6.01 EVEROLIMUS, dispersible tablets, 2mg, 3mg and 5mg, Afinitor®, Novartis

1 Purpose of Application

1.1 The submission requested an Authority Required listing for everolimus (EVR) for treatment of refractory seizures associated with tuberous sclerosis complex (TSC). This was the first time the PBAC had considered the listing of EVR for this indication. EVR is currently listed on the PBS for subependymal giant cell astrocytomas (SEGAs) and visceral tumours associated with TSC, as well as a number of other indications.

1.2 The basis for the proposed listing was cost-effectiveness versus best supportive care (placebo).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Refractory epilepsy associated with tuberous sclerosis complex.
Intervention	≥1 AED + everolimus orally once daily (target trough concentration 5 to 15ng/mL); starting dose of 5-9mg/m^2/day depends on age and concomitant treatment (i.e. enzyme inducer)
Comparator	≥1 AEDs + placebo.
Outcomes	Proportion of 'responder' patients (≥50%) and the distribution of response (<25%, ≥25% to <50%, ≥50% to <100%, 100%) defined as a reduction in average weekly seizure frequency from baseline.
Clinical claim	In patients with refractory epilepsy associated with tuberous sclerosis complex, everolimus is more effective than placebo at reducing the frequency of seizures.

Source: constructed during the evaluation based on information presented in the submission

2 Requested listing

2.1 Requested PBS listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
EVEROLIMUS					
Dispersible tablet, 2mg, 30	2	5	$2,200.01[a]		
Dispersible tablet, 3mg, 30	2	5	$3,226.01[a]	Afinitor®	Novartis
Dispersible tablet, 5mg, 30	2	5	$5,278.01[a]		

Treatment phase: initial treatment	
Condition	Tuberous sclerosis complex
Restriction	Authority required (General Schedule)
Clinical criteria	The patient must have a minimum of two partial-onset seizures per week, AND The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs, AND The treatment must be in combination with at least one anti-epileptic drug, AND The patient must not be a candidate for curative surgery
Population criteria	Patient must be at least 2 years of age

Treatment phase: continuing treatment	
Condition	Tuberous sclerosis complex
Restriction	Authority required (General Schedule)
Clinical criteria	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must be responding to treatment with this drug for this condition

[a] proposed special pricing arrangement, effective prices: 2mg (AEMP(30x1)=$[redacted], DPMQ(30x2)=$[redacted]); 3mg (AEMP(30x1)=$[redacted], DPMQ(30x2)=$[redacted]); 5mg (AEMP(30x1)=$[redacted], DPMQ(30x2)=$[redacted])

2.2 The proposed published price was equivalent to that of the current PBS listing of EVR for SEGAs and visceral tumours associated with TSC, but the proposed effective price for the dispersible tablets is cheaper (AEMP: $[redacted]/mg versus $[redacted]/mg). A maximum quantity of 60 tablets is required to provide one month's supply for most patients with refractory epilepsy. There is a wide range of potential daily doses required by patients, and most would likely require multiple prescriptions and a combination of strengths per month.

2.3 According to the draft product information (PI), initial dosing of EVR is dependent on age, body surface area (BSA) and co-administered pharmacokinetic (PK) inducers, ranging from 5mg/m^2/day to 9mg/m^2/day. It was recommended that whole blood trough concentration should be assessed approximately 1 to 2 weeks after commencing treatment or any change in dose, and dosing titrated to attain concentrations of 5 to 15ng/mL. The draft PI also noted a positive exposure-response relationship between trough concentration and seizure response, and stated that the dose of EVR may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy.

2.4 The proposed restriction did not define "responding to treatment", although the submission noted that the Sponsor was willing to work with the PBAC to determine an appropriate definition if required. The economic evaluation and financial estimates both assumed patients who demonstrated a ≥25% reduction in average weekly seizure frequencies would continue treatment. The ESC considered that a continuing treatment restriction may not be practical as treatment response measurement, particularly in relation to measuring seizure frequency in children, is difficult to quantify. There also may not be sufficient variation in treatment response

to justify a continuation rule given that 37.8% if patients in the placebo arm of the EXIST-3 trial demonstrated ≥25% reduction in seizure frequency.

2.5 Given the ability of EVR to directly block disease pathways, there is potential for use of EVR outside of the requested restrictions. It is conceivable that clinicians might focus on potential future benefits on disease sequelae rather than just epilepsy (such as the prevention/reduction of cognitive delays, behavioural issues and solid tumours). The ESC considered it might be more appropriate to consider a whole-of-disease approach to PBS subsidy of everolimus for TSC rather than individual consideration of disease presentations as more evidence becomes available, noting that the evidence presented in the submission was solely focused on the management of refractory epilepsy. Long-term data on disease sequelae of TSC was not presented nor modelled in the economic evaluation.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 EVR was submitted under TGA/PBAC parallel process and was undergoing assessment by the TGA for the proposed indication: "adjunctive treatment of patients aged 2 years and older with TSC and associated refractory seizures." At the time of evaluation, the first round TGA Clinical Evaluation Report was available. The TGA Delegate's Overview was provided with the Pre-Sub-Committee Response (PSCR), with no changes made to the proposed indication.

4 Population and disease

4.1 TSC is a rare genetic disorder associated with the deregulation of the mammalian target of rapamycin (mTOR) pathway responsible for regulating cell growth and homeostasis. The disorder can lead to many physical and physiological manifestations, including benign tumours (in the brain, kidneys, eyes, heart, skin, liver and lungs), autism, intellectual disability, cognitive impairments, behavioural issues and epilepsy. EVR blocks the aberrant mTOR activation that occurs in TSC.

4.2 Seizures associated with TSC are caused by tubers, a type of benign brain lesion characteristic of TSC. Seizures typically begin in infancy and can range in frequency up to multiple seizures per day. Many children with seizures also go on to develop other manifestations, particularly developmental deficits. The ESC noted that it is often difficult to determine when children are having seizures due to the range of presentations and the subtlety of some seizure presentations. As such, it is challenging to determine in practice the number of seizures a child has in a defined period, and the reduction in seizures achieved following treatment.

