model. These values were reported in the public summary document as adjusted overall survival. The PBAC considered that 10 years was a long duration for the model and added to the overestimation of the cost effectiveness. The QALYs gained from sunitinib treatment were [REDACTED]. The model was most sensitive to the difference in utility weights used. The model did not allow for a reduced utility value (reflecting reduced quality of life) once the disease has progressed (the post progression state).

The PBAC accepted an incremental cost effective ratio/quality adjusted life year in the range \$45,000 to \$75,000.

The most important uncertainties in the health economic model were the magnitude of the overall survival gained when treated with sunitinib, having a 10 year duration for the model and the magnitude of the quality of life gained from treatment with sunitinib.

Everolimus

Everolimus was listed on a cost minimisation basis, 8.59 mg/day equivalent to 34.24 mg/day until progression or high toxicity.

Utilisation

[REDACTED]

PBAC recommended that everolimus and sunitinib share the same market for pNET and this be reflected in any risk sharing arrangement.

PBAC decision

At the August 2013 PBAC meeting the committee recommended listing sunitinib for pNET on the basis of acceptable cost effectiveness *“in the context of high clinical need, the lack of alternative treatments, the rarity of the condition, the small number of patients predicted (approximately 60 annually) and the relatively modest overall financial impact on the PBS.”*

PBAC acknowledged the high level of uncertainty in the magnitude of the benefit but determined this was acceptable in this instance. The committee requested that DUSC undertake an evaluation of the pattern of utilisation and duration of therapy for sunitinib [and everolimus].

For further details refer to the [Public Summary Document by product](#) or [meeting](#).

Approach taken to estimate utilisation

The submissions to PBAC from Novartis and Pfizer for everolimus and sunitinib for pNET were not considered by DUSC.

The sunitinib submission used an epidemiological approach to the predicted patient use and cost. The annual incidence of islet cell carcinoma with a pancreatic primary site was based on AIHW data. The assumptions of survival (30.5 months), tumour progression rate ([REDACTED]), proportion continuing treatment after disease progression and cost of adverse events were consistent with the economic model. The proportion of patients with unresectable disease ([REDACTED]) and uptake was based on clinical opinion. At the time of the submission for sunitinib the costs were adjusted to allow for the lack of the 37.5mg strength being available at the time of listing, noting that this was the most commonly prescribed dose. This strength was later listed. This would have resulted in a small reduction in overall cost. The everolimus submission used a market share approach.

The predicted estimates for sunitinib and everolimus are presented in Table 1 below. These are sourced from the submissions to the PBAC and PBS agreed estimates of utilisation prepared before listing on the PBS.

Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET). Refer to Appendix A for additional details of the restriction. There have been no changes to the restriction since listing on the PBS.

Table 2: Listing details

Sunitinib (Sutent®)	Item Code	Initial or Continuing	No. of repeats	Effective price rebate	DPMQ at listing (DPMQ August 2017)
Capsule 12.5 mg 28	10004M	Initial	2	[REDACTED]	\$1834.41 (\$1736.75)
	10009T	Continuing	5		
Capsule 25 mg 28	2959R	Initial	2	[REDACTED]	\$3521.97 (\$3356.14)
	2842N	Continuing	5		
Capsule 37.5 mg 28	10464R	Initial	2	[REDACTED]	\$5210.11 (\$4959.60)
	10473F	Continuing	5		
Capsule 50 mg 28	2837H	Initial	2	[REDACTED]	\$6897.65 (\$6563.05)
	10010W	Continuing	5		
Everolimus (Afinitor®)					
Capsule 5 mg 30	10133H	Initial	2	[REDACTED]	\$2846.70 (\$2714.52)
	10131F	Continuing	5		
Capsule 10 mg 30	10132G	Initial	2	[REDACTED]	\$5546.70 (\$5279.52)
	10135K	Continuing	5		

DPMQ = dispensed price maximum quantity. Note that the everolimus item codes are also used for RCC. The pNET and the RCC prescriptions can only be distinguished by reference to the authority restriction code (see Table 3).

The effective price is managed using a special pricing arrangement. The Commonwealth calculates the difference between the expenditure based on the published price in the schedule (DPMQ less patient copayment) and the expenditure based on the effective price and invoices the respective pharmaceutical companies each quarter.

The DPMQ of sunitinib and everolimus was adjusted following flow on of the F1 formulary 5% statutory price reduction in 1 April 2016.

Previous reviews of sunitinib and everolimus by DUSC

Sunitinib and pazopanib for the treatment of renal cell cancer were the subject of a predicted vs actual analysis (4 years post listing for sunitinib and 1 year post listing for pazopanib) that was considered at the June 2014 meeting.¹ The key findings for sunitinib were;

- Sunitinib incident and prevalent patients were [REDACTED] more than expected in the 3rd year after listing (ie. the most recent year not confounded by the listing of

¹ <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/pazopanib-sunitinib>

pazopanib). This difference was due to there being a higher treatment discontinuation rate than expected.

- Even though prevalent patients were █% more than expected in year 3, supplied scripts were █% less than expected. This was due to the average number of scripts per patient being less than expected (i.e. predicted = 7.3, actual = 5.6 scripts per prevalent patient).

Everolimus for the treatment of Tuberous Sclerosis Complex (TSC)² and metastatic (Stage IV) breast cancer³ was the subject of a predicted vs actual analysis (2 years post listing) that was considered at the February 2017 meeting. The key findings for TSC were;

- Since listing on the PBS on 1 December 2013, 322 patients were supplied everolimus for TSC.
- The use of 2.5 mg and 5 mg prescriptions was higher than estimated, and the use of 10 mg prescriptions was lower than estimated.

The key findings for metastatic (Stage IV) breast cancer were;

- There were 1,813 patients identified as having been treated with everolimus for metastatic breast cancer over its first two years of listing. This was less than predicted.
- The duration of therapy with everolimus plus exemestane was shorter than predicted. There was a median of four prescriptions per year compared with an estimated seven prescriptions per year.
- The proportional use of the higher (10 mg) strength of everolimus was greater than predicted. As such, the predicted versus actual expenditure on everolimus was similar (based on the published prices).

DUSC also provided advice to the PBAC regarding a submission for listing of sunitinib for gastrointestinal stromal tumour (GIST) that was considered by the July 2009 PBAC.

² <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/everolimus-tuberous-sclerosis-complex-feb-2017>

³ <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/everolimus-breast-cancer-february-2017>

Methods

PBS prescription data for sunitinib and everolimus from 1 May 2009 (first listing for sunitinib) to 31 March 2017 were extracted from the DHS prescription database based on the date of dispensing (supply). Reports using the date of processing of PBS prescriptions may differ from the date of dispensing. Consequently there may be differences in data reported by date of dispensing or processing (such as that available publicly available from DHS Medicare website).

PBS prescription data were used to determine the number of prescriptions supplied and the PBS expenditure. These data were also used to count the number of patients, both incident (new to treatment) and prevalent (number treated in each time period, i.e. year or quarter).

The main analysis relates to utilisation since sunitinib was listed for the pNET indication (1 December 2013). Data prior to this were used as part of the analysis to determine the "Patient Classification" in the "Indication sequence and patient classification" section.

There is a possibility that PBS prescriptions assigned to item codes for pNET may have been used for non-pNET patients, and vice versa. Additional information on this is detailed in section 3 of the results. As this misclassification could have an effect on the patient-level analyses, a second dataset was developed to minimise the effect of misclassification in these analyses.

There are two different sets of data used in the analyses:

1. The utilisation dataset includes all the prescription information for sunitinib and everolimus prescriptions indicated for pNET based on PBS item codes and authority approval restriction codes (see Table 3 below). Refer to sections 1 and 2 of the results.
2. The patient cohort described as "Considered to be patients with pNET" (Cohort pNET) contains everolimus and sunitinib prescription data for all patients considered to definitely have pNET. Refer to section 3 of the results.

Dataset 2 was used in analyses for length of treatment with either medicine. The Kaplan Meier (aka Product-Limit) method was applied to determine the length of treatment for patients on sunitinib and everolimus for pNET. Two ways of measuring length of treatment were undertaken to account for patients stopping medicine for periods of time (called a 'break' in therapy). One analysis excluded the time of any breaks in treatment (i.e. reports the total time a patient is actually receiving regular supplies of the medicine) and the other did not. In these analyses a break in treatment was defined as a gap of more than 3 times the median time to resupply between supplies of the medicine. This represented an estimated break in treatment of at least 2 times the median time to resupply.

To account for the end of the data observation period appearing as patients stopping treatment when they would probably continuing to receive supplies of the medicine a censoring definition was applied. A patient was deemed to be continuing treatment (classified as censored in the Product- Limit method) at the end of the data period (i.e. the end of March 2017) if their last prescription is within 3 times the median time to resupply

of this end date. Otherwise the patient is deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply.

The patient-level analysis also estimates the time from cessation of medicine treatment to death (section 3.3). It was decided to determine date of death using two methods:

1. PBS prescription data to estimate a proxy for date of death. This established method uses the cessation of supply of any PBS medicine as a proxy. Refer to Appendix B for additional details on the application of this method.
2. A request for the date of death from the Medicare enrolment file for pNET patients. These data were used to validate the proxy in method 1 (see Appendix C).

Results

1. Utilisation analyses

1.1 Prescription Utilisation

The sunitinib PBS item codes included in the analysis were all pNET indication specific items (see Table 3). However this is not the case for everolimus PBS item codes. The everolimus item codes for pNET are also used for RCC. Prescriptions for pNET can only be distinguished from those for RCC by having regard to both the item code and the authority approval restriction code. As these items are not streamlined authority, the restriction code must be sourced from the DHS telephone authority approval database.

Table 3: PBS items and restriction codes for the treatment of pNET

Drug	Description	PBS Item	Authority restriction code	Initial or Continuing
everolimus	Tablet 5 mg	10133H	4861	Initial
		10131F	4837	Continuing
	Tablet 10 mg	10132G	4861	Initial
		10135K	4837	Continuing
sunitinib	Capsule 12.5 mg (as malate)	10004M	na	Initial
		10009T	na	Continuing
	Capsule 25 mg (as malate)	02959R	na	Initial
		02842N	na	Continuing
	Capsule 37.5 mg (as malate)	10464R	na	Initial
		10473F	na	Continuing
	Capsule 50 mg (as malate)	02837H	na	Initial
		10010W	na	Continuing

na = not applicable, as the pNET indication is specific to the PBS item code.

