

**5.26 TOLVAPTAN,
Tablet 15 mg,
Tablet 30 mg,
Pack containing 28 tablets 15 mg and 28 tablets 45 mg,
Pack containing 28 tablets 30 mg and 28 tablets 60 mg,
Pack containing 28 tablets 30 mg and 28 tablets 90 mg,
Jinarc[®],
Otsuka Australia Pharmaceutical Pty Ltd**

1 Purpose of Application

- 1.1 The minor submission sought the following changes to the listing of tolvaptan for the treatment of patients with autosomal-dominant polycystic kidney disease (ADPKD):
- listing of two new forms (tablet 15 mg and tablet 30 mg, in single-dose packs with 28 tablets) of tolvaptan for the treatment of patients with ADPKD;
 - to change the current General Schedule listings of tolvaptan to Section 100 (Highly Specialised Drugs Program - Community Access); and
 - to change the authority level for initial treatment from a written to telephone authority.

2 Requested listing

- 2.1 The minor submission requested the following new listings and changes to the current listings (changes in italics).

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty (Published)	Proprietary Name and Manufacturer
TOLVAPTAN				
15 mg tablet, 28	1	5	\$880.99	Jinarc [®] Otsuka Australia Pharmaceutical Pty Ltd
30 mg tablet, 28	1	5	\$880.99	
tolvaptan 15 mg tablet [28] (& tolvaptan 45 mg tablet [28], 56	1	5	\$1,816.37	
tolvaptan 30 mg tablet [28] (& tolvaptan 60 mg tablet [28], 56	1	5	\$1,816.37	
tolvaptan 30 mg tablet [28] (& tolvaptan 90 mg tablet [28], 56	1	5	\$1,816.37	

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Category / Program:	Section 100 – Highly Specialised Drugs Program (Community Access)
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
Condition:	Autosomal dominant polycystic kidney disease (ADPKD)
PBS Indication:	Autosomal dominant polycystic kidney disease (ADPKD)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a nephrologist
Clinical criteria:	Patient must have an estimated glomerular filtration rate (eGFR) between 30 and 89 mL/min 1.73 m ² at the initiation of treatment with this drug for this condition; AND Patient must have or have had rapidly progressing disease at the time of initiation of this drug for this condition.
Prescriber Instructions:	Rapidly progressing disease is defined as either of the following: A decline in eGFR of greater than or equal to 5 mL/min/1.73 m ² within one year; OR An average decline in eGFR of greater than or equal to 2.5 mL/min/1.73 m ² per year over a five year period. Application for authorisation must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Autosomal dominant polycystic kidney disease PBS Authority Application - Supporting Information Form which includes the following: (i) The eGFR at initiation of treatment; and (ii) Confirmation that the patient has rapidly progressing disease or had rapidly progressing disease at the time treatment with this drug for this condition was initiated as defined as a decline in eGFR of greater than or equal to 5 mL/min/1.73 m ² within one year or an average decline in eGFR of greater than or equal to 2.5 mL/min/1.73 m ² per year over a five year period.
Administrative Advice:	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
Cautions:	Tolvaptan has been associated with idiosyncratic hepatic toxicity. Liver function monitoring is required.

Category / Program:	Section 100 – Highly Specialised Drugs Program (Community Access)
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
Condition:	Autosomal dominant polycystic kidney disease (ADPKD)
PBS Indication:	Autosomal dominant polycystic kidney disease (ADPKD)
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a nephrologist or in consultation with a nephrologist
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have end-stage renal disease defined as an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73m ² , AND Patient must not have had a kidney transplant.
Cautions:	Tolvaptan has been associated with idiosyncratic hepatic toxicity. Liver function monitoring is required.

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

3 Background

- 3.1 Tolvaptan was TGA registered on 24 March 2017 for ADPKD in both split dose and single dose forms.
- 3.2 Tolvaptan was recommended by the PBAC for ADPKD in July 2018 and was PBS listed on 1 January 2019.

4 Requested listing changes and consideration of the evidence

Sponsor hearing

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

Consumer comments

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

New single-dose packs

- 4.3 The minor submission requested listing of two new forms of tolvaptan, 15 mg tablet and 30 mg tablet, in single-dose packs of 28 tablets. The submission stated the addition of these two new forms will increase dose flexibility as some patients require individualised doses.