4.3 In patients who develop refractory seizures to combination anti-epileptic drugs, treatment options include surgery, mTOR inhibitors such as EVR and sirolimus

(currently off-label), ketogenic diet and vagus nerve stimulation (VNS). The submission described ketogenic diet and VNS as largely last line alternatives because maintaining the diet is challenging and VNS is invasive and rarely effective. Should EVR be listed as requested it would replace off-label use of mTOR inhibitors, or 'best supportive care'.

5 Comparator

5.1 The submission nominated best supportive care (or placebo) as the main comparator. This was considered appropriate in the evaluation.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with everolimus including reduced seizure frequency and severity, improved quality of life for patients and their families, and reduced carer burden.

Clinical trials

6.3 The submission was based on one head-to-head trial (EXIST-3, N=366) comparing two doses of EVR (low trough (LT) concentration target: 3-7ng/mL; and high trough (HT) concentration target: 9-15ng/mL) to placebo.

6.4 The recommended dosing regimen (starting dose, target trough concentration and titration dose increments) in the draft PI differ to those used in EXIST-3. The submission reasonably considered that the HT EVR arm in EXIST-3 was most representative of the proposed dosing regimen in the draft PI. Based on efficacy results, the HT EVR arm in EXIST-3 was consistent with the subgroup of patients in EXIST-3 who met the target trough levels recommended in the draft PI.

6.5 Details of EXIST-3 are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EXIST-3	CRAD001M2304. A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures. French JA *et al*. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study.	16 May 2016. Interim Clinical Study Report. 28 February 2017. Extension phase synopsis. *Lancet* 2016; 388:2153-63

Source: Table 7, p22 of the submission

6.6 The key features of EXIST-3 are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Bias	Patient population	Outcomes	Use in modelled evaluation
EXIST-3	366	R, DB, MC, PC, 3-arm / 18 week	Low	TSC, refractory seizures (≥2 regimens of ≥1 AED)	Reduction in seizure frequency (≥50% and % change)	Reduction in seizure frequency (100%, ≥50% to <100%, ≥25% to <50%)

Abbreviations: DB=double blind; MC=multi-centre; PC=placebo controlled; R=randomised; TSC=tuberous sclerosis complex; AED=anti-epileptic drug

Source: compiled during the evaluation

6.7 The phase III trial consisted of an 8-week baseline phase, an 18-week double-blinded placebo controlled core phase (6-week titration period; 12-week maintenance period) and ≥48 week open-label extension phase. The submission was based on the results of the 18-week core phase as the extension phase was on going.

6.8 At the start of the core phase, 366 patients who met the selection criteria during the baseline phase were randomised 1:1:1 to LT EVR, HT EVR or placebo, stratified by age. An Interactive Response Technology (IRT) was used to randomise patients to the treatment arms, calculate the starting dose and make dose adjustments based on the target trough levels. Without unblinding, an error was detected with the IRT, which resulted in the failure to correctly titrate the doses for a maximum of 18 patients in the HT EVR arm. An amendment was made to the protocol to increase planned sample size in the HT EVR arm by 10 to mitigate against potential loss of power.

Comparative effectiveness

6.9 The outcomes reported in EXIST-3 related to the reduction in seizures associated with TSC rather than a response to other disease manifestations or reduction in disease sequelae. With respect to the treatment of refractory seizures, the clinically relevant outcomes are the reduction in seizure frequency and the proportion of patients who become seizure free. In addition to seizure freedom, the PBAC has previously accepted a 50% reduction in seizures as being clinically important for patients where median seizure frequency at baseline was 9 to 13 per 28 days (Lacosamide Public Summary Document, November 2009). On the basis of considerably higher seizure frequencies at baseline in EXIST-3 (median of 9 and mean of 17 per 7 days), the submission also nominated a 25% reduction as being clinically

important for TSC patients. The ESC questioned whether this outcome was always clinically relevant, and considered that the impact of even a 50% reduction in seizure frequency may not be clinically meaningful or significantly impact a child's care needs, particularly in children with a high baseline seizure burden.

6.10 The primary efficacy outcome in EXIST-3 was the change in seizure frequency between the 8-week baseline phase and 12-week maintenance phase, expressed in two ways to satisfy the EMA and FDA respectively:

i) ≥50% reduction in seizure frequency, and
ii) median percentage reduction in seizure frequency.

6.11 The results are summarised in Table 4. The TGA Clinical Evaluation Report recommended that the first definition should be considered as the primary outcome given there was no allowance for multiplicity in the trial protocol. Based on a ≥50% reduction in average seizure frequency, the number needed to treat (NNT) (95%CI) for the LT EVR and HT EVR arms were 8 (1,33) and 4 (3,7) respectively.

Table 4: Results of the primary outcome in EXIST-3 (ITT), expressed as ≥50% reduction in seizure frequency and median percentage reduction in seizure frequency

Outcome	LT EVR (N=117)	HT EVR (N=130)	Placebo (N=119)	LT EVR v placebo	HT EVR v placebo
≥50% response,				OR (95%CI[a]; p-value[b])	
n (%)	33 (28.2)	52 (40.0)	18 (15.1)	**2.21 (1.16, 4.20; p=0.008)**	**3.93 (2.10, 7.32; p<0.001)**
Seizure frequency per week (median range)				Diff (95%CI[c], p-value[d])	
baseline	8.63 (1.4,192.9)	9.45 (0.3, 218.4)	10.50 (1.3,231.7)	-	-
core	6.83 (0.0,193.5)	4.91 (0.0, 133.7)	8.53 (0.0,217.7)	-	-
diff	–2.13(-64.0,84.1)	–3.32 (-84.7,6.5)	–1.0(-33.5,21.7)	-	-
% diff, (95%CI)[e]	29.29% (18.82,41.88)	39.55% (35.03,48.74)	14.86% (0.11,21.71)	**15.96% (1.98, 31.68; p=0.003)**	**27.46% (16.36, 43.36; p<0.001)**

[a] Odds ratio and its 95% CI obtained using logistic regression stratified by age subgroup. Odds ratio >1 favours everolimus arm.
[b] p-values computed from the Cochran-Mantel-Haenszel test stratified by age subgroup
[c] stratified bootstrap method, stratified by age weighting by inverse variance, 95%CI of the median bootstrap percentiles
[d] from rank ANCOVA with baseline seizure frequency as covariate, stratified by age subgroup
[e] 95%CI of median based on bootstrap percentiles
Source: Table 19 and 20, pp47-49 of the submission

6.12 Table 5 presents a summary of other relevant secondary outcomes in EXIST-3, including seizure freedom, seizure response rate defined as ≥25% reduction in average weekly seizure frequency from baseline, and the distribution of seizure response across predefined categories. The ESC noted a high placebo response, with 37.8% of patients in the placebo arm of EXIST-3 achieving the outcome of ≥25% reduction in seizure frequency.