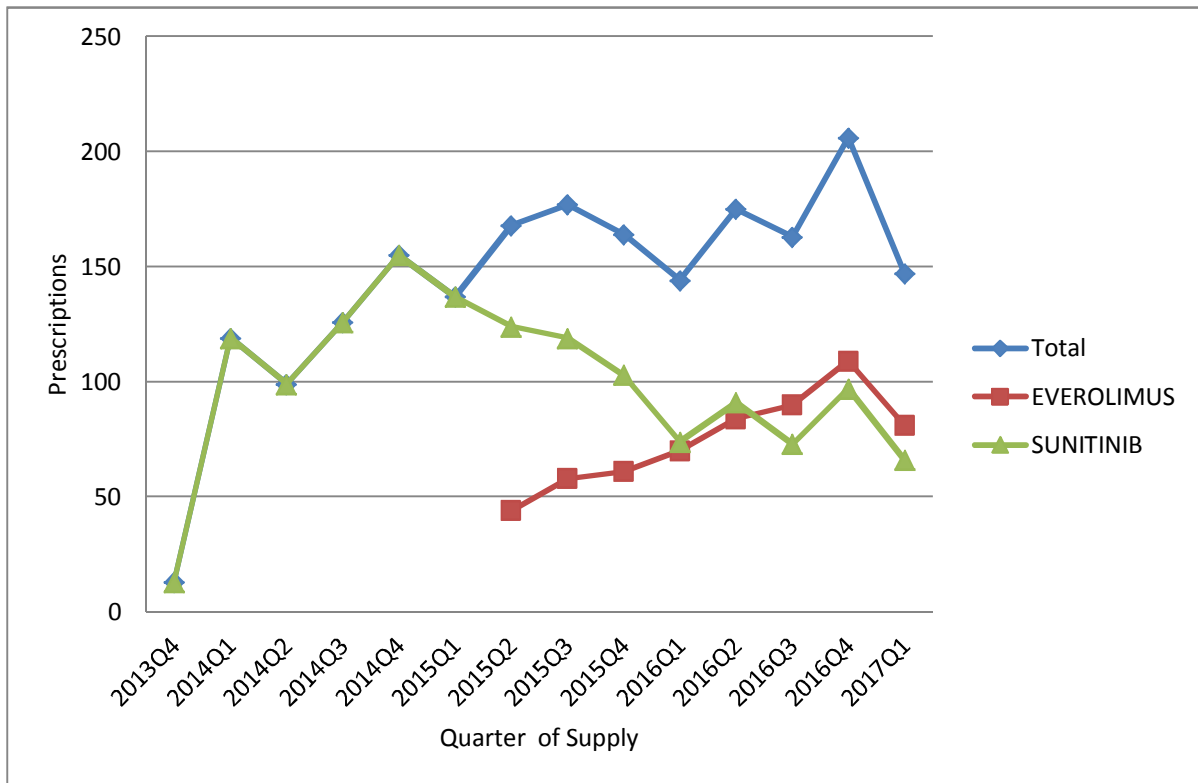


Figure 1: Prescriptions of medicines for the treatment of pNET.

Source: DHS prescription claims database (accessed 24 August 2017).

Figure 1 shows that after listing of everolimus for pNET on 1 April 2015, everolimus appeared to gradually substitute for sunitinib and exceeded sunitinib utilisation in quarter three of 2016. The submission for everolimus predicted a large number of patients would take up everolimus in preference to sunitinib. In the first year the submission predicted 50% substitution and in the second year 75%.

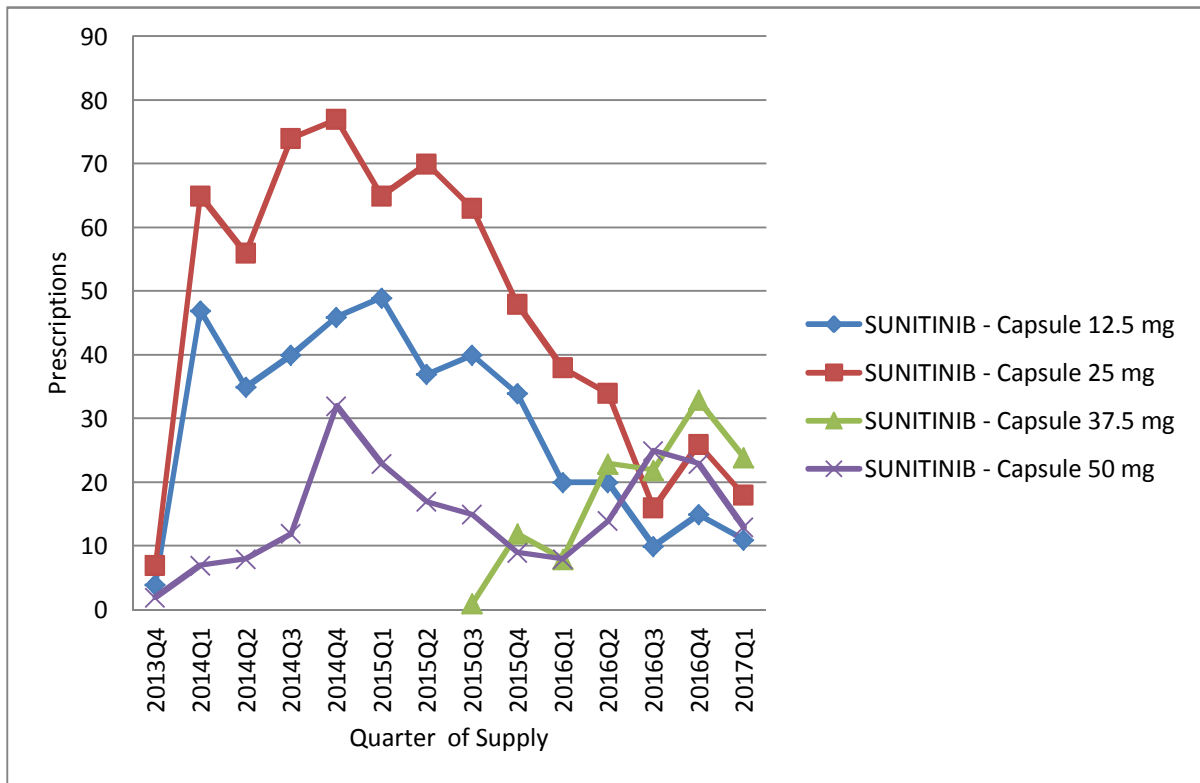


Figure 2: Sunitinib prescriptions for pNET by strength

Source: DHS prescription claims database (accessed 24 August 2017).

Figure 2 shows that the 37.5 mg strength has been substituting the 12.5 mg and 25 mg strengths since it was listed on 1 September 2015. As this involves the use of one prescription instead of two, it would have contributed to the fall in overall sunitinib prescriptions in Figure 1 from quarter 3 2015. The 25 mg was the most used strength of sunitinib until quarter 2 2016, after which the 37.5 mg strength became the most common.

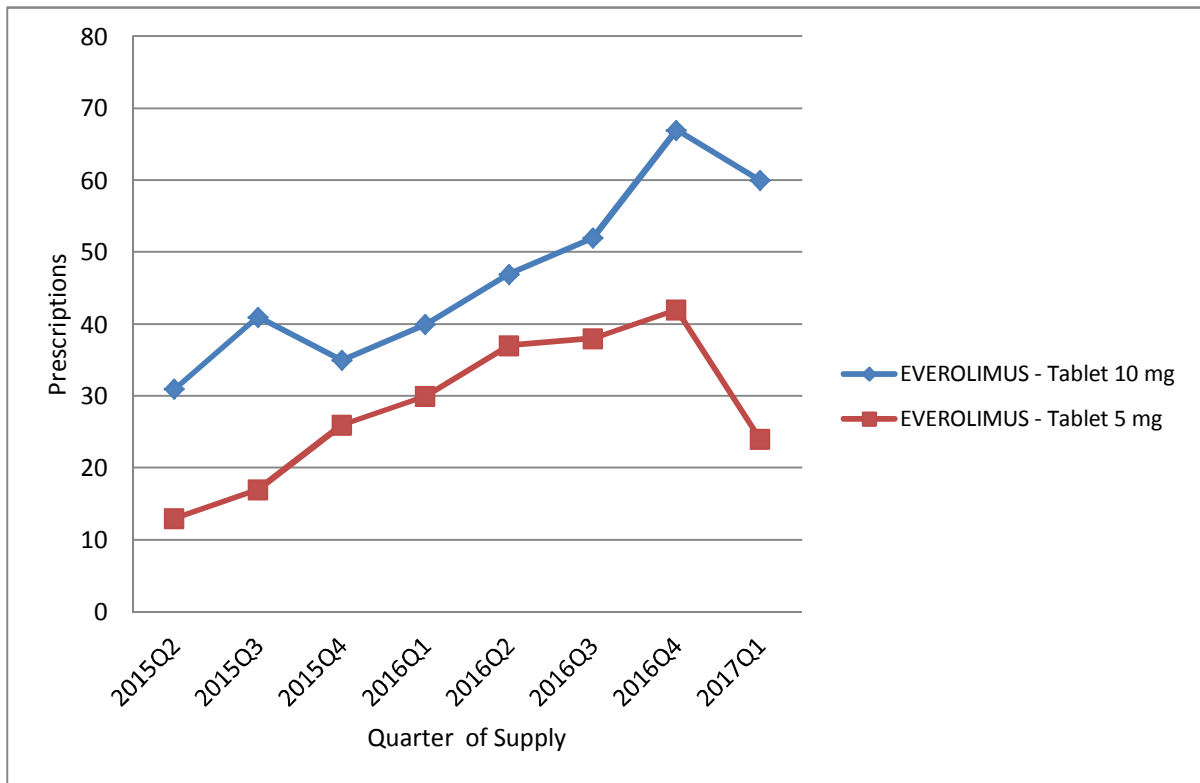


Figure 3: Everolimus prescriptions for pNET by strength

Source: DHS prescription claims database (accessed 24 August 2017).

Supply of both strengths of everolimus has increased steadily since listing, except for a decrease in quarter 1 2017.

The steady increase in prescriptions is related to Figure 5, showing a steady increase in the number of prevalent patients taking everolimus.

