Everolimus: 24 months analysis of Tuberous Sclerosis Complex (TSC)

Drug utilisation sub-committee (DUSC)

February 2017

Abstract

Purpose

The PBAC requested a 24 month review of everolimus for tuberous sclerosis complex (TSC), which is a genetic disorder characterised by the growth of numerous noncancerous tumours in many parts of the body. Everolimus was first PBS-listed for this indication on 1 December 2013.

Data Source / methodology

The analyses use data from the Department of Human Services (DHS) Medicare Supplied prescriptions database and the DHS Authority approvals database from December 2013 to September 2016.

Key Findings

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

Purpose of analysis

The PBAC requested a 24 month review of everolimus for tuberous sclerosis complex (TSC), which was first PBS-listed for this indication on 1 December 2013.

Background

Clinical situation

TSC is a genetic disorder characterised by the growth of numerous noncancerous (benign) tumours in many parts of the body. These tumours can occur in the skin, brain, kidneys, and other organs, in some cases leading to significant health problems. TSC also causes developmental problems and the signs and symptoms of the condition vary from person to person.[1]

Everolimus reduces the size of brain tumours known as subependymal giant cell astrocytoma (SEGA) that are caused by tuberous sclerosis. This may stop the tumours from causing problems as they grow, such as hydrocephalus (excessive accumulation of fluid within the brain). [2]

Everolimus may reduce the size of angiomyolipoma of the kidney that is associated with TSC. This may lower the risk of the tumour(s) causing bleeding complications and may help to preserve kidney function.

Pharmacology

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

Everolimus is approved for the treatment of SEGA associated with TSC, in patients who require therapeutic intervention but are not candidates for curative surgical resection and for TSC patients who have renal angiomyolipoma not requiring immediate surgery.

Everolimus is also registered for several other indications including 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

[1] U.S. National Library of Medicine, National Institutes of Health, https://ghr.nlm.nih.gov/condition/tuberous-sclerosis-complex

[2] Everolimus (Afinitor®), Consumer Medicine Information, Novartis Pharmaceuticals Australia Pty Limited, North Ryde NSW, June 2015

- prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant and in adult patients receiving an allogeneic hepatic transplant
- progressive, unresectable or metastatic, well or moderately differentiated, neuroendocrine tumours (NETs) of pancreatic origin
- advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.

Dosage and administration

Table 1: Dosage and administration of everolimus for TSC with SEGAs

Brand name and sponsor	Product	Dose and frequency of administration
Afinitor® Novartis Pharmaceuticals Australia Pty Limited	Everolimus 2.5 mg, 5 mg and 10 mg tablets	Individualised dosing based on the body surface area (BSA, in m^2) using the Dubois formula, where weight (W) is in kilograms and height (H) is in centimetres: $BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$ The recommended starting dose of everolimus for treatment of patients with TSC who have SEGA is 4.5 mg/m^2.

Source: Product Information for everolimus

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at December 2016)

Table 2: PBS listing of everolimus

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
2818H	everolimus 2.5 mg tablet, 30	1	5	$1404.04	Afinitor® Novartis Pharmaceuticals Australia Pty Limited
2819J	everolimus 5 mg tablet, 30	1	5	$2712.88	
2985D	everolimus 10 mg tablet, 30	1	5	$5277.88	

Source: the PBS website. Note: Special Pricing Arrangements apply.

Restriction

Everolimus for TSC is listed as an Authority Required listing. The restriction specifies the condition must be:

- subependymal giant cell astrocytomas (SEGAs) associated with TSC; or
- the condition must be visceral tumours associated with TSC; and

- the treatment must be the sole PBS-subsidised therapy for this condition; and
- the patient must not be a candidate for curative surgical resection.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The submission sought an Authority Required listing for the initial and continuing treatment of SEGA associated with tuberous sclerosis (TS) in a patient who requires therapeutic intervention but are not candidates for curative surgical resection.

At its November 2012 meeting, the PBAC considered that the clinical management algorithm in the requested listing was not reflective of how everolimus would be used in clinical practice in SEGA patients. The PBAC considered it probable that everolimus could be used prior to surgery to reduce tumour volume and vasculature to improve surgical outcomes including reducing the possible adverse events associated with surgery, such as hydrocephalus. This was confirmed as a theoretical possibility by the sponsor in their Pre-PBAC Response and also by the expert clinician at the hearing during the meeting. In addition, the PBAC considered that use of everolimus in other TS associated tumours (such as renal angiomyolipomas) was probable, which was also confirmed at the hearing. The PBAC therefore considered that a 'whole of disease' restriction to address these concerns may be appropriate. The PBAC noted, however, that no data were presented to assess the treatment effect in TS associated tumours aside from SEGAs. The PBAC recommended deferral of the submission as a cost-effectiveness ratio could not be determined due to insufficient trial data from small patient numbers. The PBAC proposed that a substantially lower price should be negotiated with the sponsor and a suitable patient registry arrangement be established, in the context of a high clinical need and uncertain clinical efficacy.