Table 5: Results of relevant secondary outcomes in EXIST-3 (ITT)

Outcome	LT EVR (N=117)	HT EVR (N=130)	Placebo (N=119)	LT EVR v Placebo OR (95%CI)	HT EVR v Placebo OR (95%CI)
100% responders, n (%)	6 (5.1)	5 (3.8)	1 (0.8)	6.55 (0.77, 55.73)	4.99 (0.57, 44.03)
≥25% responders, n (%)	61 (52.1)	91 (70.0)	45 (37.8)	**1.77 (1.05, 2.97)**	**3.82 (2.25, 6.48)**
Response distribution, n (%)					
100%	6 (5.1)	5 (3.8)	1 (0.8)	-	-
≥75% to <100%	7 (6.0)	20 (15.4)	6 (5.0)	-	-
≥50% to <75%	20 (17.1)	27 (20.8)	11 (9.2)	-	-
≥25% to <50%	28 (23.9)	39 (30.0)	27 (22.7)	-	-
≥-25% to <25%	41 (35.0)	24 (18.5)	49 (41.2)	-	-
≤-25%	15 (12.8)	15 (11.5)	24 (20.2)	-	-
missing	0	0	1 (0.8)	-	-

Source: Table 23, 24 and 25, p53-54 of the submission

6.13 Quality of life data was measured in EXIST-3 using three non-preference based disease- and age-specific questionnaires: QOLCE (<11 years); QOLIE AD-48 (≥11 to <18 years); QOLIE 31-P (≥18 years). No significant differences were observed between the EVR and PBO, although there were low completion rates.

Comparative harms

6.14 EVR has immunosuppressive properties and common adverse events in the PI include infection, impaired wound healing, mouth ulcers, stomatitis, rash, nail and skin changes, breathing problems (pneumonitis, cough, dyspnoea), reproductive concerns (irregular sperm production and menstrual cycles), fatigue, decrease in appetite, low white and red blood cell counts, low platelet counts, renal failure, oedema, high blood pressure, elevated blood sugars/cholesterol/triglycerides, diarrhoea and nausea.

6.15 Overall, the AEs experienced by patients in the EXIST-3 trial (including the extension phase) were consistent with the known safety profile of EVR. Table 6 presents a summary of adverse events reported in EXIST-3. The most common AEs that occurred more frequently with EVR than placebo were stomatitis, mouth ulcers, diarrhoea, aphthous ulcers, pyrexia, cough, rash, increased blood cholesterol and pharyngitis. The ESC considered that blinding may not have been maintained in the trial due to the presence of known adverse events of everolimus, particularly stomatitis and mouth ulcers, and this could potentially bias the outcome measurement. The pre-PBAC response (p3) noted that "while it was possible stomatitis prevalence may have impacted on the blinding, there was a dose response correlation which supports efficacy."

Table 6: Summary of adverse events in EXIST-3 (safety population)

Adverse event	LT EVR (N=117)	HT EVR (N=130)	Placebo (N=119)	LT EVR v placebo, RD (95%CI)	HT EVR v placebo, RD (95%CI)
AE summary					
Any AE	108 (92.3)	123 (94.6)	92 (77.3)	**0.15 (0.06, 0.24)**	**0.17 (0.09, 0.26)**
Any Grade 3/4 AE	21 (17.9)	31 (23.8)	13 (10.9)	0.70 (-0.02, 0.16)	**0.13 (0.04, 0.22)**
Any SAE	16 (13.7)	18 (13.8)	3 (2.5)	**0.11 (0.04, 0.18)**	**0.11 (0.05, 0.18)**
AEs resulting in discontinuation	6 (5.1)	4 (3.1)	2 (1.7)	0.03 (-0.01, 0.08)	0.01 (-0.02, 0.05)
AEs resulting in death	0	0[a]	0	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)
AEs requiring dose change	28 (23.9)	46 (35.4)	9 (7.6)	**0.16 (0.07, 0.25)**	**0.28 (0.18, 0.37)**
AEs requiring therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common AEs more frequent with EVR					
Stomatitis	33 (28.2)	40 (30.8)	4 (3.4)	**0.25 (0.16, 0.34)**	**0.27 (0.19, 0.36)**
Mouth ulcers	28 (23.9)	28 (21.5)	5 (4.2)	**0.20 (0.11, 0.28)**	**0.17 (0.09, 0.25)**
Diarrhoea	20 (17.1)	28 (21.5)	6 (5.0)	**0.12 (0.04, 0.20)**	**0.16 (0.08, 0.25)**
Aphthous ulcers	5 (4.3)	19 (14.6)	2 (1.7)	0.03 (-0.02, 0.07)	**0.13 (0.06, 0.19)**
Pyrexia	23 (19.7)	18 (13.8)	6 (5.0)	**0.15 (0.06, 0.23)**	**0.09 (0.02, 0.16)**
Cough	13 (11.1)	13 (10.0)	4 (3.4)	**0.08 (0.01, 0.14)**	**0.07 (0.01, 0.13)**
Rash	7 (6.0)	13 (10.0)	3 (2.5)	0.03 (-0.02, 0.09)	**0.07 (0.02, 0.13)**
Increased blood cholesterol	6 (5.1)	9 (6.9)	1 (0.8)	0.04 (-0.00, 0.09)	**0.06 0.01, 0.11)**
Pharyngitis	6 (5.1)	8 (6.2)	1 (0.8)	0.04 (-0.00, 0.09)	**0.05 (0.01, 0.10)**

[a] One patient in the HT group died during the study, but the death was attributed to 'Other, sudden unexplained death from epilepsy', not to an AE; this death was not suspected to be related to the study drug.

Bold typography indicate statistically significant differences across the treatments

Source: Table 31 and 32, pp62-65 of the submission

6.16 Long-term safety data for EVR is still emerging and is immature. Potential risks such as impacts on cerebral and gastrointestinal haemorrhages, muscle wasting, male and female fertility as well as impacts on brain development would be concerning given use of EVR on the PBS for refractory seizures associated with TSC is intended to begin in childhood and continued life-long.

