PUBLIC SUMMARY DOCUMENT
Product: Everolimus, tablets, 2.5 mg, 5 mg and 10 mg, Afinitor®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought an Authority Required listing for the initial and continuing treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in a patient who meets certain criteria.

2. Background

This was the first time the PBAC had considered the listing of everolimus for SEGA associated with TS.

Everolimus is currently listed on the PBS for prophylactic therapy to manage rejection in patients who have received a renal transplant or cardiac allograft.

3. Registration Status

Everolimus was approved by the TGA on 16 January 2012 for the following indication:

- Patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection.

Everolimus is also indicated for the treatment of patients with:

- 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.

4. Listing Requested and PBAC's View

Authority Required

Initial treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.

Continuing treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who have previously been issued with a PBS authority for everolimus and are deriving clinical benefit from that treatment.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

TS complex is a genetic disorder involving multiple bodily systems including the central nervous system, skin, lungs, kidneys, heart and retina. An estimated 5-15% of patients with TS develop benign tumours including subependymal giant cell astrocytomas (SEGAs) in the brain. TS-associated SEGAs (TS-SEGA) are rare and predominantly affect children and teenagers. Seizures are the most common manifestation and source of morbidity in patients with TS complex (Lennert B et al, 2012), and are estimated to occur in 60-90% of patients. Seizure control can be difficult and seizures have the potential to exacerbate long-term cognitive and behavioural disorders. Consequently, most patients are expected to be

receiving anti-epileptic medications. Skin abnormalities such as facial angiofibromas and hypomelanotic macules, developmental delay, autistic spectrum disorder, renal cysts and rhabdomyoma are also common comorbidities. Although SEGAs are slow-growing and benign, a major problem with a growing tumour is that there are potentially serious complications of intracranial pressure and hydrocephalus. SEGA volume increases progressively after serial growth is observed.

The submission stated that the goal of treating patients with TS-SEGA is to shrink the volume of a SEGA tumour.

The clinical management algorithm presented in the submission suggested that everolimus would be administered in patients with a growing SEGA, either before or after partial resection. In the algorithm, everolimus could be administered after incomplete removal of the SEGA by surgical resection but not after complete removal. The clinical management algorithm was not consistent with the requested listing (i.e. patients who are not candidates for curative surgery). Instead, the algorithm split patients into asymptomatic and symptomatic. Patients from either of these groups could either receive everolimus or undergo surgical resection if they had a growing SEGA. It was unclear whether the risk/benefit profile for everolimus would be the same in symptomatic and asymptomatic patients.

6. Comparator

The submission nominated best supportive care as the main comparator and the PBAC considered this appropriate.

7. Clinical Trials

The submission presented one double-blinded phase III randomised trial (M2301) comparing everolimus with placebo in 117 patients (randomised 2:1) with tuberous sclerosis with associated SEGA and a mean age of 10 years. The trial was double-blinded, however once a patient in the placebo arm experienced a SEGA progression they received open-label everolimus. This occurred in 6/39 (15%) of patients in the placebo group.

The submission also presented a phase II trial (C2485) of everolimus in 28 patients with TS-SEGA. This trial was unpublished.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
M2301 Bebin et al.	Everolimus in subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis (TS): Results of EXIST-1, a double-blind placebo-controlled phase III trial.	*European Journal of Cancer 47* (2011); (Suppl. 2): 4–5.

8. Results of Trials

The primary outcome presented in the submission was 'SEGA response rate': the proportion of patients with a SEGA response at 48 weeks. A SEGA response was defined as:

1) Reduction in SEGA volume of greater than or equal to 50% relative to baseline, where SEGA volume is the sum of the volumes of all target SEGA lesions identified at baseline; AND

2) Absence of unequivocal worsening of non-target SEGA lesions; AND
3) Absence of new SEGA lesion greater than or equal to1.0 cm in longest diameter; AND
4) Absence of new or worsening hydrocephalus, defined by independent central radiological assessment of ventricular configuration changes, ventricular cap signs (peri-ventricular oedema) and qualitative assessment of cerebral spinal fluid (CSF) flow dynamics.