1.2 Initiating and prevalent patient counts

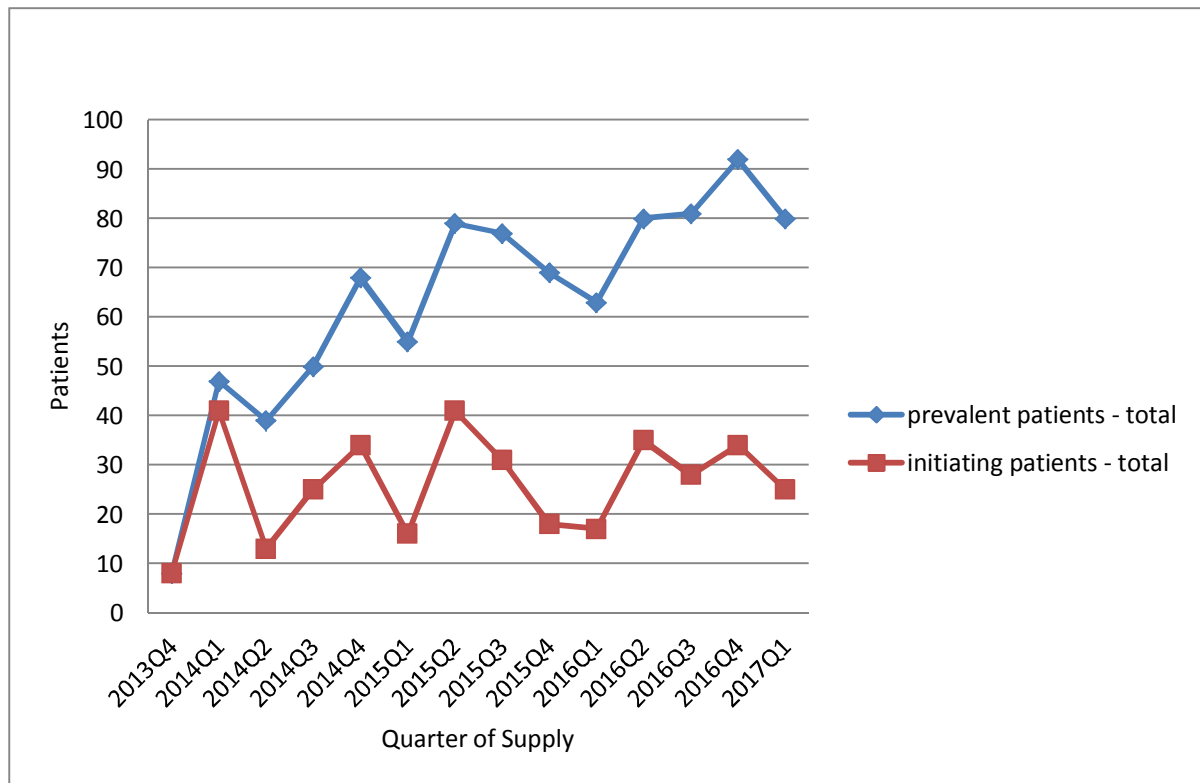


Figure 4: Number of patients initiating and prevalent to therapy for pNET.

Source: DHS prescription claims database (accessed 24 August 2017). Note: “therapy” means supply of everolimus or sunitinib

The number of unique therapy initiating patients was greatest in quarter 1 2013 (41 patients), the first full quarter after sunitinib was listed for pNET, and again in quarter 2 2015 (41 patients), the first full quarter after everolimus was listed for pNET on 1 April 2015. Overall the trend of uptake for initiators is constant. The number of prevalent patients may have plateaued but this analysis does not provide sufficient observation time to be confident of this.

This graph only counts patients once so that those patients who have switched from sunitinib to everolimus after 1 April 2015 or who subsequently switch are not double counted. The following graph (Figure 5) provides the number of patients who are initiating and prevalent for each medicine separately. This shows the uptake of both drugs.

Comparison of Figure 4 and Figure 5 shows the extent of substitution of everolimus for sunitinib in the therapeutic market for treatment of pNET.

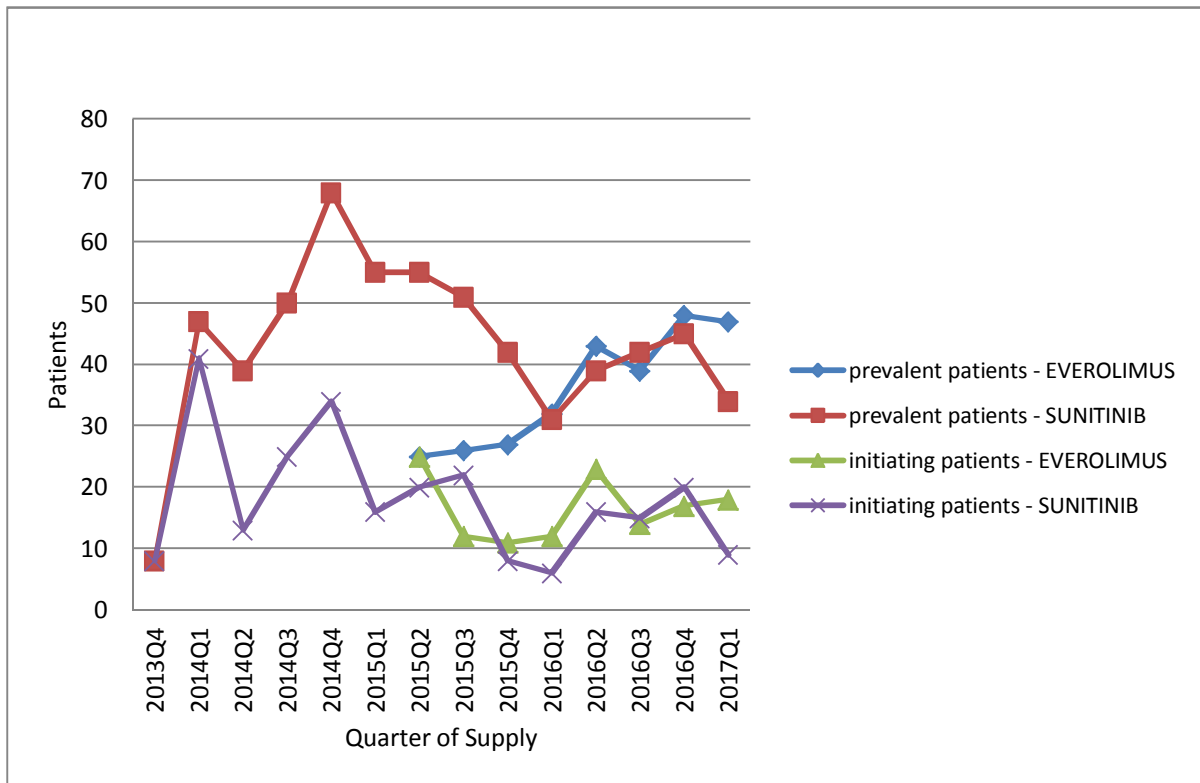


Figure 5: Number of patients initiating and prevalent to everolimus and sunitinib for pNET. Source: DHS prescription claims database (accessed 24 August 2017).

The total number of patients on everolimus was higher than the total number of patients on sunitinib by the end of the period. The number of patients initiating everolimus was also higher than for sunitinib. A proportion of patients who initiated on or after 1 April 2015 may have switched from sunitinib to everolimus, and subsequently from everolimus to sunitinib.

2. Analysis of predicted versus actual utilisation

This analysis compares the predicted and actual use of use of sunitinib and everolimus for pNET. The predicted use was extracted from final agreed estimates between the sponsor and the Department of Health. The PBS items and restriction codes included in this analysis of actual utilisation are specified in Table 3.

Table 4: Predicted vs Actual analysis – sunitinib for pNET

		Year1	Year 2	Year 3
		Dec13 to Nov14	Dec14 to Nov15	Dec15 to Nov16
Prevalent eligible (incidence 0.22/100,000 * median survival (30.5months) * 75% with unresectable disease)		■	■	■
Incident eligible population per year		■	■	■
Uptake of treatment with sunitinib		■	■	■
Treated eligible patients	Actual (A)	106	118	87
	■	■	■	■
Prescriptions	■	■	■	■
	■	■	■	■
	Actual (A)	453	514	335
	■	■	■	■
Prescriptions per patient	■	■	■	■
	Actual (A)	4.3	4.4	3.9
	■	■	■	■
R/PBS expenditure (published)	Actual (A)	\$1,498,960	\$1,835,211	\$1,389,243
	■	■	■	■

Source: Final agreed estimates

* The predicted number of prescriptions was based on the ■% of patients on a dose of 37.5 mg having only one prescription. However, this was incorrect and these patients would have required 2 prescriptions (one each for the 12.5 mg and 25 mg strengths) up until the 37.5 mg strength was listed in September 2015. Thus the Year 1 and 2 figures have been adjusted in this report to take this into account. Year 3 is not adjusted as the listing of the 37.5 mg strength was not anticipated in the submission.

extracted from the submission estimates and agreed PBS estimates spreadsheets.

Table 4 shows that the number of patients prevalent to sunitinib in Year 1 and 2 ■ that predicted. In Year 3 it was ■ more than predicted. In contrast the number of prescriptions was less than predicted. This is due to the number prescriptions per patient per year being ■ that predicted (using the adjusted number of

predicted prescriptions).

Table 5: Predicted vs Actual analysis – everolimus for pNET

		Year1	Year 2
		Apr15 to Mar16	Apr16 to Mar17
Treated Prevalent patients (PBS & RPBS)	Predicted (P)	█	█
	Actual (A)	60	94
	% Difference (A-P)/P	█	█
Prescriptions	Predicted (P)	█	█
	Actual (A)	233	367
	% Difference (A-P)/P	█	█
Prescriptions per patient	Predicted (P)	█	█
	Actual (A)	3.9	3.9
	% Difference (A-P)/P	█	█
R/PBS expenditure (published)	Predicted (P)	█	█
	Actual (A)	\$1,081,798	\$1,590,009
	% Difference (A-P)/P	█	█

Source: Final agreed estimates

Table 5 shows that the number of patients prevalent to everolimus was █ that predicted in Year 2. █, the number of prescriptions per patient per year was █ that predicted. This resulted in the number of prescriptions and the R/PBS expenditure being less than expected.