Benefits/harms

6.17 A summary of the comparative benefits and harms for HT EVR versus placebo is presented in the table below. As noted above, the HT EVR arm in EXIST-3 is most representative of the proposed dosing regimen recommended in the draft PI.

Table 7: Summary of comparative benefits and harms for HT EVR and placebo

	HT EVR	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				HT EVR	Placebo	
Benefits						
Seizure free, n (%)	5/130	1/119	4.58 (0.54,38.61)	3.8	0.8	0.03 (-0.01, 0.07)
≥50% reduction in seizures, n (%)	52/130	18/119	**2.64 (1.64, 4.25)**	40.0	15.1	**0.25 (0.14, 0.35)**
≥25% reduction in seizures, n (%)	91/130	45/119	**1.85 (1.43, 2.39)**	70.0	37.8	**0.32 (0.20, 0.44)**
Harms						
	HT EVR	**Placebo**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				HT EVR	**Placebo**	
Any SAE	18/130	3/119	**5.49 (1.66, 18.17)**	13.8	2.5	**0.11 (0.05, 0.18)**
AE requiring therapy	[redacted]	[redacted]	[redacted]	86.2	52.9	**0.33 (0.22, 0.44)**
AE requiring hospital	[redacted]	[redacted]	[redacted]	17.7	2.5	**0.15 (0.08, 0.22)**

* Median duration of exposure: 18 weeks

Abbreviations: HT EVR = high trough everolimus; RD = risk difference; RR = risk ratio; SAE=serious adverse event; AE=adverse event

Source: Compiled during the evaluation

6.18 On the basis of direct evidence presented by the submission, for every 100 patients treated with HT EVR in comparison to placebo over a median duration of exposure of 18 weeks;

- Approximately 32 additional patients would achieve a ≥25% reduction in seizure frequency from baseline;
- Approximately 25 additional patients would achieve a ≥50% reduction in seizure frequency from baseline;
- No additional patients would become seizure free based on the evidence (but the trial was not powered to detect this);
- Approximately 11 additional serious adverse events would occur;
- Approximately 33 additional adverse events would require treatment;
- Approximately 15 additional adverse events would require hospitalisation.

Interpretation of clinical evidence

6.19 The submission described EVR as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care. This claim was adequately supported. With respect to safety, the claim focused on AEs that occurred during the clinical trial, however as EVR treatment is potentially life long, starting as early as infancy, long term safety concerns such as cerebral and gastrointestinal haemorrhages, fertility issues, muscle-wasting / muscle-loss as well as potential developmental problems should also be considered.

6.20 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.21 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.22 The submission presented a modelled economic evaluation comparing EVR with best supportive care for refractory seizures associated with TSC. The costs and outcomes calculated for EVR in the model reflected the medication and administration costs and outcomes in HT EVR arm of EXIST-3. Consistent with the trial evidence, model outcomes were solely based on the reduction in seizure frequency reported in EXIST-3, and did not include potential benefits associated with other disease manifestations or disease sequelae. The ESC also noted that costs associated with adverse events (particularly hospitalisation costs) were not included in the model although such costs may not substantially affect the base-case ICER.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 18 weeks in trial
Outcomes	QALYs
Methods used to generate results	Cohort expected value analysis
Health states	A simple Markov model with four health states based on reduction in seizure frequency from baseline: "Seizure free (100%)", "Responder (≥50% to <100%)", "Partial responder (≥25% to <50%)" and "Discontinued (<25%)"; death was not modelled. The model assumed: i. patients achieve immediate benefits from treatment, ii. patients who experience AEs discontinue treatment at 18 weeks, iii. patients who achieve <25% response discontinue treatment at 24 weeks, iv. there is no change in treatment efficacy over time, v. patients who discontinue are ineligible for re-treatment, and vi. a relative reduction in seizure frequency is valued the same regardless of baseline seizure frequency (range in EXIST-3: 0.3 to 231.7 per week).
Utilities	Extracted from Messori et al 1998. Seizure free (100%): 0.96, Responder (≥50% to <100%): 0.91, Partial responder (≥25% to <50%): 0.79, Discontinued (<25%): 0.40. The nominated utilities were not adequately justified and may not be applicable to the severe and heterogeneous population in terms of baseline seizure frequencies
Cycle length	7 days; however there are no transitions after week 24.
Transition probabilities	The model assumed patients commence in the health states based on seizure response in EXIST-3 (18 weeks). 3% of patients cease at week 18 due to AEs and all patients with <25% response cease at week 24.

Source: compiled during the evaluation

6.23 Table 9 summarises the key drivers of the model.

Table 9: Key drivers of the model

Description	Method/Value	Impact
No change in efficacy over time	Assumed no change in treatment efficacy over 5 years implies there is no waning of effect. This assumption was not tested given the structure of the model but likely favoured EVR, particularly if patients remain on treatment. However, should doctors dose EVR for better seizure control in clinical practice (within the target range), there may also be the potential for some improvement in seizure control over time.	Unclear
Discontinuation of EVR <25% response at 24 weeks	Discontinuation of treatment <25% response assumed clinicians would cease EVR rather than add on additional AEDs to EVR or change other AEDs first. This may not be reasonable given the lack of response criteria in the proposed PBS listing, severity of disease, lack of alternatives and potential impact on other disease sequelae via the mTOR pathway.	Moderate, favoured EVR
Utilities	Values applied to health states by relative seizure response (i.e. 100%, ≥50% to <100%, ≥25% to <50%, <25%) were extracted from health states in Messori et al 1998 described by absolute seizures per month (none, ≥1, 2-9) and "presence of drug-related side effects". The applicability of these utilities to patients with TSC was questionable. The ESC considered that the utilities from Messori et al lacked face validity and were likely to be unreasonably high. There is a wide variation of utility scores in the epilepsy literature. The ESC considered that utilities from Verdian et al might be more reflective of the population.	High, favoured EVR