The patient relevance of 'SEGA response rate' was unclear. A link between reduced tumour volume and seizure frequency, skin lesion reduction, reduction in the need for TS-SEGA surgery or other neurological symptoms and patient quality of life was not established in the submission.

Results of SEGA response rate in the M2301 trial during double-blind phase are shown in the table below.

	Everolimus N=78	**Placebo N=39**	**RD (95% CI)**	**NNT**	**OR (95% CI)**
SEGA response category: n (%)					
Response	27 (34.6%)	0 (0%)	**0.35 (0.24, 0.45)[a] 0.346 (0.152, 0.524)[b]**	**3 (2, 4)**	**0.14 (0.04, 0.50)**
Stable disease	49 (62.8%)	36 (92.3%)	**–0.29 (–0.43,–0.16)**	**NE**	**0.68 (0.56, 0.83)**
Progression	0 (0%)	3 (7.7%)	–0.08 (–0.16, 0.01)	NE	NE
Not evaluable	2 (2.6%)	0 (0%)	0.03 (–0.01, 0.06)	NE	NE

Median follow-up 44.5 weeks for everolimus and 41.2 weeks for placebo
[a] Exact 95% confidence interval obtained from the Clopper-Pearson method.
[b] Difference in response rates (everolimus minus placebo). Exact 95% confidence interval obtained from the exact unconditional confidence limits.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EIAED = enzyme-inducing anti-epileptic drug; n = number of participants with event; NE = not evaluable; NNT = number needed to treat; OR = odds ratio; RD = risk difference; SEGA = subependymal giant cell astrocytomas; **bold** = statistically significant.

Other outcomes reported in M2301 included SEGA progression and seizure frequency, neither of which were statistically significantly different. Everolimus was associated with a reduction in skin lesions compared to placebo. No surgery for TS-SEGA was reported in either arm during the trial.

Everolimus had immunosuppressive properties and common side-effects included mouth ulcers, stomatitis, fever, pneumonia, respiratory infections and fatigue. A summary of the key adverse events (AEs) from Study M2301 is provided in the table below.

A summary of key adverse events in the M2301 trial is shown the table below.

	Everolimus (N=78)	Placebo (N=39)	RD (95% CI)	RR (95% CI)	NNH (95% CI)
AEs[a]	75 (96%)	35 (90%)	0.06 (–0.04, 0.17)	1.07 (0.96, 1.20)	16 (-25, 6)
Suspected to be drug-related	65 (83%)	17 (44%)	**0.40 (0.22, 0.57)**	**1.91 (1.32, 2.77)**	**3 (2, 5)**
Grade 3–4 AEs	26 (33%)	9 (23%)	0.10 (–0.07, 0.27)	1.44 (0.75, 2.78)	10 (-15, 4)
Serious AEs	15 (19%)	3 (8%)	0.12 (–0.01, 0.24)	2.50 (0.77, 8.12)	9 (-167, 4)
AEs requiring dose interruption and/or reduction	38 (49%)	4 (10%)	**0.38 (0.24, 0.53)**	**4.75 (1.83, 12.35)**	**3 (2, 4)**
AEs requiring additional therapy[b]	73 (94%)	31 (79%)	0.14 (0, 0.28)	1.18 (0.99, 1.40)	7 (4, 333)
Clinically notable AEs suspected to be drug-related	61 (78%)	11 (28%)	**0.50 (0.33, 0.67)**	**2.77 (1.66, 4.64)**	**2 (1, 3)**

AE = adverse event; CI = confidence interval; NE = not evaluable; NNH = number need to harm; RD = risk difference; RR = relative risk.
The AE groupings of clinically notable AEs consisted of events for which there is a specific clinical interest in connection with everolimus.
Bolded text indicates a significant difference between treatment groups.
[a] Only AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment and before the start of open-label everolimus are summarised.
[b] Additional therapy includes all non-drug therapy and concomitant medications.

The occurrence of AEs suspected to be treatment-related was nearly double in the everolimus treatment group compared to the placebo group (83% versus 44%). Nearly half of everolimus patients required everolimus dose reductions or interruptions due to adverse events. The AE profile of everolimus was a potential problem given the extent of serious AEs experienced in a vulnerable population who, the submission claimed, would have normal life expectancy.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials from the latest Periodic Safety Update Report 6 (PSUR 6) (covering the period 1/10/11 to 31/03/12) and a search of the literature.