3. Patient-level duration of therapy

Indication sequence and patient classification issues

Applications for authority to prescribe sunitinib and everolimus for pNET are obtained via the PBS telephone authority approval systems operated by DHS. The first supply of a medicine by a dispensing pharmacy is cross-checked against the authorities database at the time the prescription is supplied (via the PBS Online claiming system). The information checked is that an authority approval exists for the prescription and that the dispensed PBS items matches the one assigned in the authority approval. Subsequent repeats could be misclassified at the time of dispensing.

A cohort of patients identified using first original prescriptions specifically for pNET was assumed to be the least likely to have misclassification bias. It was still possible for a small number of subsequent original and repeat prescriptions to be entered in the pharmacy claim database with an inaccurate item number. This possibility was considered and the extent and possible effect of misclassification was explored.

Construction of dataset 2 containing patients with pNET and minimal misclassification

In order to identify an 'as accurate as possible' cohort of patients with pNET with a full medication history for sunitinib and everolimus, all PBS supplied prescriptions from the DHS pharmacy claim database for sunitinib and everolimus (1 May 2009, first listing for sunitinib, to 31 March 2017) were extracted.

Patients were classified as being likely to have pNET or non-pNET based on the indication sequence of original prescriptions in relation to the pNET indication listing date of 1 December 2013. That is, if a patient's first original prescription after 1 December 2013 was indicated for pNET and they did not receive a non-pNET indicated original prescription prior to 1 December 2013 then it was considered that the patient was being treated for pNET (Cohort pNET - 219 patients). Otherwise the patient was considered to be treated for a non-pNET condition (Cohort non-pNET – 7,524 patients).

Non-pNET PBS indications for sunitinib are;

- metastatic or unresectable malignant gastrointestinal stromal tumour (GIST); and
- stage IV clear cell variant renal cell carcinoma (RCC).

Non-pNET PBS indications for everolimus are;

- tuberous sclerosis complex (TSC);
- metastatic (Stage IV) breast cancer;
- stage IV clear cell variant renal cell carcinoma (RCC); and
- management of renal and cardiac allograft rejection.

Table 6 shows indication sequences for all sunitinib and everolimus original prescriptions (i.e. including all PBS item codes for these medications) and subsequent patient classifications.

Table 6: Original prescription indication sequence

Patient classification	Original prescription indication sequence	Patients	% Patients
Considered to be patients with pNET (Cohort pNET)	All original prescriptions were indicated for pNET	159	2.1%
	First original prescription was post 1 December 2013 was indicated for pNET, but patients also had at least one non-pNET original after this.	60	0.8%
	Sub-total	219	2.8%
Considered to be patients with a non-pNET condition (Cohort non-pNET).	First original prescription post 1 December 2013 was indicated for pNET, but patients also had at least one non-pNET original prior to 1 December 2013. Not clear if pNET post 1 December entry was an error.	10	0.1%
	All original prescriptions were indicated for non-pNET PBS item numbers	6,273	81.0%
	Patients whose first original authority prescription was for non-pNET but at least one subsequent original authority prescription was for pNET. Later originals could have been for either indication	1,241	16.0%
	Sub-total	7,524	97.2%
Total		7,743	100.0%

The total number of patients in the previous analyses (sections 1 & 2), which only had regard to pNET indicated prescriptions (both originals and repeats), was 366. This means that $366 - 219 = 147$ patients that were included in the previous analysis were possibly misclassified as pNET patients. For the purpose of patient-level analysis of utilisation these patients did not have a complete prescription history for both sunitinib and everolimus as all non-pNET indicated prescription supplies were not included for these 147 patients which would introduce additional bias in determining duration of therapy related analyses.

The subsequent analyses in this report use dataset 2 (i.e. all sunitinib and everolimus prescriptions for Cohort pNET patients) and were designed to compare parameters assumed in the submissions with an estimate of the parameters observed in practice (e.g. length of treatment, time to resupply, number prescriptions per patient). This parameter estimation is most accurate if based on a cohort of patients in which there was a high degree of confidence that they were pNET patients and that they had their full sunitinib and everolimus prescription history; even if some prescriptions were misclassified as being for a non-pNET patient (147 patients).

3.1 Time to resupply and length of treatment for Cohort pNET patients

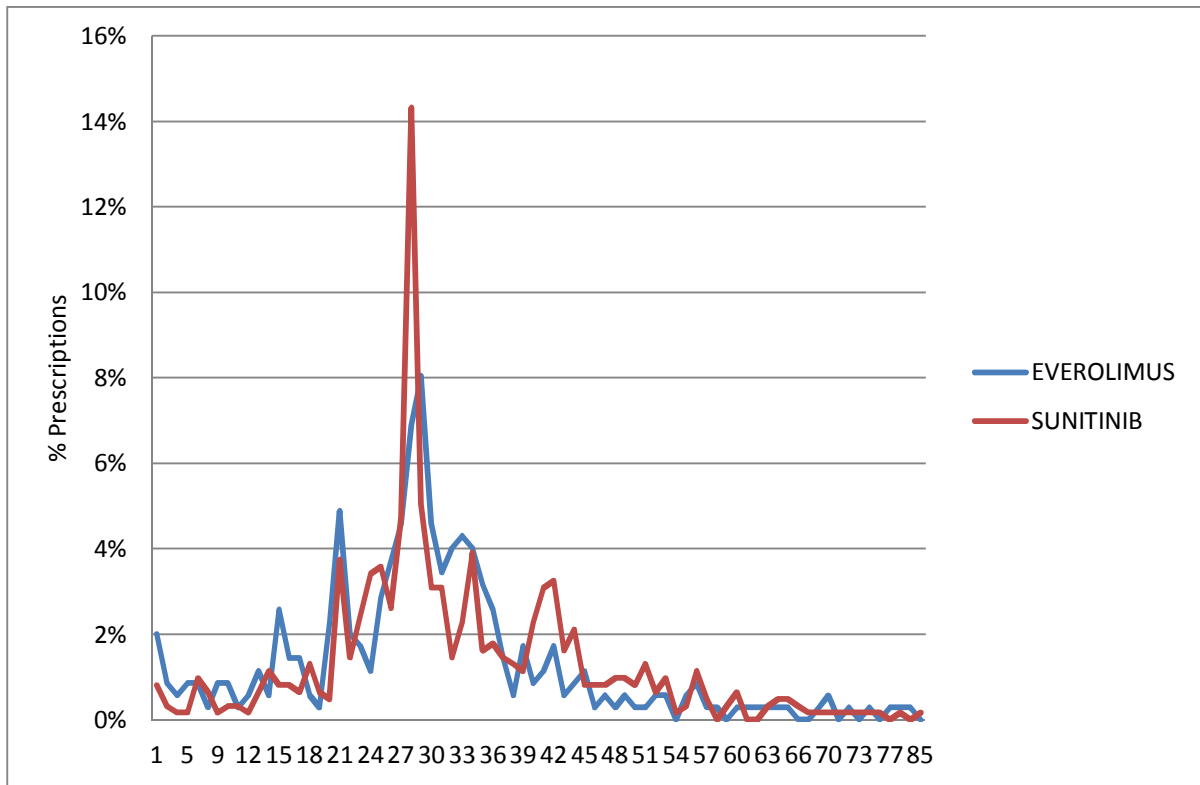


Figure 6: Number of days to prescription resupply for Cohort pNET patients by drug.

Source: DHS prescription claims database (accessed 24 August 2017). Note: does not include prescriptions with no resupply and resupply > 90 days.

Figure 6 shows the percentage distribution of prescriptions rather than the number of prescriptions so that the drugs are easier to compare. The distribution of time to resupply was similar for the two drugs, except that sunitinib has more resupply around 42 days. Both drugs have a median time to resupply of 29 days.

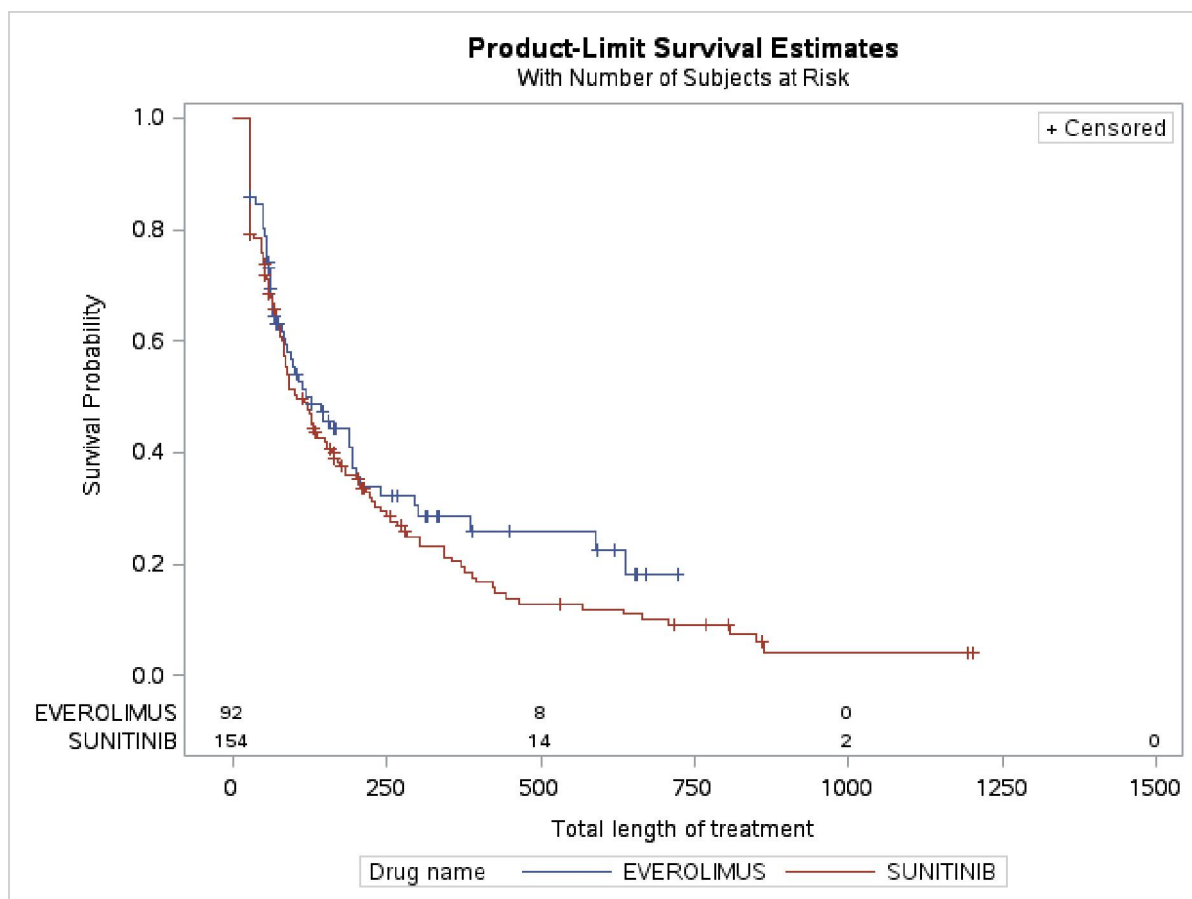


Figure 7: Length of treatment for Cohort pNET by drug.