Source: compiled during the evaluation

6.24 Table 10 presents the results of the economic evaluation.

Table 10: Results of the stepped economic evaluation

Component	HT EVR	PBO	Increment
Step 1: trial-based costs and outcomes			
Drug costs only (18 weeks)	$[redacted]	$0	$[redacted]
50% responder (18 weeks)	0.40	0.15	0.25
25% responder (18 weeks)	0.70	0.38	0.32
Incremental cost/extra 50% responder gained (18 weeks)			**$[redacted]**
Incremental cost/extra 25% responder gained (18 weeks)			**$[redacted]**
Step 2: modelled evaluation (five years)			
Costs (undiscounted)	$[redacted]	$0	$[redacted]
Cost (discounted)	$[redacted]	$0	$[redacted]
QALYs (undiscounted)	1.58	0.83	0.74
QALYs (discounted)	1.43	0.76	0.67
Incremental cost/extra QALY gained (undiscounted)			**$[redacted]**
Incremental cost/extra QALY gained (discounted)			**$[redacted]**

Source: Tables 44 and 54, p87 and p99 of the submission

6.25 The ICER was highly sensitive to the utilities assumed, increasing from $75,000 - $105,000/QALY to more than $200,000/QALY based on utility estimates extracted from Verdian et al 2008 and Selei et al 2002. The ESC considered that utilities from Verdian et al might be more appropriate, as the population in the study was children with Lennox-Gastaut Syndrome who had a high baseline seizure frequency.

6.26 The model's focus on epilepsy meant that other potential long-term benefits such as prevention of cognitive delays and behavioural issues, reduction of other disease sequelae (i.e., solid tumours) and quality of life improvements for parents and/or carers were not captured. The PSCR (p1) considered that the exclusion of these possible benefits underestimates the cost-effectiveness of everolimus.

6.27 The ESC considered that given the outcome measure used in the model may not be clinically meaningful yet additional benefits of treatment with EVR were not captured in the model, determining true cost-effectiveness of everolimus in this population was difficult based on the available information.

6.28 The submissions presented a sensitivity analysis whereby the ICER decreased to $15,000/QALY - $45,000/QALY when an average incremental utility gain of 2.0 over five years (consistent with the gain applied in the PBAC's previous consideration of EVR for SEGAs and visceral tumours) was assumed. In its consideration of EVR for SEGAs and visceral tumours associated with TSC, the PBAC considered that "an average QALY gain of 0.4 (per year, averaged across all patients) might be plausible, although difficult to substantiate." However, it is noted that not all patients with refractory seizures due to TSC necessarily go on to develop SEGAs/tumours, as in EXIST-3, only 17% and 41% of population had SEGAs and angiomyolipomas (AMLs) respectively. Likewise, in the SEGAs/tumours population previously considered by the PBAC, not all patients had refractory epilepsy. The ESC considered that it might not be appropriate for the average QALY gain per patient that was applied in the consideration of EVR for SEGAs and visceral tumours to be applied in the current requested population.

Drug cost/patient/year

6.29 $[redacted]/patient/year, assuming an average daily dose of 9.84mg (HT EVR arm of EXIST-3) and an effective ex-manufacturer price of $[redacted]/mg (365.25 x 9.84 x [redacted]). Lifelong treatment is anticipated given adequate response and tolerance. Given there is a wide range of potential daily doses depending on age, BSA and co-administration of PK inducers, there is a wide range of potential costs per patient per year for EVR.

Estimated PBS usage & financial implications

6.30 This submission was not considered by DUSC.

6.31 An epidemiological approach was undertaken to estimate the use and financial implications for EVR for refractory seizures associated with TSC. Disease prevalence estimates were sourced from international and Australian literature, average doses were sourced from the trial evidence; uptake rates, distribution of prescription strengths, compliance and monitoring rates were assumed. The low uptake rates were assumed to exclude patients either:

- aged under 2 years
- suitable for surgical resection or
- eligible for EVR under the current TSC listing.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
TSC population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSC population with refractory epilepsy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Treated[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On tx, 1st year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On tx, 2nd year		[redacted]	[redacted]	[redacted]	[redacted]
On tx, 3rd year			[redacted]	[redacted]	[redacted]
On tx, 4th year				[redacted]	[redacted]
On tx, 5th year					[redacted]
Number of scripts[b]					
2mg (60)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3mg (60)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5mg (60)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS (monitoring)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

[a] assuming probability of ceasing treatment in year 1 was [redacted]% and [redacted]% thereafter;
[b] Assuming 6.94 scripts in the first year (half-cycle correction) and 13.87 thereafter; 95% compliance rate and proportional split of 2mg, 3mg and 5mg scripts were 30.5%, 25% and 44.5% respectively.
Source: Excel workbook "Afinitor TSC seizures Section E FINAL.xls"

6.32 The total cost for the government health budget over the first 5 years of listing was estimated to be less than $10 million. There is potential for the net cost/year to the government to be greater than the estimate in the submission for the following reasons:

- the prevalence of TSC may be higher than estimated (Tuberous Sclerosis Australia stated >2000 patients)
- the average daily dose may be higher in practice should clinicians dose to efficacy as recommended in the draft PI, and
- fewer patients may cease treatment after the first 6 months.

6.33 There is also potential for use of EVR beyond the requested listing, given EVR is the only treatment with clinical evidence of reducing seizures associated with TSC which targets the growth of tubers in the brain through the mTOR pathway. There may be some motivation for use earlier in the treatment algorithm, as first- or second- line therapy. The PSCR (p3) noted that a February 2017 DUSC review of the first two

years of listing of everolimus for SEGA and visceral tumours indicated usage had been relatively consistent with expected utilisation, and considered that this is likely to be similar for the current requested population.

Financial Management – Risk Sharing Arrangements

6.34 The submission proposed a special pricing arrangement for the proposed listing that included an effective price cheaper than the current PBS listing for TSC (i.e., SEGAs, visceral tumours) on a cost/mg basis. It was anticipated that there would also need to be a Deed of Agreement for the proposed indication of refractory seizures associated with TSC and the Sponsor is willing to discuss the content with the PBAC.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred its decision about whether to extend the listing of everolimus to include the treatment of refractory seizures associated with tuberous sclerosis complex (TSC), to allow for negotiations to establish the appropriate restriction, and a price for treatment that could be considered cost-effective.