At its April 2013 meeting, the PBAC considered that the benefit of mTOR inhibitors, such as everolimus, in patients with TS was to reduce tumour burden. Therefore the clinically appropriate approach was to make everolimus available for all TS patients in whom it is indicated. The PBAC noted that there were a number of visceral manifestations of TSC that should be considered, including SEGA and renal angiomyolipomas. The PBAC considered that cutaneous manifestations of TS should be excluded from subsidised treatment with everolimus.

The sponsor provided a revised estimate of the number of patients treated using a clinician survey and global prevalence estimates, and accounting for three manifestations of TS – SEGA, renal angiomyolipomas and skin lesions (angiofibromas). The PBAC was not convinced by the sponsor's epidemiological approach for estimating the number of patients treated, which it considered was likely to considerably overestimate the number of patients who have visceral disease manifestations that require treatment with everolimus.

The PBAC considered that the sponsor's estimate of patient numbers was uncertain and that a suitable risk sharing arrangement should be negotiated using a conservative estimate of patient numbers and an expenditure cap.

For further details refer to the Public Summary Document from the April 2013 PBAC meeting.

Approach taken to estimate utilisation

The submission used an epidemiological approach. Key assumptions of prevalence of TSC and prevalence of SEGAs in TSC were taken from published literature. The search undertaken by the submission did not identify any Australian prevalence data and so used international prevalence data as reported in published literature, which reported the prevalence of TSC for the total population, rather than by age. Hong et al. (2009)[3] reported the lowest rate, which was so much lower than the remaining studies that it was considered to be an outlier. The prevalence reported in Devlin et al (2006)[4] was considered to be an approximate midpoint between the remaining studies and this rate was chosen for the base case.

The submission identified literature which reported the rate of SEGAs in patients with TSC using histopathological and radiological methods. The submission stated that in Australia SEGAs are more typically confirmed by MRI scan, and therefore used the rate of SEGAs in patients with TSC reported in Adriensen et al (2009),[5] which was a meta-analysis of studies that confirmed SEGAs in TSC using radiological methods.

The search did not identify any data regarding the proportion of patients with TSC who would not be candidates for surgery, and therefore expert opinion was used to inform the eligibility estimates.

Following the positive recommendation from the PBAC, the estimates for everolimus in TSC were adjusted to include patients expected to be treated for renal angiomyolipomas.

Previous reviews by the DUSC

Everolimus has not previously been reviewed by DUSC. A separate review of everolimus in breast cancer is being considered at the February 2017 DUSC meeting.

[3] Hong, C. H., T. N. Darling, et al. (2009). "Prevalence of tuberous sclerosis complex in Taiwan: a national population-based study." Neuroepidemiology 33(4), pages 335-341.
[4] Devlin, L., C. Shepherd, et al. (2006). "Tuberous sclerosis complex: clinical features, diagnosis, and prevalence within Northern Ireland " Developmental Medicine & Child Neurology 48, pages 495-499.
[5] Adriensen, M. E., C. M. Schaefer-Prokop, et al. (2009). "Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature." Eur J Neurol 16(6): pages 691-696.

Methods

Data sources

The analyses use data from the Department of Human Services (DHS) Authority approvals database and the DHS Medicare Supplied prescriptions database. Authorities data were extracted from 1 December 2013 (date of first PBS-listing) to July 2016. Prescription data for everolimus were extracted from December 2013 to July 2016.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data.[6]

Extraction of data for the use of everolimus to treat TSC

Two of the PBS listings of everolimus for TSC share the same PBS item codes (2819J and 2985D) as metastatic (Stage IV) breast cancer. TSC has an additional PBS item code for the 2.5 mg strength (2818H), which is not listed for breast cancer. These are general schedule Authority Required listings with no identifier in the claims data to directly identify use for a specific indication. To separate use for TSC, patients receiving an Authority for this indication were matched to claims records for PBS items 2819J and 2985D. Prescriptions were matched to an approval if the de-identified patient identification number (PIN) and item codes matched for both the approval and supplied prescription. The date of authority approval had to be earlier than the supply date for it to be assigned as the corresponding approval. An approval was matched to a supply in 99.3% of cases.