Source: DHS prescription claims database (accessed 24 August 2017).

Figure 7 shows the Kaplan Meier estimates of total length of treatment (including breaks) for the two medicines. The median lengths of treatment for sunitinib and everolimus were 104 days (3.4 months) and 118 days (3.9 months) respectively.

An alternative measure of length of treatment, which excluded any breaks, was also calculated. The median length of treatment (excluding breaks) for sunitinib and everolimus were 92 days (3.0 months) and 118 (3.9 months) days respectively. This indicates that there was a $104 - 92 = 12$ day break on average for patients on sunitinib and the breaks in treatment for patients on everolimus were not sufficient for there to be a difference in the median value of the two measures (i.e. both were 118 days).

Total length of treatment (excluding breaks) is the time that patients received supplies of medicine not counting the time that patients did not have medicine supplied (i.e. were having a break between episodes of treatment).

A break is defined as a gap of more than 3 times the median time to resupply (i.e. $3 \times 29 = 86$ days) between supplies, which is an estimated break in treatment of at least 2 times the median time to resupply (i.e. 2×29 days = 58 days).

Total length of treatment (including breaks) is the time that patients received supplies of medicine and counts the additional time that patients were not receiving supply of medicine between episodes of treatment.

These analyses both allow patients to stop treatment (ie. no more supplies of medicine) or be censored (i.e. deemed to be continuing treatment at the end of the data period). See Method section above for more details.

Note that 27 of the total 219 patients that were treated with both drugs and their length of treatment were calculated separately for each drug.

3.2 Age and gender of Cohort pNET patients

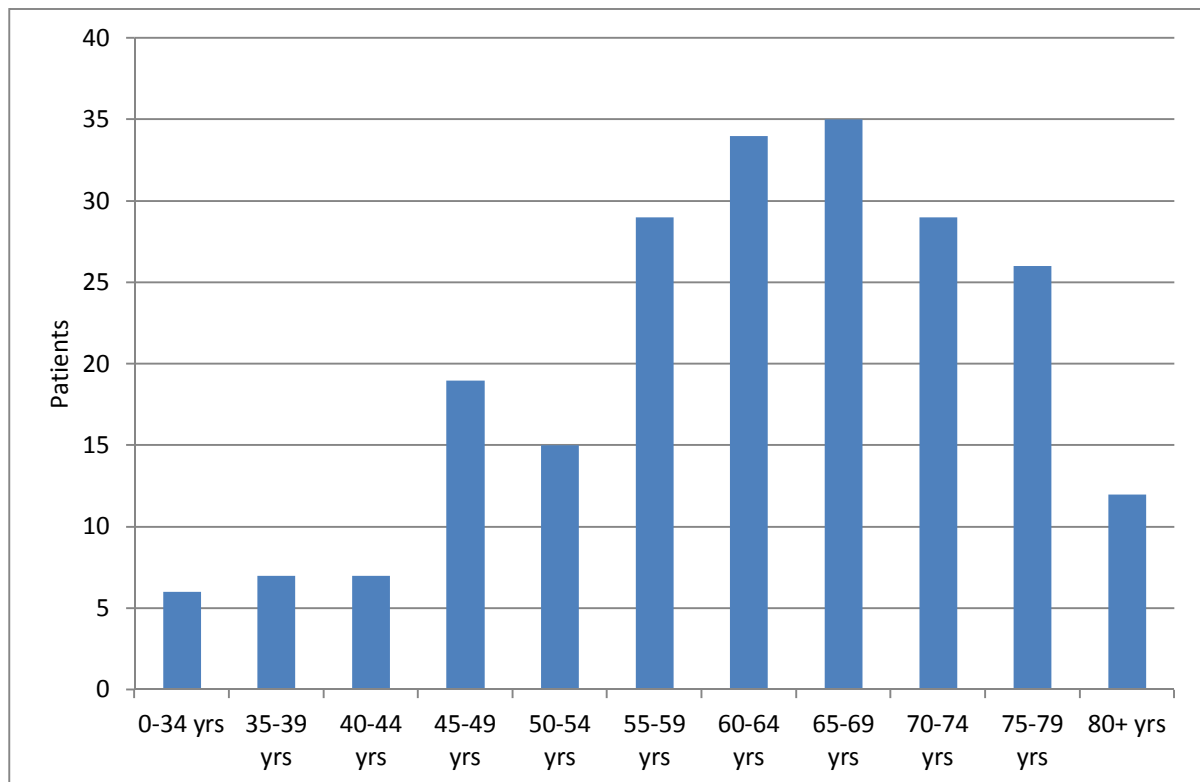


Figure 8: Age at initiation to therapy with either sunitinib or everolimus for Cohort pNET patients. Source: DHS prescription claims database (accessed 24 August 2017).

Figure 8 shows that patient age at initiation to pNET therapy peaks in the age range 65-69 years. The median age is in the range 60-64 years.

Overall there are 112 males (51.1%) and 107 females (48.9%) in Cohort pNET. Figure 9 shows the gender split by initiation to drug.

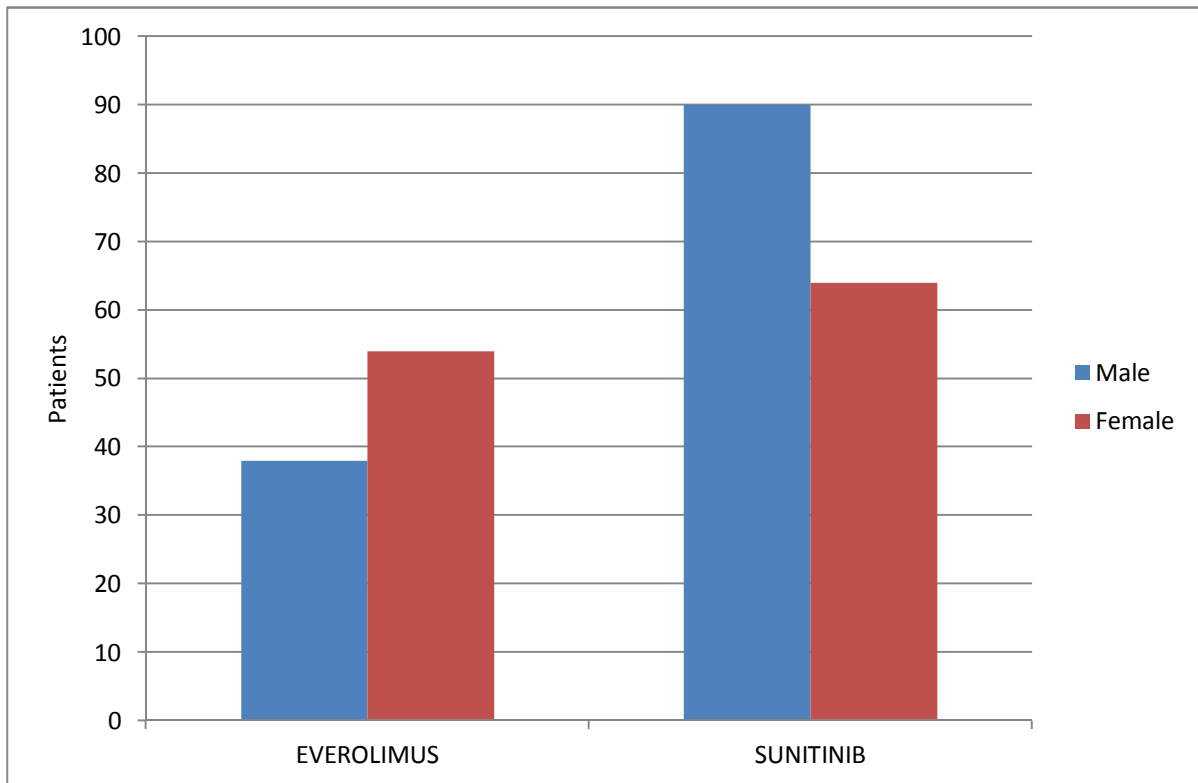


Figure 9: Patient gender by initiation to drug for Cohort pNET patients.

Note: 27 patients initiated to both drugs in the period December 2013 to the end of March 2017 and so are represented under each drug. Source: DHS prescription claims database (accessed 24 August 2017).

Figure 9 shows that sunitinib was initiated by more males than females and vice versa for everolimus.

3.3 Estimation of time from cessation of treatment to death

The PBS restriction that states “Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment with this drug.” That is, it is expected that patients will not use these medicines for the treatment of pNET after disease progression and up to their date of death. This implies that there should be a period of time between receiving everolimus or sunitinib and death for a large proportion of patients.

A proxy for date of death was estimated by first measuring the time to next supply for all prescriptions (i.e. all drugs not just sunitinib and everolimus) supplied to Cohort pNET patients (see Methods for more details).