7.2 The PBAC agreed with the ESC that it might be appropriate to consider a whole-of-disease approach to PBS subsidy of everolimus for TSC, given the ability to block the disease pathway, rather than individual consideration of disease presentations as more evidence becomes available, noting that the evidence presented in the submission was solely focused on the management of refractory epilepsy. For this reason, and for the reasons noted by ESC, the PBAC agreed that a continuation rule based on seizures was problematic, and that the restriction be predicated on the whole of disease approach.

7.3 The PBAC agreed that best supportive care was the appropriate comparator, noting the comments in the pre-PBAC response (p1) that 85% of patients in the key trial had previously failed four or more AEDs, and 39% had failed six or more AEDs, indicating that this is a highly refractory population.

7.4 The PBAC noted that there were potential long-term benefits of everolimus treatment in TSC that were not captured in the submission, which focused on reduction of seizure frequency. However, based on the available information, it was not possible to quantify any potential benefits. Additionally, the PBAC noted from the pre-PBAC response the claim that clinicians aim to reduce seizure severity, as well as frequency, however no evidence for the effect on seizure severity was provided in the submission.

7.5 Furthermore, the Committee noted that there was no difference in the quality of life outcome reported in the study, although it was acknowledged that the completion rates for this outcome were low.

7.6 The PBAC noted that long-term safety remained uncertain, with potential risks

including cerebral and GI haemorrhage, fertility issues, and muscle wasting/loss.

7.7 The PBAC agreed that everolimus was superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care.

7.8 The PBAC agreed with the ESC that utilities from Verdian et al were likely to be more reflective of the patient population than those used in the submission. Applying the Verdian et al utilities in the model increased the ICER to more than $200,000/QALY, although the PBAC also noted that as long-term benefits of treatment were not modelled, the ICER may be overestimated. As noted above, insufficient information was available to reliably model any potential long-term benefits. Based on the information provided, the PBAC considered that the ICER was unacceptably high and uncertain, and that the cost effectiveness was therefore unacceptable.

7.9 The PBAC considered that the estimated use and financial implications were likely to have been underestimated, due to the likelihood that the number of TSC patients (with or without refractory epilepsy) is higher than predicted, potential for more use of higher doses than estimates, and the possibility that fewer patients would cease treatment than estimated in the submission.

7.10 The PBAC acknowledged the unmet clinical need in this patient population, and the likelihood that everolimus would provide an important benefit in at least some patients, but did not consider that the current submission provided an appropriate basis to support a listing. The PBAC therefore requested that the Department work with the sponsor on the proposed restriction, price, and estimation of financial impact.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The Sponsor will continue to work with the Department to make everolimus available for this rare condition.

Addendum to the December 2017 PBAC Minutes:

14.06 EVEROLIMUS, Dispersible tablets, 2mg, 3mg and 5mg, Afinitor®, Novartis Pharmaceuticals Australia Pty Limited

1 Purpose of Reconsideration

1.1 Subsequent to its deferral at the December 2017 PBAC meeting, the Sponsor, Novartis Pharmaceuticals Australia Pty Ltd, requested that the PBAC reconsider its decision to defer the application for everolimus for tuberous sclerosis complex (TSC).

2 Nature of Sponsor Request

2.1 The Sponsor did not alter any of the parameters used in its original submission considered by the PBAC at its December 2017 meeting.

2.2 In its request to the PBAC to reconsider its deferral of the application, the sponsor noted the following points regarding its application:

- Whilst the base case ICER for everolimus in the TSC indication is high, the model does not include additional short-term benefits in other TSC manifestations, nor the long-term benefits of reduced seizure burden;
- [redacted];
- The sponsor anticipates that, if listed, everolimus dispersible tablets will move to the F2 formulary at the same time as the standard tablet, and that the dispersible form will not be exempt from statutory price reductions or price disclosure; and
- The sponsor notes, however, that the TGA has not declared the standard and dispersible forms of everolimus to be bioequivalent, and the standard tablet is not TGA registered for TSC.

2.3 These points notwithstanding, the Sponsor argued it was important to seek reimbursement for rare conditions (such as TSC) and requested the PBAC review its decision from the December 2017 meeting.

3 PBAC Outcome

3.1 The PBAC again deferred its decision about whether to extend the listing of everolimus to include the treatment of refractory seizures associated with tuberous sclerosis complex (TSC) on the basis there were significant remaining uncertainties relating to the proposed population and achieving price certainty.

3.2 The PBAC re-affirmed it considered it might be appropriate to consider a whole-of-disease approach to PBS subsidy of everolimus for TSC, given the ability to block the disease pathway, rather than individual consideration of disease presentations as more evidence becomes available and it noted a proposal for this population was not included in the request.

3.3 In deferring the application again, the PBAC noted it had previously considered the submission had an uncertain incremental cost-effectiveness ratio (ICER) and considered a price reduction was necessary to ensure a cost-effective listing for everolimus for TSC. The Committee also noted that the sponsor argued that price reductions could be realised soon as everolimus would be subject to generic competition and therefore statutory price reductions and price disclosure. However, the Committee considered that price disclosure is unreliable as a means to obtain price certainty, as the magnitude of price reductions cannot be determined prospectively.

3.4 The PBAC however also noted that the dispersible tablet form of everolimus may not be subject to these price reductions if the sponsor is successful in obtaining an exemption under Section 84AH of the *National Health Act 1953*, which states that the Minister may determine a pharmaceutical item is an exempt item if:

- There is only one listed brand of the relevant item; and
- There are no listed brands of other pharmaceutical items that are bioequivalent or biosimilar to the listed brand of the relevant item; and
- The relevant item and at least one listed brand of another pharmaceutical item have the same drug; and
- The Minister is satisfied, having regard to advice (if any) given to the Minister by the Pharmaceutical Benefits Advisory Committee, that:
    - The listed drug in the relevant item represents suitable therapy for a particular patient population; and
    - The relevant item is suitable for use by a particular subgroup of the population because of either or both of the form and manner of administration of the drug in the item; and
    - No other pharmaceutical item that has a drug is suitable for use by that subgroup because of either or both the form and manner of administration of the drug in the other item.

[redacted]

3.5 The PBAC requested that the Department liaise further with the sponsor to work towards a cost-effective listing of everolimus for TSC in an appropriate population under the conditions it had outlined at its December 2017 meeting.

Outcome:
Deferred

4 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

5 Sponsor's Comment

The Sponsor will continue to work with the Department to make everolimus available for this rare condition.

