

Tolvaptan for autosomal dominant polycystic kidney disease: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2021

Abstract

Purpose

To compare predicted and actual utilisation of tolvaptan for autosomal dominant polycystic kidney disease, as requested by DUSC at its June 2021 meeting.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Tolvaptan was PBS listed 1 January 2019.

Data Source / methodology

Data extracted from the PBS database maintained by Department of Health, processed by Services Australia were used for analyses.

Key Findings

- There were 362 and 500 patients treated with tolvaptan during the first and second year of listing respectively, which was lower than estimated.
- There were 2,323 and 4,421 tolvaptan prescriptions dispensed during the first and second year of listing respectively, which was lower than estimated.
- The most common age group of patients initiating tolvaptan treatment was 45-49 years old (17.7% of patients), and overall, there was a similar gender ratio of female and male initiating patients.
- The data were too immature to analyse the time on tolvaptan treatment, the median treatment duration was not reached by 30 June 2021.
- The most common dosing regimen were patients only supplied the lowest split dose of 45 mg + 15 mg tablets (43.8%).

Purpose of analysis

To compare predicted and actual utilisation of tolvaptan for autosomal dominant polycystic kidney disease, as requested by DUSC at its June 2021 meeting.

Background

Clinical situation

Polycystic kidney disease (PKD) occurs when thousands of cysts (fluid filled sacs) in the kidneys grow larger in size. This leads to the kidneys becoming larger than normal, compressing blood vessels and the urinary collecting system.¹

PKD is a genetic condition caused by a mutation in the PKD1 or PKD2 genes. A mutation in the PKD1 gene leads to severe and early onset of symptoms, whereas a mutation in the PKD2 gene leads to less severe and later onset of symptoms. The PKD1 and PKD2 genes code for the Polycystin 1 and Polycystin 2 proteins, respectively. The Polycystin 1 and 2 proteins are components of the primary cilium, which are responsible for receiving sensory information regarding urine flow. As urinary filtrate passes through the primary cilium, Polycystin 1 and 2 proteins respond by allowing an influx of calcium, inhibiting cell proliferation. If either Polycystin 1 or 2 is missing, the signal to inhibit growth is not received, resulting in abnormal cell proliferation and expression of proteins causing water to be transported into the lumen of the cyst making them larger, compressing surrounding tissue.^{2,3}

There are two types of PKD: autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD).⁴

Autosomal dominant polycystic kidney disease is the most common form of PKD. It is often referred to as adult polycystic kidney disease as symptoms manifest in adulthood at approximately 30 to 40 years of age. ADPKD accounts for approximately 5% to 10% of end stage renal disease (ESRD) cases, requiring Renal Replacement Therapy (RRT) including dialysis or kidney transplant.^{5,6} Autosomal recessive polycystic kidney disease is rare form

¹ Chapman A.B, Guay-Woodford L.M, Grantham J.J, Torres V.E, Bae K.T, Baumgarten D.A et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney International* 2003 (64): 1035-1045

² Hateboer N, v Dijk M.A, Bogdanova N, Coto E, Saggat-Malik A.K, San Millan J.L et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. *The Lancet* 1999 (353): 103-107

³ Gonzalez-Perrett S, Kim K, Ibarra C, Damiano A.E, Zotta E, Batelli M. Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca²⁺- permeable nonselective cation channel. *PNAS* 2001, 98(3): 1182-1187

⁴ Kidney Health Australia. Factsheet Polycystic Kidney Disease 2019. Accessed 30 July 2021:

<https://kidney.org.au/resources/factsheets-and-photosheets/polycystic-kidney-disease-factsheet>

⁵ Spithoven E, Kramer A, Meijer E, Orskov B, Wanner C, Abad J.M et al. Renal replacement therapy for autosomal dominant kidney disease (ADPKD) in Europe: prevalence and survival – an analysis of data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2014, 29: 15-25

⁶ Gabow P.A, Autosomal Dominant Polycystic Kidney Disease. *The New England Journal of Medicine* 1993, 329 (5): 332-342

of PKD. It is often referred to infantile polycystic kidney disease as symptoms manifest during infancy.