Summary data were presented in the submission describing the extent and nature of the case reports received for safety monitoring, taken from PSUR 6. It was difficult to assess the relevance of the figures to the current submission since the data involved a mixture of indications and patient populations, mostly in adult cancer.

Based on the European Marketing Authority (EMA) assessor reports of the last PSUR 5 and Risk Management Plan, additional identified and potential risks were re-instated for close monitoring, namely:

Identified risks:
Cardiac failure, cytopenia, hemorrhages, thrombotic and embolic events (thromboembolism), pre-existing infection (reactivation, aggravation, or exacerbation), secondary amenorrhea in post-adolescent females, and safety in patients with hepatic impairment.

Potential risks:
Developmental toxicity, reproductive (teratogenicity) toxicity, male infertility, intestinal obstruction/ileus, pancreatitis, and cholelithiasis.

9. Clinical Claim

The submission described everolimus as superior in terms of comparative effectiveness and having manageable toxicity in terms of comparative safety over best supportive care.

The PBAC did not fully accept the claim of therapeutic superiority, due to the uncertainty about the extrapolation of reduction in tumour volume to clinical outcomes.

10. Economic Analysis

Based on the claim of superior efficacy, the submission presented a cost-effectiveness analysis.

The submission calculated an ICER in the range of $15,000 - $45,000 per additional responder, based on taking the response rate outcome from the trial and applied to the intended PBS population.

Extrapolation of the outcome 'SEGA progression-free months' to three years duration (from 48 weeks in the trial) provided an ICER of less than $15,000 per SEGA progression-free month.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC acknowledged that there is a high clinical need for treatment of patients with SEGA associated with TS and that there is currently no alternative therapy listed on the PBS for this condition.

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 treatment effect in TS associated tumours aside from SEGAs.

The PBAC noted that the comparator nominated in the submission was best supportive care (BSC) and accepted that BSC was appropriate.

The submission presented key clinical evidence from Study M2301, a double-blinded phase III randomised trial comparing everolimus with placebo in 117 patients (randomised 2:1) with a mean age of 10 years, which allowed crossover on SEGA progression (15% of the placebo group). Results from this extension open label phase are still pending. The primary clinical outcome from the study was 'SEGA response rate', defined as a reduction in SEGA volume of at least 50% relative to baseline, absence of worsening of existing SEGA lesions and development of new lesions of 1 cm or greater diameter, and absence of new or worsening hydrocephalus. A SEGA response rate of 34.6% (95% CI: 15.1%, 52.4%; p<0.0001) compared to placebo was shown for everolimus. The PBAC noted that no survival advantage was evident from the trial, however recognised the limitations of the available evidence in this rare condition. Secondary outcomes reported in M2301 included time to SEGA progression and seizure frequency with no significant improvement observed. The relevance of reduced tumour volume on the clinical manifestations of TS-SEGA such as seizure frequency, developmental delay and patient quality of life (QoL) in practice therefore remains unclear and the occurrence and impact of surgery in participants was also not reported in either arm of the trial. The submission also presented a phase II trial (C2485) of everolimus in 28 patients.

Study M2301 showed that the occurrence of adverse events suspected to be treatment related was far greater in the everolimus group (83%) compared to the placebo group (44%). Key adverse events included mouth ulceration, stomatitis, fever and infection, consistent with the known safety profile of everolimus. The PBAC noted that the relatively short treatment duration within the trial (24 to 79 weeks) is unlikely to have captured the harms of treatment with everolimus. The PBAC considered that the use of everolimus in SEGA would likely be long-term, if not indefinite, and that no long term safety data in the paediatric population were provided. The PBAC further considered that the potential risks of long term treatment including developmental toxicity, teratogenicity, male infertility, intestinal obstruction, and pancreatitis was of concern and that the harms associated with treatment were likely to have been significantly underestimated.