- 4.4 The submission noted some patients require a reduced dose if on medicines that inhibit the CYP3A liver enzyme and furthermore, some patients require temporary dose reduction for individual reasons. Based on European marketing data, the submission estimated 1-5% of total use would be for these single dose packs.
- 4.5 The submission proposed the AEMP per tablet be the same as that of the currently available multi-dose packs, such that the AEMP per day of treatment among patients on a once daily regimen would be half that of the split-dose regimen. Further, the AEMP of two single strength packs would be equal to that of a split-dose pack. (Table 1)

Table 1: Published and effective prices for tolvaptan single and split dose packs (General Schedule)

Form	Presentations	Max qty	Published		Effective	
			AEMP	DPMQ	AEMP	DPMQ
Single dose	15 mg tablet, 28	1	\$840.00	\$939.96	\$ [REDACTED]	\$ [REDACTED]
	30 mg tablet, 28					
Split dose	tolvaptan 15 mg tablet [28] (&) tolvaptan 45 mg tablet [28], 56	1	\$1,680.00	\$1816.37	\$ [REDACTED]	\$ [REDACTED]
	tolvaptan 30 mg tablet [28] (&) tolvaptan 60 mg tablet [28], 56					
	tolvaptan 30 mg tablet [28] (&) tolvaptan 90 mg tablet [28], 56					

Source: Table 6 and Table 7 of submission

- 4.6 The submission did not present estimated utilisation and financial estimates but claimed there may be a modest cost saving to the PBS as a result of a small number of patients who may temporarily use a once-daily regimen.
- 4.7 The submission did not request any changes to the existing Special Pricing Arrangement (SPA) or subsidisation caps under the current Deed of Agreement. However, the Sponsor indicated a willingness to discuss any amendments to the Deed of Agreement if considered appropriate by the PBAC.

Program change to Section 100 – Highly Specialised Drugs Program

- 4.8 The submission requested the current listings of tolvaptan be changed from General Schedule to Section 100 – Highly Specialised Drugs Program (Community Access). The Sponsor argued the change of program will allow the Sponsor to maintain current distribution arrangements.
- 4.9 The Sponsor stated that at present, tolvaptan is supplied via a single distributor to assist it in managing a patient monitoring program as part of its agreed Risk Management Plan (RMP) with the TGA.

- 4.10 The TGA advised the following regarding their interpretation of the distribution arrangements of the RMP:

'a restricted access program need not be limited to just a single distribution channel. While the sponsor has elected to implement this program using a single distributor to supply product to pharmacies in response to orders from certified prescribers who have confirmed patient suitability to initiate or continue treatment, we anticipate that a model involving multiple wholesalers would also be possible. The program requires that the product is only dispensed on the prescription of a certified prescriber and following confirmation that the prescriber has determined that the patient's liver function supports continued therapy. It may be possible for the sponsor to allow multiple wholesalers to distribute the product under the existing model. An alternative model that could be explored would be to require pharmacists to confirm the prescriber's certification and confirmation of liver function prior to dispensing.'

- 4.11 The minor submission argued tolvaptan meets the criteria for the Highly Specialised Drugs Program outlined in the Australian Statistics for Medicines 2010 report¹. These criteria are outlined below. These criteria predate the introduction of S100 HSD - Community Access.

- Ongoing specialised medical supervision required.
- Treatment of longer term medical conditions, not episodes of in-patient treatment or treatment of acute conditions.
- Drug highly specialised and an identifiable patient target group.
- High unit cost.

- 4.12 The Pre-PBAC Response argued further that tolvaptan meets the definition of being highly specialised, as the risk of liver toxicity led to measures being implemented to ensure traceability and correct distribution of the drug. The Pre-PBAC Response also noted instances where tolvaptan had been incorrectly dispensed following TGA registration, which has led to further controls on the supply chain being implemented and made compliance with the Community Service Obligation (CSO) of General Schedule listings difficult.