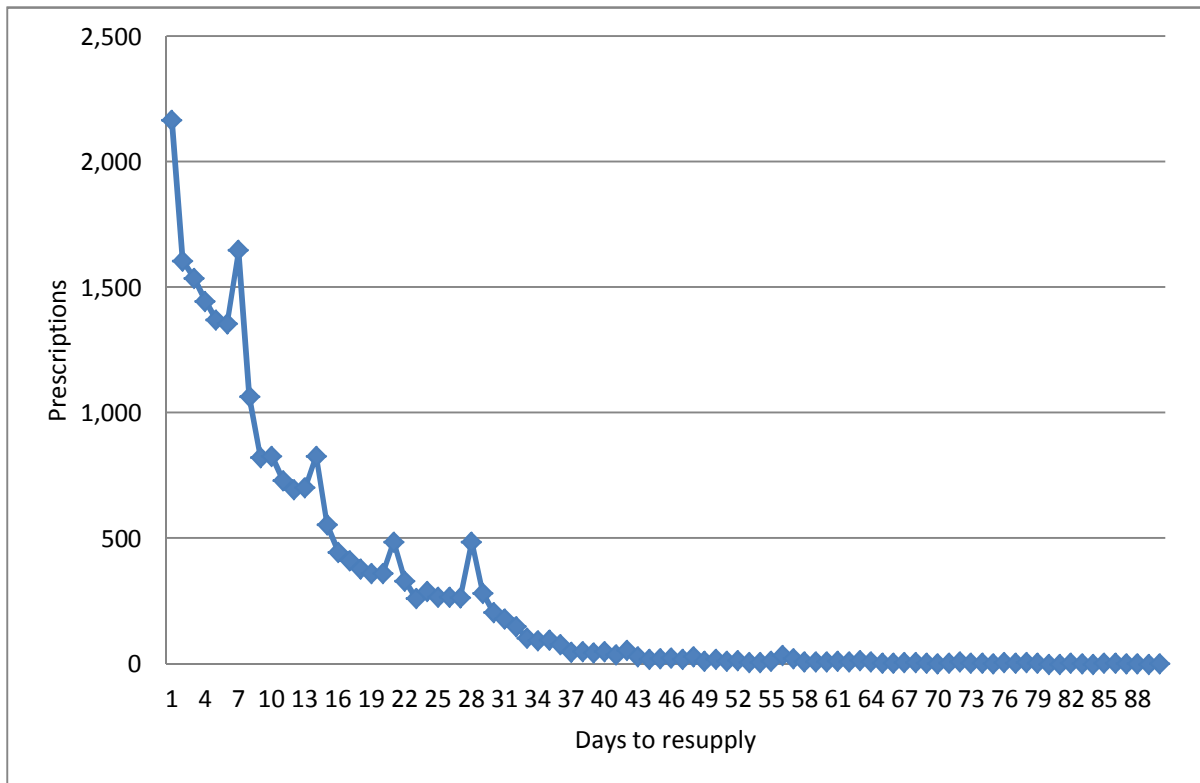


Figure 10: Number of days to next supply for Cohort pNET patients

Note: does not include prescriptions with no next supply (ie. patients with only one prescription).

Source: DHS prescription claims database (accessed 24 August 2017).

The median time to next supply of any prescription (i.e. any drug or strength) in Figure 10 was 8 days. Surprisingly the most common number of days to next supply was 1 day. 98.3% of scripts had the next supply within 90 days.

Using this information, a patient was estimated to have died if they had no supply of a prescription in the 90 days after their last prescription in the PBS data. If this was the case, the date of death was estimated to be the date of last supply plus 8 days (i.e. the expected number of days to next supply).

Using this method, of the 219 pNET patients, 93 were estimated to have died and 126 estimated to still be alive at the end of the data period (31 March 2017).

The estimated date of death was used to estimate the time between cessation of treatment with sunitinib or everolimus and death for the Cohort pNET patients. The results are shown in Figure 11.

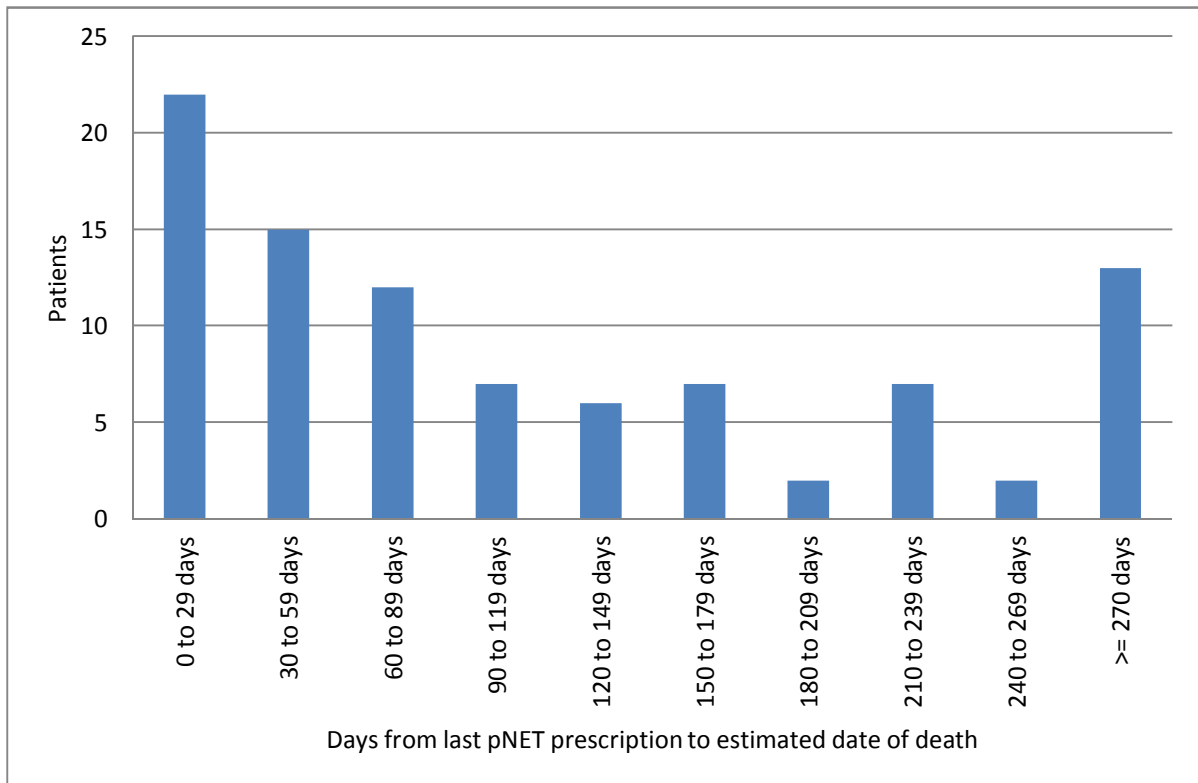


Figure 11: Days from last pNET prescription to estimated date of death for cohort pNET patients who were estimated to have died (n=93).

Source: DHS prescription claims database (accessed 24 August 2017).

The median value from the last pNET prescription to the estimated date of death was 85 days (almost 3 months). This analysis shows that time from cessation of medicine for pNET and the date of death (assumed) is highly variable. This analysis cannot determine if the reason for discontinuation of therapy was disease progression.

3.4 Somatostatin analogue use prior to initiation of everolimus or sunitinib

The PBS restriction that states that the “Patient must be symptomatic (despite somatostatin analogues); OR * Patient must have disease progression.” That is, if a patient does not have disease progression, then they are expected to be treated with a somatostatin analogue. There are three of these drugs listed on the PBS: octreotide, lanreotide and pasireotide. Table 7 shows the drug initiation sequence for patients in the Cohort pNET patients.

Table 7: Drug initiation sequence for Cohort pNET patients.

Drug initiation sequence	Patients	% Patients
SUNITINIB	57	26.0%
OCTREOTIDE->SUNITINIB	32	14.6%
EVEROLIMUS	29	13.2%
LANREOTIDE->SUNITINIB	22	10.0%
OCTREOTIDE->EVEROLIMUS	18	8.2%
OCTREOTIDE->SUNITINIB->EVEROLIMUS	8	3.7%
LANREOTIDE->EVEROLIMUS	7	3.2%
SUNITINIB->EVEROLIMUS	6	2.7%
SUNITINIB->OCTREOTIDE	6	2.7%
Other drug initiation sequences	24*	15.5%
Total	219	100%

* 14 of the 24 patients in this group initiated a somatostatin analogue prior to everolimus or sunitinib.
Source: DHS prescription claims database (accessed 24 August 2017).

Approximately half of patients (112 of 219, 51.1%) had a somatostatin analogue prior to everolimus or sunitinib. This could be explained by;

1. the remaining patients had fulfilled the restriction criterion by having disease progression, not by being “symptomatic despite somatostatin analogues”; or
2. the results are unreliable due to incomplete data (see below).

The somatostatin analogue medicines are listed in the S100 HSD part of the PBS Schedule. The PBS items are divided into those that are used in private hospital or clinic setting and those that are used in the public hospital setting. The private items are Authority Required and the public hospital items are Authority Required (Streamlined). Patient level prescription data is complete for the private hospital items, but only complete for the public hospital items from July 2013. Prior to July 2010, all public hospital HSD items were processed through a bulk payments system where the patient ID was not recorded. Between July 2010 and the end of June 2013 this system was phased out and supply was processed through the normal PBS processing system which does record the patient ID.

It was attempted to supplement the prescription data with data from the DHS Authority Approval database, which has a record of all non-Streamlined authority approvals and includes a patient ID. However this approach did not work as the public hospital items for these medicines were all Authority Required (Streamlined) and so not recorded in the DHS Authority Approval database.

Thus patients who initiated sunitinib soon after it was listed in December 2013 would have had a limited lookback period (as short as 5 months) to detect prior somatostatin analogues. Patients who initiated everolimus soon after it was listed in April 2015 would have lookback period of at least 21 months. The lookback periods would have been greater than these periods because;

- most patients initiated after the after the month of listing; and

- the public hospital HSD patient level data was not totally absent prior to July 2013, just incomplete.

To improve the reliability of the results in Table 7, only patients that initiated pNET therapy after 1 September 2014 were included. This means that each patient had at least a 14 month lookback period (i.e. to July 2013) to detect the supply of a prior somatostatin analogue. The results are shown in Table 8.

Table 8: Drug initiation sequence for Cohort pNET patients who initiated everolimus or sunitinib after 1 September 2014.

Drug initiation sequence	Patients	% Patients
SUNITINIB	35	30.4%
EVEROLIMUS	29	25.2%
LANREOTIDE->SUNITINIB	8	7.0%
OCTREOTIDE->SUNITINIB	7	6.1%
SUNITINIB->EVEROLIMUS	6	5.2%
OCTREOTIDE->EVEROLIMUS	5	4.3%
Other	25*	21.7%
Grand Total	115	100%

* 13 of the 25 patients in this group initiated a somatostatin analogue prior to everolimus or sunitinib.
Source: DHS prescription claims database (accessed 24 August 2017).