The submission described everolimus as having superior comparative efficacy and manageable toxicity in terms of comparative safety over best supportive care and therefore claimed therapeutic superiority. The submission therefore presented a cost-effectiveness analysis using response rate over 12 months and calculated an ICER in the range of $15,000 - $45,000 per additional responder which was based on the response rate from the M2301 trial, applied to the intended Australian PBS population. The PBAC did not fully accept the claim of therapeutic superiority, due to the uncertainty about the extrapolation of reduction in tumour volume to clinical outcomes. The PBAC therefore considered that there was a high degree of uncertainty in estimating cost-effectiveness.

A second analysis presented in the submission extrapolated the M2301 trial outcome 'SEGA progression-free months' from 48 weeks to 36 months which resulted in an ICER of less than $15,000 per SEGA progression free month. The PBAC noted that extrapolation of this outcome was highly uncertain due to the small number of patients that had progressed in the trial. The PBAC also noted that the translation into clinical outcomes was not established and that no improvement in seizures was observed in the trial. The PBAC noted that estimation

of QALYs was not possible as no suitable utility values were identified from the literature. The PBAC further noted that a key driver in the model was the assumption that surgical costs only applied to non-responders, which translated to cost savings for everolimus, despite the relationship between response rate and surgery not being addressed in the M2301 trial. In addition, the PBAC considered that costs associated with adverse events from everolimus treatment were inappropriately excluded from the model causing an underestimation of the incremental cost, therefore favouring everolimus.

Sensitivity analyses showed that the ICERs were particularly sensitive to the tumour response rate, the proportion of patients eligible for surgery in the trial, rate of SEGA progression beyond 12 months and the dose of everolimus, indicating that the cost-effectiveness of everolimus may be overestimated in these circumstances, likely favouring everolimus.

While the PBAC acknowledged the difficulty in estimating utility values in this rare condition, the lack of QoL data from the trial made assessment of the cost-effectiveness claim particularly problematic. The PBAC noted the results of the threshold analyses performed by the Economics Sub-Committee (ESC) that indicated in order to achieve an ICER of approximately $60,000, there would need to be a total mean gain in QALYs of 0.243 over 12 months, assuming an incremental cost of less than $15,000 and the price proposed in the submission. The PBAC considered a QALY gain of this magnitude to be implausible.

The PBAC noted that the submission proposed that, based on the response rate of tumour volume and skin lesions seen in M2301, PBS listing of everolimus would decrease the frequency of MRIs, surgery and skin lesion treatments required and also lead to fewer inpatient and outpatient hospital visits for patients, therefore reducing the overall burden of TS on State and Territory health budgets. The PBAC considered that these cost savings may have been overestimated in the submission and were not well supported. Also the submission did not allow for the costs associated with the occurrence of adverse events.

The PBAC noted the sponsor's willingness to enter into a Risk Share Arrangement and instead considered that negotiation with the sponsor regarding the establishment of a patient registry in collaboration with an independent organisation such as a tertiary hospital specialising in treating patients with SEGA, may be an option. A registry may address some of the concerns arising as a result of the limited data available in a very small treatment population such as the uncertainty surrounding the duration of treatment, effect on quality of life and survival in clinical practice, monitoring of adverse effects and safety, and cost offsets associated with surgery. Such a registry would also help to ensure that everolimus treatment is restricted to the patients most in need of treatment, in light of the unknown safety of long term everolimus treatment, particularly in children. The PBAC also considered that a substantial reduction in the price of everolimus would also be needed in order to achieve acceptable cost-effectiveness. The PBAC considered that it was not possible to accurately establish the cost-effectiveness of everolimus for TS associated SEGA on the basis of the data presented. The PBAC considered that should evaluation of data from a patient registry not support the cost-effectiveness of everolimus in this condition after a five year period, discussions with the sponsor regarding treatment cost would be required to establish reasonable cost-effectiveness.

Therefore, 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.

The PBAC acknowledged and noted the consumer comments on this item. In addition the PBAC noted the advice provided by the Australasian Tuberous Sclerosis Society in support of this submission and acknowledged it to be useful in the Committee's consideration of this item. The PBAC further acknowledged the input provided by the expert clinician in the sponsor's hearing during the meeting.

Recommendation:
Defer

13. 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.

14. Sponsor's Comment

Novartis welcomes the opportunity to work with the PBAC to make everolimus available to patients with TS complex.