Patient level analyses

The matched dataset described above was used to derive patient counts for the first two full listing years (December 2013 to November 2014 and December 2014 to November 2015) and the third listing year (December 2015 to September 2016) which is incomplete; and by quarter.

The number of prevalent patients was determined by counting the number of people supplied at least one PBS or RPBS prescription using non-identifying person specific numbers in the data for the specified time periods.

Patient initiation to everolimus was defined as the date of supply of the first PBS or RPBS prescription.

[6] PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

Results

Analysis of drug utilisation

Overall utilisation

The analysis identified 322 unique patients who had been supplied everolimus for TSC since it was PBS-listed on 1 December 2013.

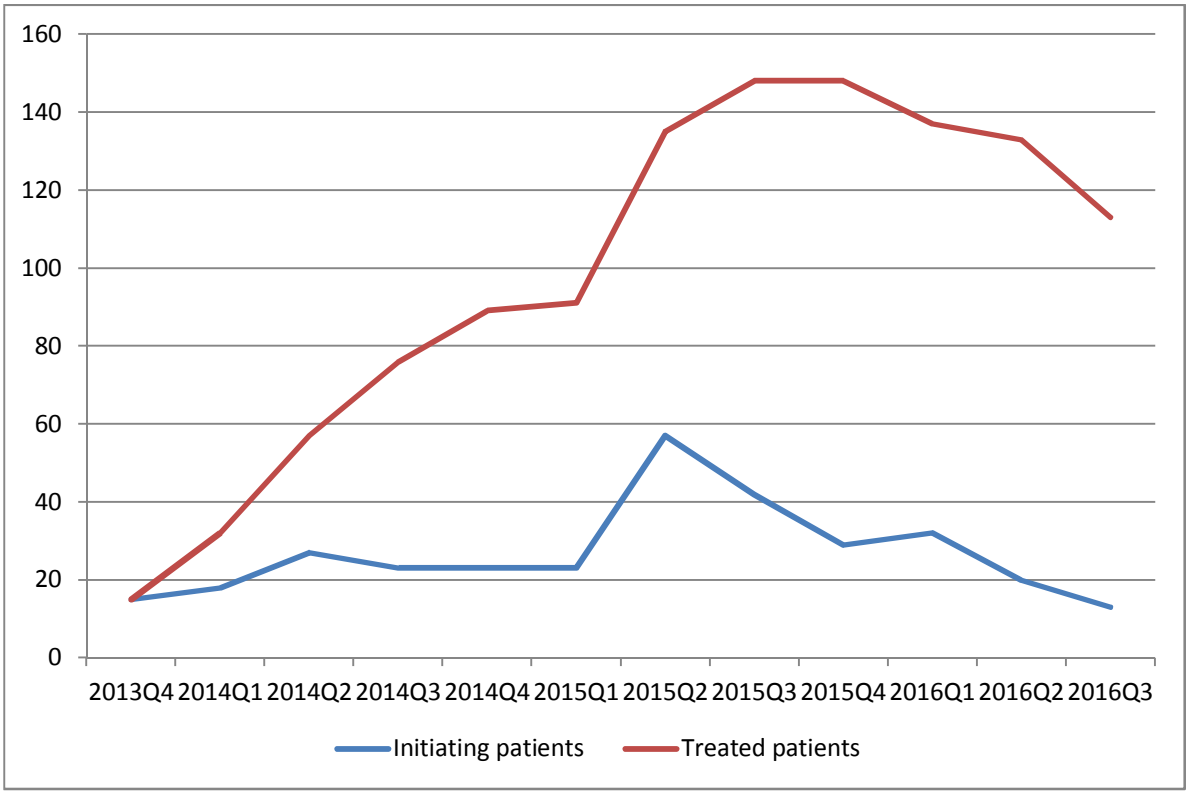

Figure 1: Initiating and treated patients for everolimus for TSC over time by quarter

Figure 1 suggests that the use of everolimus for TSC appears to be decreasing after initial take up.

Analysis of actual versus predicted utilisation

Changes were made to the submission's estimates of use because the PBAC recommended a broader indication than was requested by the sponsor.