In the data behind Table 8, 34 of 115 patients (29.6%) had a somatostatin analogue prior to everolimus or sunitinib. Also, 30.5% (18 of 59) of patients who initiated everolimus had a prior somatostatin analogue and 31.4% (22 of 70) of patients that initiated sunitinib had a prior somatostatin analogue.

The initial concern was that missing HSD data would have led to an underestimate of the number of patients having a prior somatostatin. However, the result was that by excluding the early initiators (i.e. from December 2013 the end of August 2014) the rate of patients having a prior somatostatin went down from 51.1% to 29.6%. This means that the early initiators had a higher rate of prior somatostatin (despite the fact that some instances of prior somatostatin may not have been detected in the early initiators).

Risk Sharing Arrangements

Commercial-in-confidence

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

End commercial-in-confidence

Discussion

The actual prescription utilisation and R/PBS expenditure was less than predicted for both sunitinib and everolimus. However the number of patients treated was more than expected for both drugs (■% more than expected for sunitinib in Year 3 after listing and ■% more than expected for everolimus in Year 2 after listing). This means that the number of prescriptions per patient per year for both drugs was much less than predicted.

Prescriptions per patients

The predicted prescriptions per patient per year for sunitinib were an overestimate because predicted duration of treatment was overestimated. In each post listing year, each prevalent patient was predicted to receive on average ■ months of treatment. This was based on ■ of patients without tumour progression and ■ of patients with tumour progression and ■ of progressed tumour patients who continue treatment.

In addition the predicted prescriptions per patient per year assumed that ■% of prevalent patients in a year would not progress and receive on average ■ months of treatment in the following year also.

This analysis estimated actual length of treatment with sunitinib was a median of 3.4 months including breaks and 3.0 months excluding breaks. This was a patient's overall length of treatment and not confined to a particular year. Thus the actual length of treatment with sunitinib was considerably less than predicted in a single year (i.e. ■) let alone a patient's total treatment across multiple predicted years.

In addition the predicted prescriptions per patient per year was inflated as it did not allow patients to commence or cease treatment part way through the year (often referred to as a part cycle correction) and is likely to have the greatest effect in the first few years of listing i.e. until the market reaches stable equilibrium.

It was a similar scenario for the predicted prescriptions per patient per year for everolimus. The submission predicted an average of [REDACTED] months of treatment per prevalent patient per year. This analysis estimated actual length of treatment with everolimus was a median of 3.9 months (including or excluding breaks).

Number of treated patients

The number of patients treated was more than expected for both sunitinib and everolimus. The number of sunitinib patients was based on [REDACTED]. This definition may have been too narrow for the source of patients who end up with pNET.

The number of everolimus patients was based on [REDACTED]. The everolimus submission underestimated the number of sunitinib patients at [REDACTED] in 2013, however Table 4 shows that there was 106 such patients in the first year of listing of sunitinib for pNET (December 2013 to November 2014).

Time from cessation of treatment to death

The ceasing of treatment before death may be due to progression of the disease (as per the PBS restriction) or treatment may cease at a later stage. Study A6181111 presented in the sunitinib submission to the August 2013 PBAC meeting reported a median progression free survival (PFS) of 11.4 months and a median overall survival (OS) of 30.5 months for patients treated with sunitinib. The difference between these two is 19.1 months (583 days), which is considerably longer than 85 days (2.8 months) calculated in this analysis for the median time from last pNET prescription to estimated death.

For everolimus, a comparison of PFS and OS was not available in the minor re-submission to the March 2014 PBAC. However the results of the everolimus study used in the re-submission, RADIANT-3 (Study CRAD001C2324), are published online⁴ and the median PFS was 11.04 months and the median OS was 44.02 months. The difference between these (33.0 months) is larger than for sunitinib.

Even though it appears to be the case that most patients are not ceasing PBS treatment upon progression of disease (ie. outside of the PBS restriction), it is not possible to be sure. This is because the 93 patients that are estimated to have died in the Cohort pNET (n=219) may be a biased sample. That is, they may have been the sickest patients and have relatively short periods between progression and death. By the time the whole 219 patients have died the median time from last pNET script to death may be considerably longer.

Somatostatin analogue use prior to initiation of everolimus or sunitinib

The PBS restriction that states that the “Patient must be symptomatic (despite somatostatin analogues); OR * Patient must have disease progression.” This analysis

⁴ <https://clinicaltrials.gov/ct2/show/results/NCT00510068?sect=X90156#outcome3>

indicates that approximately half of patients (51.1%) had a somatostatin analogue prior to initiation of everolimus or sunitinib. This implies that the other half of patients qualified for treatment because they had disease progression.

DUSC consideration

The DUSC considered that:

- The increase in total number of prescriptions has slowed but is still growing.
- The number of patients was greater than expected. The proportion of incident patients remained steady while the prevalent patients continue to increase slowly.
- The actual number of prescriptions and costs are lower than predicted. DUSC noted that the submission methods overestimated the prescriptions per patient and therefore costs per patient.
- The actual median duration of treatment per patient is lower than expected in the submission. It is possible that this is a result of a patient selection bias associated with the characteristics of patients taking up treatment soon after listing: the uptake of treatment was in patients with more advanced and potentially more severe disease which leads to shorter duration on therapy than may be seen when less severe patients are treated. There may also be some use in patients with moderately differentiated tumours rather than well differentiated which is outside the eligible population for subsidised treatment. This may explain the lower duration of treatment than time on treatment in the clinical trial. Given the long time that patients have this condition the committee considered that the duration of therapy, and consequently the number of prescriptions and costs per patient will increase in the next few years. Therefore DUSC did not consider that the risk share agreement should be lapsed at the end of 5 years without a further reanalysis of the market for pNET.
- Considering the use of prior somatostatin analogues in 51% of patients implies that 49% were eligible because of disease progression.

DUSC noted the congruence of the two methods measuring the time from ceasing treatment to death. This confirmed the usefulness of using PBS prescription supply in medicines used at the end of life where patients have conditions that require a regular supply of PBS medicine and the medicines of interest are used relatively close to the end of life such as late stage tumour therapy. This method has not been tested for medicines treating chronic disease.

There is considerable variation in the time from cessation of everolimus or sunitinib to death. It was difficult to interpret the significance of the time from ceasing everolimus or sunitinib and the date of death. While some patients may be continuing treatment beyond disease progression it is also possible that some progress to later stage treatment. DUSC noted that patients who progress could have nuclear medicine therapy which is funded by a limited number of State hospitals or private health insurers so there is limited incentive to continue pharmacotherapy treatment after disease progression for these patients.

DUSC clarified that the claim in Appendix B that the method used in the Mealing et al (2012)⁵ paper to calculate a date of death proxy used only cancer drugs, was not correct. This paper used all PBS prescriptions, not just those for cancer drugs, to calculate their PBS proxy.

DUSC actions

- The report, Sponsor responses, and DUSC minutes were referred to the PBAC noting.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Pfizer Australia Pty Ltd (sunitinib): The sponsor has no comment.

Novartis Pharmaceuticals Australia Pty Limited (everolimus): The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date

⁵ Mealing NM, Dobbins TA, Pearson S-A. Validation and application of a death proxy in adult cancer patients. *Pharmacoepidemiol Drug Saf* 2012; 21: 742–8.

when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A: PBS Restrictions

Sunitinib

Treatment Phase: Initial treatment

Authority Required

Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET)

Clinical criteria:

- Patient must be symptomatic (despite somatostatin analogues); OR
- Patient must have disease progression,

AND

- The treatment must be as monotherapy.

Disease progression must be documented in the patient's medical records.

Patients who have developed progressive disease on everolimus are not eligible to receive PBS-subsidised sunitinib for this condition.

Patients who have developed intolerance to everolimus of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised sunitinib.

Treatment Phase: Continuing treatment

Clinical criteria:

- Patient must have previously been issued with an authority prescription for this drug,

AND

- Patient must not have disease progression,

AND

- The treatment must be as monotherapy.

Disease progression must be documented in the patient's medical records.

Patients who have developed progressive disease on sunitinib are not eligible to receive PBS-subsidised everolimus.

Patients who have developed intolerance to sunitinib (*everolimus in the case of the everolimus restriction*) of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised everolimus (*sunitinib in the case of the everolimus restriction*).

Treatment Phase: Continuing treatment

Authority Required

Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET)

Clinical criteria:

- Patient must have previously been issued with an authority prescription for this drug,

AND

- Patient must not have disease progression,

AND

- The treatment must be as monotherapy.

Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment with this drug.

Appendix B: Method use for estimating time of death from PBS prescription supply.

The proxy was estimated by first measuring the time to next supply for all prescriptions (ie. all drugs not just sunitinib and everolimus) supplied to Cohort pNET patients. The phase “next supply” is used rather than “resupply” to clarify that the supply is not necessarily for the same drug or strength. Scripts supplied prior to the collection of under copayment prescriptions (April 2012) were excluded. This is because prior to this time, patient histories may be incomplete and so time to next supply of any prescription may be overestimated. It was established that the median time to next supply was 8 days and that 98.3% of scripts had a next supply within 90 days. Thus a patient was estimated to have died if they have no supply of any prescription in the 90 days after their last prescription in the PBS data. The date of death was estimated to be the date of last supply plus 8 days (ie. the expected number of days to next supply). This was then used to calculate the time from the last sunitinib or everolimus supply to the estimated date of death for each patient.

Date of death proxies based on PBS data have been calculated by other researchers. Mealing et al. (2012)⁶ used a similar method to this analysis. In addition, they validated the proxy against actual date of death data. A sensitivity analysis indicated that a 90 day or greater delay between a patient’s last prescription and the end of the data period was the best indicator of death compared to shorter and longer delays (i.e. 30, 60 and 180 days).

⁶ Mealing NM, Dobbins TA, Pearson SA. Validation and application of a death proxy in adult cancer patients. *Pharmacoepidemiol Drug Saf* 2012; 21: 742–8.

Appendix C: validation of date of death proxy

Methods

The date of death (DoD) proxy was estimated as per Appendix B.