- 4.13 The Secretariat noted the policy intent for the Community Access program is for initiation of treatment under the S100 HSD Private or Public Hospital stream, before switching to the Community Access stream once safety and efficacy are established for the patient. With the exception of HIV and Hepatitis B medicines, listings on the Community Access stream have been limited to continuation therapy only, e.g. clozapine and lanreotide. Initiation of these medicines is within Private or Public hospitals.

¹ http://www.pbs.gov.au/info/statistics/asm/asm-2010#specialised_drug_programs_3

- 4.14 The Sponsor proposed that the AEMP for a S100 listing be equivalent to the Price to Pharmacy for the current General Schedule listings, i.e. AEMP plus wholesale mark-up (essentially requesting a price increase to the current ex-manufacturer prices). The Sponsor stated that their intent was for a cost neutral change to listing and claimed this may be able to be achieved through adjustments to the existing financial arrangements. However, prices are agreed at the ex-manufacturer level, and it is inappropriate to revise the ex-manufacturer prices due to differences in supply chain costs.

Change to telephone authority for initial treatment

- 4.15 The submission requested the authority level for initial treatment be amended from a written authority to a telephone authority, on the basis that the written authority was inconsistent with the July 2018 PBAC recommended listing.
- 4.16 While the initial PBAC minutes sent to the sponsor were for a telephone authority, a corrigendum was issued to correct this to be a written authority. The Public Summary Document for the recommendation of tolvaptan in July 2018 specifies the PBAC recommendation that initial therapy should be a written authority.
- 4.17 The current written authority form requires prescribers to declare their status as a nephrologist, provide the patient’s current eGFR and whether the patient is defined as having rapidly progressing disease by specified decline in eGFR levels over time. The submission claimed that these authority requirements could be adequately assessed via a telephone authority.

Current utilisation of tolvaptan

- 4.18 The utilisation of tolvaptan over the first six months (by number of prescriptions) since listing on 1 January 2019 is presented in the table below.
- 4.19 Based on current utilisation trends, tolvaptan is currently on track to reach [REDACTED] of the year 1 cap.

Table 2: Tolvaptan prescriptions dispensed 1 January 2019 – 30 June 2019

Item and description	Prescriptions 1 January 2019 – 30 June 2019
<i>Initial treatment</i>	
11588X, tolvaptan 30 mg tablet [28] (&) tolvaptan 90 mg tablet [28], 56	84
11597J, tolvaptan 30 mg tablet [28] (&) tolvaptan 60 mg tablet [28], 56	46
11602P, tolvaptan 15 mg tablet [28] (&) tolvaptan 45 mg tablet [28], 56	211
Total initial treatment	341
<i>Continuing treatment</i>	
11593E, tolvaptan 30 mg tablet [28] (&) tolvaptan 60 mg tablet [28], 56	95
11596H, tolvaptan 30 mg tablet [28] (&) tolvaptan 90 mg tablet [28], 56	38
11600M, tolvaptan 15 mg tablet [28] (&) tolvaptan 45 mg tablet [28], 56	109
Total continuing treatment	242

Source: PBS Statistics website report from http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