Table 3: Analysis of actual versus predicted utilisation

	Year 1	Year 2	Year 3	Year 4	Year 5
Submission's estimates					
Total number of patients treated per year	69	84	99	115	124
2.5 mg prescriptions	140	314	376	440	491
5 mg prescriptions	332	745	894	1,046	1,167
10 mg prescriptions	17	39	47	55	61
Total packs per year	489	1,098	1,317	1,541	1,720
Estimates of use for SEGA and visceral tumours					
Total number of patients treated per year	93	172	228	236	248
2.5 mg prescriptions	94	174	232	240	252
5 mg prescriptions	165	305	406	420	441
10 mg prescriptions	283	522	695	720	756
Total packs per year	543	1,001	1,332	1,379	1,449
Actual use (percentage comparison to estimates for SEGA and visceral tumours)					
Total number of patients treated per year	98 (+5%)	223 (+30%)	194 (-15%)	N/A	
2.5 mg prescriptions	123 (+31%)	333 (+91%)	278 (+20%)		
5 mg prescriptions	357 (+116%)	641 (+110%)	557 (+37%)		
10 mg prescriptions	174 (-39%)	374 (-28%)	331 (-52%)		
Total packs per year	654 (+20%)	1,348 (+35%)	1,166 (-12%)		

Note: Year 3 actual figures include nine months of data, from December 2015 to September 2016 inclusive.

Discussion

Figure 1 shows that the number of treated patients per quarter increased from 91 to 135 between the first and second quarters of 2015, and the number of initiating patients increased from 23 in the first quarter of 2015 to 57 in the second quarter of 2015. This equates to a mean increase of 11 patients initiating per month. This increase may be due to consumer awareness or prescriber confidence. Table 3 shows the number of treated patients in year 2 of listing, which captures this quarterly increase was 30% higher than predicted, which equates to 51 patients.

Figure 1 also shows that the number of patients treated with everolimus for TSC per quarter appears to be decreasing. This decrease may be due to the tolerability of the drug or a reduction in patients' symptoms. Although the duration of therapy is not limited in the PBS restriction, the submission noted the median duration in the clinical trial was 41.9 weeks.

The analysis of actual versus predicted utilisation of the 2.5 mg, 5 mg and 10 mg prescriptions presented in Table 3 shows that the 2.5 mg and 5 mg packs are being supplied

more than was expected, and there is less use of the 10 mg packs than expected. Possible reasons for this may be patients taking lower doses due to tolerability. The product information notes that the most frequent adverse reactions from the pooled safety database of the clinical trials were stomatitis, upper respiratory tract infections, amenorrhea, hypercholesterolemia, nasopharyngitis, acne, irregular menstruation, sinusitis, otitis media and pneumonia.

The mean daily dose of everolimus for TSC in each listing year was 6.79 mg, 6.62 mg and 6.88 mg respectively. The submission used the ongoing mean dose from Study C2485, which was 5.3 mg/m^2/day. Study M2301 was used for sensitivity analysis and the mean dose in this study was 6.16 mg/m^2/day. The final estimates assumed the average dose per day in patients with SEGAs and angiomyolipomas would be 8.25 mg across all years of listing.

At the time of its positive recommendation being given, the PBAC considered that the sponsor's estimate of patient numbers was uncertain and that a suitable risk sharing arrangement should be negotiated using a conservative estimate of patient numbers and an expenditure cap. Following the positive recommendation from the PBAC, the estimates for everolimus in TSC were adjusted to include patients expected to be treated for renal angiomyolipomas. The number of patients treated with everolimus for TSC and the number of PBS prescriptions of everolimus for TSC was higher than estimated in the first two years of listing; however, the use was managed with a risk sharing arrangement.

DUSC consideration

DUSC noted that the PBAC (November 2012) considered it probable that everolimus could be used prior to surgery to reduce tumour volume and vasculature to improve surgical outcomes. This included reducing the possible adverse events associated with surgery, such as hydrocephalus. DUSC noted that the PBS restriction does not allow for use in patients who are candidates for curative resection. DUSC commented that the use of everolimus prior to resection would likely be for short durations.

DUSC noted that the number of treated patients per quarter had decreased in 2016. DUSC considered that use prior to resection is a potential factor in the short durations of use. DUSC commented that the decrease in treated patients may also be due to a reduction in patients' tumour size and improved tumour-related symptoms. The tolerability of the drug may also be a factor, DUSC noted that everolimus is associated with a high rate of adverse events.

DUSC noted that there was a greater use of the lower doses compared with the 10 mg dose than expected. Possible reasons for this may be patients taking lower doses due to tolerability. DUSC considered that it may also relate to use in children and commented that analyses by patient age would have been informative.

DUSC noted the sponsor response which considered that the findings were reasonable.

DUSC actions

The report was provided to the PBAC.

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

Novartis Pharmaceuticals Australia Pty Limited: The sponsor has no comment

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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 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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