Date of Death data were requested from DHS for the 7,760 patients that had received a prescription for sunitinib or everolimus from 1 May 2009 (first listing for sunitinib) to 31 March 2017. Only the Medicare PINs for the 7,760 patients were supplied to DHS. These were matched with the Medicare enrolment file and dates of death (DHS DoD) were found for 3,756 patients. The dates of death were available up to 31 December 2016 (data extracted 4 September 2017).

The method for estimating a proxy DoD (Appendix B) could only detect estimated dates of death up to 7 January 2017. That is, the latest possible DoD would be for a patient whose last script was on 30 December 2016 and so had 91 days without a prescription before the end of the data period on 31 March 2017. The estimated DoD for this patient would be 30 December 2016 + 8 days = 7 January 2017. There were 18 patients in total that had a proxy DoD between 1 and 7 January 2017, only one of which was in Cohort pNET. These 18 patients were removed from the comparison of proxy DoD and DHS DoD, as the DHS DoD data was not available for this period (i.e. they were up to 31 December 2016).

Results

1. Comparison of patient alive / dead status

There were 7,760 patients that had received a prescription for sunitinib or everolimus from 1 May 2009 (first listing for sunitinib) to 31 March 2017.

Patients were classified as being likely to have pNET or non-pNET based on the indication sequence of original prescriptions in relation to the pNET indication listing date of 1 December 2013. That is, if a patient's first original prescription after 1 December 2013 was indicated for pNET and they did not receive a non-pNET indicated original prescription prior to 1 December 2013 then it was considered that the patient was being treated for pNET (Cohort pNET - 219 patients). Otherwise the patient was considered to be treated for a non-pNET condition (Cohort non-pNET – 7,541 patients).

All PBS prescriptions for all 7,760 patients were extracted from January 2003 to the end of March 2017. Subsequently, prescriptions supplied prior to the collection of under copayment prescriptions (April 2012) were excluded. This was because prior to this time, patient histories may be incomplete and so time to next supply of any prescription may be overestimated. This exclusion resulted in the Cohort non-pNET reducing to 6,565 and the Cohort pNET remaining at 219 patients.

Table C1: Proxy vs DHS patient status for Cohort pNET

	Proxy patient status		
DHS patient status	Alive	Dead	Total
Alive	125	7	132
Dead	1	85	86
Total	126	92	218

Note: One patient was excluded from Cohort pNET as their proxy DoD was on or after 1 January 2017 and there were no DHS DoD data available for this period. See Methods for details.

Table C1 compares the proxy patient status (based whether or not a patient has a proxy DoD) with the DHS patient status (based whether or not a patient has a DHS DoD). The agreement rate between the two measures was 96.3% (i.e. $(125 + 85) / 218$). Most of the disagreement was where the proxy status = Dead and the DHS status = Alive (i.e. 7 patients). This disagreement is likely to be due to an error in the proxy status, but not necessarily so. It is possible that there are late death registrations which will modify the DHS status when the data is received by State governments and then flows through to DHS.

Table C2: Proxy vs DHS patient status for Cohort non-pNET

	Proxy patient status		
DHS patient status	Alive	Dead	Total
Alive	3,630	210	3,840
Dead	15	2,693	2,708
Total	3,645	2,903	6,548

Note: 17 patients were excluded from Cohort non-pNET as their proxy DoD was on or after 1 January 2017 and there were no DHS DoD data for this period. See Methods for details.

Table C2 is the equivalent of Table C1 for Cohort non-pNET; this is a much larger cohort. The same parameters were used to estimate the proxy DoD for this cohort (i.e. more than 90 days from last prescriptions indicates death and for such patients, the estimated time from last prescription to death was 8 days). These parameters were used after it was checked that the “days to next supply for any prescription” statistics for this cohort were almost identical to Cohort pNET (i.e. both had median = 8 days and mode = 1 day).

The agreement rate between the two measures in Table 2 was 96.6% (i.e. $(3,630 + 2,693) / 6,548$). Most of the disagreement was where the proxy status = Dead and the DHS status = Alive (ie. 210 patients).

The distribution of the delay between a patient’s final prescription and DHS DoD is shown for all patients (pNET and non-pNET) in Figure C1.

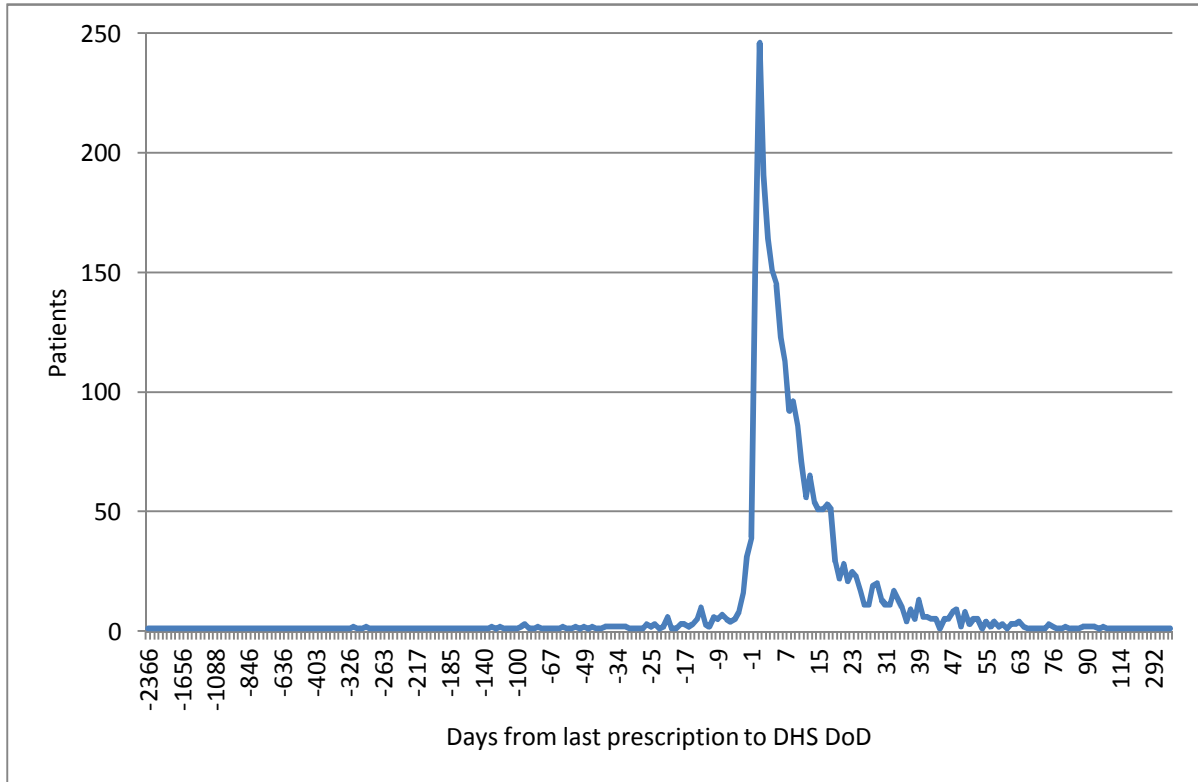


Figure C1: Days from last prescription to DHS DoD for all patients with a DHS DoD

Figure C1 shows that there were some patients that had prescriptions supplied after their DHS DoD (i.e. negative values on the x-axis). It was considered reasonable that a patient could be supplied a prescription in error up to 28 days after death, but any longer than this was considered to be a data error. That is, the error could be in the DHS DoD or it could be that the dead patient's Medicare PIN was being attributed to prescriptions supplied to another person.

Thus it was considered reasonable to exclude patients from the analysis if they appeared to have a prescriptions supplied more than 28 days after their DHS DoD. Tables C3 and C4 show the proxy vs DHS patient status comparisons for pNET and non-pNET patients respectively after the removal of these patients.

Table C3: Proxy vs DHS patient status for Cohort pNET (excluding 4 patients with a prescription supply more than 28 days after DHS DoD)

DHS patient status	Proxy patient status		Total
	Alive	Dead	
Alive	125	7	132
Dead	0	82	82
Total	125	89	214

After the exclusion of patients, the agreement rate between the two measures increased slightly to 96.7% (i.e. $(125 + 82) / 214$). The one instance of proxy status = Alive and DHS status = Dead in Table C1 has now been removed in Table C3.

Table C4: Proxy vs DHS patient status for Cohort non-pNET (excluding 130 patients with prescription supply more than 28 days after DHS DoD)

DHS patient status	Proxy patient status		Total
	Alive	Dead	
Alive	3,630	210	3,840
Dead	3	2,575	2,578
Total	3,633	2,785	6,418

After the exclusion of patients, the agreement rate between the two measures increased slightly to 96.7% (i.e. $(3,630 + 2,2,575) / 6,418$). The 15 instances of proxy status = Alive and DHS status = Dead in Table C2 was reduced to 3 in Table C4.

2. Difference between proxy DoD and DHS DoD.

For patients where the proxy and DHS patient status both are “Dead”, the difference between the dates of death in days is summarised in Table C5.

Table C5: Days from proxy DoD to DHS DoD

Cohort	n	mean	mode	median
pNET	82	2.4	-6	-2
non-pNET	2,575	3.9	-7	-2

The median number of days from the proxy DoD to the DHS DoD was -2 days (i.e. proxy DoD was 2 days after DHS DoD) for both cohorts. This difference would not have made a large impact on the analysis in Figure 12 of section 3.3 (i.e. days from last pNET prescription to estimated date of death for cohort pNET patients who were estimated to have died) if the DHS DoD had been used instead of the proxy. In section 3.3, the median time from the last pNET prescription to the estimated date of death was 85 days. If the DHS DoD had been used instead of the proxy DoD, this would have been approximately 83 days.

The mode of -7 days for the non-pNET cohort means that a patient is most likely to die on the day after their last prescription (the proxy DoD is 8 days after the last prescription of those patients that are estimated to have died).

Conclusion

The proxy DoD performed well, scoring 96.7% agreement with the Alive / Dead status derived from the DHS DoD for both cohorts. When both the proxy and DHS status measures agreed that the patient was dead, there was only a 2 day median difference in the date of death for both cohorts.

The generalisability of this method of calculating a proxy for DoD is unknown. It is most likely to be accurate for diseases that are terminal and have a need for some sort of PBS medication (not necessarily the medication used to treat the main disease) up to a patient’s death. It is not likely to be accurate for diseases that require acute treatment after which the patient recovers and is well enough to require no other PBS medication. The generalisability may need to be tested in the future for other conditions.