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

5 PBAC Outcome

- 5.1 The PBAC recommended the listing of tolvaptan, in the form of tablet 15mg and tablet 30mg, for the treatment of ADPKD, under the same conditions for which tolvaptan is currently listed. The PBAC also recommended the initial treatment phase for the current and new listings of tolvaptan be changed from Authority Required (in writing) to Authority Required (telephone/electronic).
- 5.2 In making these recommendations, the PBAC considered the addition of the two single-dose packs will improve dose flexibility for patients who require dose modification.
- 5.3 The PBAC considered that the information required to administer the restriction could be adequately met by a telephone/electronic authority and the risk of use outside the intended patient population as a result of this change was relatively low.
- 5.4 The PBAC did not recommend the request to change the listings of tolvaptan from the General Schedule to S100 HSD – Community Access. The PBAC considered tolvaptan was not a highly specialised drug, as its eligibility and patient monitoring requirements were not complex and did not appear to require administration in an institutional, hospital or specialised environment. Compared with S100 HSD – Public/Private Hospital listings, the S100 HSD – Community Access arrangements do not require patients and prescribers to be affiliated with a hospital setting. The PBAC noted that (with the exception of HIV and Hepatitis B medicines) drugs in the S100 HSD – Community Access stream have been limited to continuation therapy for patients who have previously received treatment through a S100 HSD – Public/Private hospital listing. The PBAC considered that given there was no clinical need for patients to receive initial treatment with tolvaptan in a hospital setting, the requested change to the program was not adequately justified.
- 5.5 The PBAC noted the Sponsor had advised of difficulties with tolvaptan prescribing and dispensing practices, and changes to these arrangements had impacted the ability of the Sponsor to maintain compliance with the Community Service Obligation (CSO) for General Schedule listings. The PBAC requested the Department, Sponsor and TGA investigate alternatives to maintain compliance with both TGA and PBS requirements.
- 5.6 The PBAC considered the proposed listing of the single dose packs at an equivalent AEMP per tablet to currently-listed forms was reasonable, and agreed it was appropriate for these additional listings to be included within existing caps in the Risk Sharing Arrangement (RSA). The PBAC noted that where patients are on a once daily regimen, this would present a cost saving to the PBS; while patients dispensed two single dose forms on a split-dose regimen would be cost neutral.
- 5.7 The PBAC reaffirmed its July 2018 advice that tolvaptan is not suitable for prescribing by Nurse Practitioners.

- 5.8 The PBAC reaffirmed its July 2018 advice that the Early Supply rule should not apply to tolvaptan.
- 5.9 The PBAC reaffirmed its July 2018 advice that tolvaptan should not be treated as interchangeable with any other drugs.
- 5.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.
- 5.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the new single-dose packs are not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over currently listed forms of tolvaptan, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

Outcome:

Recommend

6 Recommended listing

- 6.1 Add new item and amend listings as follows:
- Add 15mg and 30mg single-dose packs under same circumstances as current listings
 - Amend current initial treatment phase listings (11588X, 11597J and 11602P) to Authority Required (telephone/electronic)

Name, Restriction, Manner of administration and form	PBS item code	Max.qty packs	No.of Rpts	Proprietary Name and Manufacturer	
TOLVAPTAN 15 mg tablet, 28	NEW	1	5	Jinarc®	Otsuka Australia Pharmaceutical Pty Ltd
30 mg tablet, 28	NEW	1	5		
tolvaptan 15 mg tablet [28] (& tolvaptan 45 mg tablet [28], 56	11602P	1	5		
tolvaptan 30 mg tablet [28] (& tolvaptan 60 mg tablet [28], 56	11597J	1	5		
tolvaptan 30 mg tablet [28] (& tolvaptan 90 mg tablet [28], 56	11588X	1	5		

Category / Program:	General Schedule
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
Condition:	Autosomal dominant polycystic kidney disease (ADPKD)

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PBS Indication:	Autosomal dominant polycystic kidney disease (ADPKD)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a nephrologist
Clinical criteria:	Patient must have an estimated glomerular filtration rate (eGFR) between 30 and 89 mL/min 1.73 m ² at the initiation of treatment with this drug for this condition; AND Patient must have or have had rapidly progressing disease at the time of initiation of this drug for this condition.
Prescriber Instructions:	Rapidly progressing disease is defined as either of the following: A decline in eGFR of greater than or equal to 5 mL/min/1.73 m ² within one year; OR An average decline in eGFR of greater than or equal to 2.5 mL/min/1.73 m ² per year over a five year period. Application for authorisation must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Autosomal dominant polycystic kidney disease PBS Authority Application – Supporting Information Form which includes the following: (i) The eGFR at initiation of treatment; and (ii) Confirmation that the patient has rapidly progressing disease or had rapidly progressing disease at the time treatment with this drug for this condition was initiated as defined as a decline in eGFR of greater than or equal to 5 mL/min/1.73 m ² within one year or an average decline in eGFR of greater than or equal to 2.5 mL/min/1.73 m ² per year over a five year period.
Administrative Advice:	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
Cautions:	Tolvaptan has been associated with idiosyncratic hepatic toxicity. Liver function monitoring is required.

No changes to continuing treatment.

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

7 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.

8 Sponsor's Comment

The sponsor had no comment.