

5.25 TACROLIMUS, Capsule 3 mg (once daily prolonged release), Advagraf XL[®], Astellas Pharma Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested the listing of an additional strength of tacrolimus, a 3 mg once daily formulation, under the same conditions as existing 0.5 mg, 1 mg and 5 mg prolonged-release listings on the General Schedule and Section 100 (Highly Specialised Drugs (HSD) Program).

2 Requested listing

- 2.1 The submission requested the following new listing.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are in italics and deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TACROLIMUS 3 mg modified release capsule, 50	1	50	3	\$371.41	Advagraf XL [®] Astellas Pharma Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input checked="" type="checkbox"/> Unrestricted
Cautions:	<i>Careful monitoring of patients is mandatory.</i>

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TACROLIMUS 3 mg modified release capsule, 50	2	100	5	\$658.20 – Public Hospital \$691.92 – Private Hospital	Advagraf XL Astellas Pharma Australia Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Management of rejection in patients following organ or tissue transplantation
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined – Public and Private Hospital

Clinical criteria:	The treatment must be under the supervision and direction of a transplant unit AND The treatment must include initiation, stabilisation, and review of therapy as required
Cautions:	<i>Careful monitoring of patients is mandatory</i>

- 2.3 The Secretariat has added ‘careful monitoring of patients is mandatory’ as a caution for the proposed listing, consistent with all other PBS listed strengths of tacrolimus.
- 2.4 The submission proposed a maximum quantity and repeats consistent with current listings of tacrolimus (modified-released) on the PBS (one pack with three repeats for General Schedule listings and two packs with five repeats for S100 listings). The pack size for the 3 mg dose (50 capsules) is larger than the 0.5 mg and 5 mg doses (30 capsules) and smaller than the 1 mg dose (60 capsules). For the General Schedule listings, assuming one capsule per day is required, the maximum quantity and repeats provides for four months’ supply of 0.5 mg and 5 mg capsules, and about six months’ supply of 3 mg capsules on the General Schedule. For the S100 HSD Program listings, assuming one capsule per day is required, the maximum quantity and repeats provide 12 months’ supply of 0.5 mg and 5 mg capsules, and 16 months’ supply per script of 3 mg capsules.
- 2.5 In the pre-PBAC response the sponsor acknowledged that with the proposed maximum quantity and number of repeats, a single S100 script could provide more than 12 month’s supply, however the sponsor argued that the proposed number of repeats is consistent with the recently approved tacrolimus (immediate release) 750 micrograms and 2 mg, both of which come in packs of 100. Additionally, some patients may require more than 1 tablet daily as the dosing regimens for transplants are variable, which would change the period of supply. The Sponsor also argued that patients can be on multiple strengths of tacrolimus, and the 3 mg strength having a different number of repeats would cause confusion for patients, clinicians and pharmacists.

For more detail on PBAC’s view, see section 6 PBAC outcome.

3 Background

Regulatory status

- 3.1 The 3 mg strength of prolonged release tacrolimus was TGA registered on 19 July 2019. The approved indication is the same as for the strengths of Advagraf XL that are currently listed on the PBS, specifically:

‘For use as an adjunct to liver, kidney, lung or heart allograft transplantation in adults and children.’

Previous PBAC considerations

- 3.2 The PBAC recommended tacrolimus for PBS listing for the prevention of rejection in primary liver transplant recipients at its June 1997 meeting. In September 1999 the listing was extended to include prevention of rejection in kidney transplants, and extended further in November 2007 and March 2008 to include cardiac transplants and lung transplants, respectively. The current Section 100 (HSD) listing for all brands of tacrolimus is management of rejection in patients following organ or tissue transplantation.
- 3.3 The current PBS listed strengths of once-daily, prolonged release capsules (0.5 mg, 1 mg and 5 mg) were recommended at the July 2010 PBAC meeting and were listed on the PBS on 1 November 2010.
- 3.4 In March 2016 a minor submission requested an additional two strengths of tacrolimus (immediate release) 750 micrograms and 2 mg (in addition to 0.5 mg, 1 mg and 5 mg). The PBAC recommended listing the additional strengths under the same circumstances and based on a same (ex-manufacturer) price per mg as the currently listed strengths of tacrolimus (paragraph 6.1; Tacrolimus Public Summary Document; March 2016 PBAC meeting).

4 Comparator

- 4.1 The submission assumed that the new 3 mg strength of tacrolimus would be used by patients who currently receive 3 x Advagraf XL (tacrolimus) 1 mg once daily, prolonged release capsules.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 5.3 As a minor submission, no clinical trials were presented in the submission.

Clinical claim

- 5.4 The submission stated that all strengths of tacrolimus once daily-prolonged release capsules have consistent formulation, dissolution studies and prior bioavailability studies. As there was no reason to suggest a non-linear pharmacokinetic profile for the 3 mg strength concerning bioavailability compared to other strengths, the Sponsor did not perform additional clinical studies with the 3 mg strength capsules.

- 5.5 The submission argued that the addition of a new strength of tacrolimus would reduce the pill burden on patients.

Economic analysis

- 5.6 As a minor submission, there was no economic evaluation presented.
- 5.7 The submission requested pricing based on the ex-manufacturer price per tacrolimus 1 mg once-daily prolonged release capsule as outlined below.