Addendum to the March 2018 PBAC Minutes:

4.02 EVEROLIMUS
Dispersible tablets, 2mg, 3mg and 5mg, Afinitor®, Novartis Pharmaceuticals Australia Pty Limited

6 Purpose of Item

6.1 To update the PBAC with regards to pricing matters relating to the December 2017/March 2018 consideration of everolimus for tuberous sclerosis complex (TSC).

7 Background

7.1 At its December 2017 meeting, the PBAC deferred its decision about whether to extend the listing of everolimus to include the treatment of refractory seizures associated with TSC to allow for negotiations to establish the appropriate restriction, and a price for treatment that could be considered cost-effective.

7.2 At its March 2018 meeting, the sponsor requested the PBAC reconsider its deferral of the submission for everolimus for TSC without providing any additional data or a lower price offer. The sponsor noted, however:

- Whilst the base case ICER for everolimus in the TSC indication is high, the model does not include additional short-term benefits in other TSC manifestations, nor the long-term benefits of reduced seizure burden;
- Given the imminent loss of exclusivity (i.e. patent expiry) for everolimus, and the fact that several generic brands of the standard everolimus tablet are now registered in the ARTG, it was anticipated that PBS listing of generic forms of everolimus will generate significant price reductions which will improve its cost-effectiveness;
- The sponsor anticipated that, if listed, everolimus dispersible tablets will move to the F2 formulary at the same time as the standard tablet, and that the dispersible form will not be exempt from statutory price reductions or price disclosure; and
- The sponsor noted, however, that the TGA has not declared the standard and dispersible forms of everolimus to be bioequivalent, and the standard tablet is not TGA registered for TSC.

7.3 The PBAC again deferred its decision about whether to extend the listing of everolimus on the basis the significant remaining uncertainties relating to the proposed population and cost-effectiveness had not been resolved.

7.4 The PBAC noted that, in response to the sponsor arguments that the dispersible tablet form of everolimus may not be subject to price reductions associated with the listing of generics and subsequent price disclosure, if the sponsor were successful in obtaining an exemption under Section 84AH of the *National Health Act 1953*. However, the PBAC considered it was unclear if market exclusivity for the dispersible tablet form would continue following patent expiry of the standard tablet, and noted that if generic forms of dispersible everolimus entered the market that any such exemption would no longer apply.

For more detail on PBAC's view, see section 5 PBAC outcome.

8 Current situation

8.1 Whilst not making an explicit submission to address the outstanding concerns raised by the PBAC, the Sponsor advised the Department on the 18th of May 2018 that the first generic forms of everolimus would be listed on 1 June 2018. At the time of the PBAC Executive meeting, generic brand(s) of everolimus had been listed on the PBS (Everolimus Sandoz, Sandoz Pty Ltd). The sponsor advised that everolimus would take a price reduction at that time.

8.2 The Secretariat sought the advice of the Pricing Section and obtained updated ex-manufacturer prices (AEMPs) of everolimus. Everolimus pricing is based on a flat per milligram price, and at 1 June 2018 prices, the price of everolimus was determined to be $5.31 per mg, a decrease of 15.04% at AEMP. A comparison of Pre- and Post- 1 June 2018 prices and the primary pricing sensitivity analysis in the original submission are presented in Table 1 below.

Table 1: Comparison of Pre- and Post- 1 June prices for proposed everolimus dispersible tablet

Form and strength	Approved ex-manufacturer price (AEMP)	Dispensed price for maximum quantity (DPMQ)
Pre- 1 June 2018 ($6.25/mg)		
Everolimus 2 mg tablet, 60 (30 tablets, max qty 2)	$750.00	$839.41
Everolimus 3 mg tablet, 60 (30 tablets, max qty 2)	$1,125.00	$1241.55
Everolimus 5 mg tablet, 60 (30 tablets, max qty 2)	$1,875.00	$2017.81
Post- 1 June 2018 ($5.31/mg) (15.04% reduction)		
Everolimus 2 mg tablet, 60 (30 tablets, max qty 2)	$637.20	$713.89
Everolimus 3 mg tablet, 60 (30 tablets, max qty 2)	$955.80	$1066.43
Everolimus 5 mg tablet, 60 (30 tablets, max qty 2)	$1,593.00	$1725.93
December 2017 submission sensitivity analysis ($5.25/mg) (16% reduction)		
Everolimus 2 mg tablet, 60 (30 tablets, max qty 2)	$630.00	$705.89
Everolimus 3 mg tablet, 60 (30 tablets, max qty 2)	$945.00	$1,055.25
Everolimus 5 mg tablet, 60 (30 tablets, max qty 2)	$1,575.00	$1,707.31

Source: Compiled by the PBAC Secretariat. Source AEMPs for Pre- June 2018 from Sponsor Spreadsheet (Afinitor TSC Section E, Pricing Calculation); Source AEMPs for Post-1 June 2018 derived by the PBAC Secretariat, cross referenced with currently listed everolimus forms and strengths.

8.3 The Secretariat notes the magnitude of the price decrease of everolimus is less than that presented in the pricing sensitivity analysis in the original submission.

For more detail on PBAC's view, see section 5 PBAC outcome.

9 Consideration of the evidence

Economic Analysis

9.1 The PBAC Secretariat applied the current price of everolimus to the economic model spreadsheets provided in the original submission, which are compared in the table below.

Table 2: Comparison of ICERs between Pre- and Post- 1 June 2018 pricing

	Original model ($6.25/ mg price)	Post- 1 June 2018 ($5.31/mg price)
Incremental cost	$6,605,835.67	$5,655,446.58
ICER	$[redacted]/QALY	$[redacted]/QALY

Source: Compiled by the PBAC Secretariat. Original model from Sponsor Spreadsheet (Afinitor TSC Section D, economic model); Post- 1 June 2018 derived by the PBAC Secretariat based on updated prices and sponsor model.

9.2 The reduced price of everolimus from 1 June 2018 reduced the ICER by 14.39%. The Secretariat noted that the PBAC considered the cost-effectiveness of everolimus for TSC was unacceptably high and uncertain. The Secretariat further noted the Committee previously considered that utilities from Verdian *et al* were likely to be more reflective of the patient population than those used in the submission. When

applied to the original proposed price, the ICER of everolimus was more than $200,000/QALY, however the PBAC noted that such an ICER may be overestimated as the long-term benefits of treatment were not modelled and insufficient information was available to reliably model any potential long-term benefits.