Table 1: Proposed Pricing of Advagraf® XL (tacrolimus) Capsule 3 mg

Advagraf® XL Capsule 1 mg (once-daily, prolonged release)	
Approved Ex-manufacturer Price	\$131.64
Capsules per pack	60
Ex-manufacturer Price per 1 mg capsule	\$2.194
Advagraf® XL Capsule 3 mg (once-daily, prolonged release)	
Ex-manufacturer Price per 3 mg capsule (= \$2.194 x 3)	\$6.582
Capsules per pack	50
PROPOSED Ex-manufacturer Price	\$329.10

Source: Table 5 p. 5 of the submission (pricing)

Estimated PBS usage & financial implications

- 5.8 The submission used a market share approach to estimate the number of 1 mg scripts replaced by the 3 mg dose.
- 5.9 The submission stated that approximately 10% of all tacrolimus 1 mg once-daily, prolonged release scripts are for patients requiring 3 mg per day based on advice from clinicians.
- 5.10 The submission argued that, while a modest number of patients could be up-titrated with the addition of a new strength, this would be balanced by the number of patients who would be down-titrated, and the narrow therapeutic range of tacrolimus would limit the number of changes. This is consistent with the PBAC’s consideration of the 0.75 mg and 2 mg IR doses of tacrolimus (paragraph 6.2, Tacrolimus 750mcg, 2mg capsule, Public Summary Document, March 2016 PBAC meeting).
- 5.11 The minor submission estimated a net cost to the PBS of less than \$10 million in Year 6 of listing, with a total net cost to the PBS of less than \$10 million over the first 6 years of listing. The additional cost to the PBS is due to fewer patient co-payments resulting from fewer scripts being required to receive the same dose. This is partially offset by a reduction in the mark-up and dispensing fees associated with the reduction in the number of scripts required. The estimated scripts and cost for 3 mg tacrolimus and the scripts and costs offset from reduced use of 1 mg tacrolimus is shown in Table 2.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated financial implications of tacrolimus (Advagraf XL 3mg)						
Number of scripts dispensed ^a	█	█	█	█	█	█
Cost to PBS/RPBS	█	█	█	█	█	█
Co-payments	█	█	█	█	█	█
Cost to PBS/RPBS less co-payments	█	█	█	█	█	█
Estimated financial implications for tacrolimus (Advagraf XL 1mg)						
Number of scripts offset ^b	█	█	█	█	█	█
Cost to PBS/RPBS (offset)	█	█	█	█	█	█
Co-payments	█	█	█	█	█	█
Cost to PBS/RPBS less co-payments (offset)	█	█	█	█	█	█
Net financial implications						
Net cost to PBS/RPBS	█	█	█	█	█	█

^a As estimated in Advagraf 3mg utilisation-and-cost-model by the submission.

^b D30:l:30 of worksheet 2d. Scripts – market Advagraf 3mg utilisation-and-cost-model.

Source: Advagraf 3mg utilization-and-cost-model.xlsx (Sheet 3b. Impact-new (PUB), Sheet 4b. Impact-changed (PUB), Sheet 5. Impact-net)

The redacted table shows that in year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

- 5.12 The submission suggested that there would be a net saving to the Department of Human Services (DHS) based on the reduced number of Authority Required scripts for processing.
- 5.13 The submission performed a sensitivity analysis where the assumed substitution rate was increased from 10% to 25%. This resulted in a total net cost to the PBS of \$580,658 over the first 6 years of listing.
- 5.14 As a minor submission, the financial estimates have not been independently evaluated.

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC outcome

- 6.1 The PBAC recommended the listing of tacrolimus, in the form of capsule 3 mg, under the same conditions as the currently listed strengths of tacrolimus on the General Schedule and under special arrangements under Section 100 (HSD Program).
- 6.2 The PBAC noted that the submission assumed that the new 3 mg strength of tacrolimus would be used by patients who currently receive 3 x Advagraf XL (tacrolimus) 1 mg once daily, prolonged release capsules. The PBAC considered the addition of a new strength of tacrolimus would reduce the pill burden on patients.
- 6.3 The PBAC considered that, due to the different pack size compared with 1 mg capsules, a reduction in the number of repeats, to give an appropriate duration of

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treatment for patients requiring one capsule per day, similar to the strengths that are currently listed, would be appropriate.

- 6.4 The PBAC considered the proposed pricing of tacrolimus on a cost per milligram basis compared with the 1 mg capsule to be appropriate, calculated at the ex-manufacturer price.
- 6.5 The PBAC noted that there was a clinical place for the additional strength, and considered that the addition of the new strength may encourage patients to be up-titrated, but this was likely to be balanced out with patients being down-titrated. The PBAC noted that while the new strength is priced at the same cost per mg, there may be a small cost to the PBS due to decreased patient co-payments.
- 6.6 The PBAC advised that, because tacrolimus 3 mg is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over currently listed forms of tacrolimus, or address a high and urgent unmet clinical need, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 6.7 The PBAC recommended that the Early Supply Rule should not apply.
- 6.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	No. of Rpts	Proprietary Name and Manufacturer	
TACROLIMUS 3 mg modified release capsule, 50	1	50	2	Advagraf XL®	Astellas Pharma Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input checked="" type="checkbox"/> Unrestricted
Cautions:	Careful monitoring of patients is mandatory.

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	No. of Rpts	Proprietary Name and Manufacturer	
TACROLIMUS 3 mg modified release capsule, 50	2	100	3	Advagraf XL	Astellas Pharma Australia Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

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PBS Indication:	Management of rejection in patients following organ or tissue transplantation
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined – Public and Private Hospital
Clinical criteria:	The treatment must be under the supervision and direction of a transplant unit AND The treatment must include initiation, stabilisation, and review of therapy as required
Cautions:	Careful monitoring of patients is mandatory

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.