Drug cost/patient/year

9.3 $19,084/patient/year, assuming an average daily dose of 9.84mg (HT EVR arm of EXIST-3) and an effective ex-manufacturer price of $5.31/mg (365.25 x 9.84 x 5.31). Lifelong treatment is anticipated given adequate response and tolerance. The previous drug cost per patient per year was calculated to be $22,463/patient/year, based on an everolimus price of $6.25/mg.

Estimated PBS usage & financial implications

9.4 The estimated PBS use and financial implications table from the November 2017 submission was updated to reflect the current price of everolimus.

Table 3: Estimated use and financial implications (updated June 2018)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
TSC population					
TSC population with refractory epilepsy					
Uptake	7%	15%	19%	21%	22%
Treated[a]					
On tx, 1st year					
On tx, 2nd year					
On tx, 3rd year					
On tx, 4th year					
On tx, 5th year					
Number of scripts[b]					
2mg (60)					
3mg (60)					
5mg (60)					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$	$	$	$	$
Net cost to MBS (monitoring)	$	$	$	$	$
Estimated total net cost					
Net cost to PBS/RPBS/MBS (Jun-18)	**$**	**$**	**$**	**$**	**$**
December 2017 reference cost	**$**	**$**	**$**	**$**	**$**

[a] assuming probability of ceasing treatment in year 1 was % and % thereafter

Source: Everolimus (TSC) PBAC December 2017 minutes, updated with 1 June 2018 prices as advised by the PBS Pricing Section.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000.

9.5 The cost to government in year 5 was estimated to be less than $10 million based on the effective prices of everolimus as at 1 June 2018, a reduction of $313,305 from the December 2017 submission. The total cost to government over years 1-5 was

estimated to be less than $10 million, a reduction of $1,100,728 from the December 2017 submission.

For more detail on PBAC's view, see section 5 PBAC outcome.

10 PBAC Outcome

10.1 The PBAC recommended the listing of everolimus (in a dispersible tablet form) for the treatment of refractory seizures associated with tuberous sclerosis complex (TSC) and is satisfied that everolimus provides, for some patients, a significant improvement in efficacy over best supportive care.

10.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of everolimus would be acceptable at the current price of everolimus on a pragmatic basis, accounting for the small patient population and high clinical need for effective treatments for symptoms associated with TSC.

10.3 The PBAC recalled it had identified a range of issues with the original submission, including (from the December 2017 outcome):

- A whole-of-disease approach to PBS subsidy of everolimus for TSC was preferable, given the ability to block the disease pathway rather than individual consideration of disease presentations (paragraph 7.2);
- There were potential long-term benefits of everolimus treatment in TSC; however the evidence presented made it difficult to quantify potential benefits. However, the PBAC noted the Pre-PBAC response claim that a reduction in seizure severity, as well as frequency, was a valid clinical aim, however noted no evidence on seizure severity was included in the submission (paragraph 7.4);
- The long-term safety remained uncertain, with potential risks including cerebral and gastrointestinal haemorrhage, fertility issues and muscle wastage (paragraph 7.6);
    - There were substantial uncertainties in the economic model, and the utilities from Verdian et al were likely to be more reflective of the patient population than those used in the submission. Applying the Verdian et al utilities increased the ICER to more than $200,000/QALY, although the PBAC also noted that as long-term benefits of treatment were not modelled, the ICER may be overestimated (paragraph 7.8); and
- The estimated use and financial implications were likely to have been underestimated due to the likelihood the number of TSC patients (with or without refractory epilepsy) is higher than predicted and there is potential for more use of higher doses than the estimates, and the possibility fewer patients would cease treatment than estimated in the submission (paragraph 7.9).

10.4 The PBAC noted that none of these issues had been addressed in subsequent

correspondence regarding the listing of everolimus for TSC. The PBAC also noted the only element of the submission that had changed was the price of everolimus had reduced due to the loss of market exclusivity for everolimus and price reductions related to the listing of generic brands on the PBS.

10.5 The PBAC reiterated its preference for a whole-of-disease approach in this high needs population for a PBS listing of everolimus for the treatment of TSC. However, the Committee considered there was a clinical need for an achievable listing in the near-term, and the currently defined sub-population was the only present basis on which to formulate a PBS listing, and requested the Department work further with the sponsor to develop an appropriate restriction that reflects this defined subpopulation.

10.6 The PBAC recalled it had previously considered there was a high clinical need for treatments for seizures associated with TSC and agreed there was a clinical place for everolimus in this setting.

10.7 The PBAC recalled it had previously agreed best supportive care was the appropriate comparator.

10.8 The PBAC recalled it had previously considered everolimus would provide an important benefit in at least some patients.

10.9 The PBAC reiterated its concerns that the incremental cost-effectiveness ratio (ICER) was very high and uncertain in the original submission, and noted that everolimus had reduced in price by approximately 15% since previously considered for this indication. The PBAC noted that at this new price the ICER reduced by 14% to $75,000/QALY – $105,000/QALY. Whilst the PBAC considered this to still be high, the Committee noted the high clinical need in this small population and considered this would be acceptable on a pragmatic basis, given this population would be a small contributor to the overall cost of everolimus.

10.10 The PBAC decided not to provide advice to the Minister that the dispersible tablet form of everolimus may be declared as an exempt item under Section 84AH of the *National Health Act 1953*, as there remained residual uncertainties because the marketing status of dispersible forms of everolimus was unclear.

10.11 The PBAC considered the utilisation and financial estimates remained uncertain for the reasons outlined in its original consideration, however also noted that it was likely, given the known safety profile of everolimus, only patients who obtain a noticeable benefit are likely to persist with treatment.

10.12 The PBAC noted it has previously advised that everolimus should not be treated as interchangeable on an individual patient basis with any other drugs.

10.13 The PBAC advised that everolimus is not suitable for prescribing by nurse practitioners.

10.14 The PBAC recommended that the Early Supply Rule should not apply as it does not currently apply to other forms of everolimus.

10.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

11 Recommended listing

11.1 Add new item:

Restriction to be finalised.

12 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

13 Sponsor's Comment

The sponsor had no comment.