Pharmacology

Tolvaptan is a vasopressin antagonist. It prevents the vasopressin hormone from binding to receptors in the kidneys, slowing the development of kidney cysts in patients with ADPKD, reducing symptoms of the disease and increasing urine production.⁷

Therapeutic Goods Administration (TGA) approved indications

Tolvaptan is only indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

The Product Information contains a boxed warning referring to the need for regular liver function monitoring.⁷

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations in bilirubin-total (BT). To help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of JINARC, then continually monthly for 18 months, then every 3 months thereafter during treatment with JINARC. Prescriber education and certification on the risk of liver injury and the importance of regular liver function monitoring is mandatory. These are available through the IMADJIN® Program, which is run and maintained by, or for, the sponsor of JINARC.

Dosage and administration

Treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.

Tolvaptan is administered orally. Tablets must be swallowed without chewing and with a glass of water.

Tolvaptan is to be administered twice daily in split-dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The morning dose is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. According to the split-dose regimens the total daily doses are 60 mg, 90 mg, or 120 mg.

The initial dose is 60 mg tolvaptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken prior to the morning meal and 15 mg taken 8 hours later). The initial dose is up-titrated to a split-dose regimen of 90 mg (60 mg + 30 mg) per day, then if tolerated, up-titrated to a split-dose-regimen of 120 mg (90 mg + 30 mg) per day. Up-titration steps must

⁷ Jinarc (tolvaptan). Australian Approved Product Information. Chatswood: Otsuka Australia Pharmaceutical Pty Ltd. Approved 24 March 2017, updated 26 June 2020. Available from <https://www.tga.gov.au/product-information-pi>

be separated by at least 1 week. Dose titration has to be performed cautiously to ensure high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose.⁷

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

PBS listing details (as at August 2021)

Table 1: PBS listing of tolvaptan

Item	Name, form & strength, pack size	Max. quant units	Rpts	DPMQ	Brand name and manufacturer
11602P 11600M	tolvaptan 15 mg tablet [28] (&) tolvaptan 45 mg tablet [28], 56	1	5	\$1827.93	Jinarc Otsuka Australia Pharmaceutical Pty Ltd
11597J 11593E	tolvaptan 30 mg tablet [28] (&) tolvaptan 60 mg tablet [28], 56	1	5	\$1827.93	
11588X 11596H	tolvaptan 30 mg tablet [28] (&) tolvaptan 90 mg tablet [28], 56	1	5	\$1827.93	
12460T 12457P	tolvaptan 15 mg tablet, 28	28	5	\$945.93	
12461W 12462X	tolvaptan 30 mg tablet, 28	28	5	\$945.93	

Note: Special Pricing Arrangements apply.

Caution: Tolvaptan has been associated with idiosyncratic hepatic toxicity. Liver function monitoring is required.

Source: the [PBS website](#).

Restriction

Treatment phase: Initial treatment

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/1.73m² 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.

Rapidly progressing disease is defined as either of the following:

A decline in eGFR of greater than or equal to 5 mL/min/1.73m² within one year;

OR

An average decline in eGFR of greater than or equal to 2.5mL/min/1.73m² per year over a five year period.

Treatment phase: Continuing treatment

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/1.73m²,

AND

- Patient must not have had a kidney transplant.

For details of the current PBS listing refer to the [PBS website](#).

Date of listing on PBS

Tolvaptan was PBS listed 1 January 2019.

Changes to listing

1 April 2020: The initial treatment phase was changed from Authority Required (Written) to Authority Required (Telephone/Electronic). The PBAC recommended this change at its November 2019 Meeting.

1 June 2021: Listing was extended to include 15 mg and 30 mg tablets. The PBAC recommended the extension of listing at its November 2019 PBAC Meeting.

Current PBS listing details are available from the [PBS website](#).

Approach taken to estimate utilisation

March 2017 PBAC Meeting

The submission used an epidemiological approach and assumed the prevalence of ADPKD would remain constant throughout Years 1 to 5. The submission estimated a prevalence of 330 to 390 per million population, based on an unpublished European systematic review by Willey et al.⁸ The approach disregarded incident patients and discontinuation due to death or progression to ESRD. The submission considered the approach to be appropriate due to the small number of incident patients and the chronic and non-curative nature of the disease. The submission assumed the number of newly diagnosed cases and death/progression to ESRD would cancel each other out.

Proposed eligibility criteria included a confirmed diagnosis of ADPKD with CKD stage 1 to 3 and the patient to have had rapidly progressing disease as assessed on the rate of annual GFR changes or Mayo classification (1C to 1E).⁹

The submission assumed uptake rates to be ■% in Year 1 and up to ■% in Year 5.

To estimate the number of tolvaptan packs dispensed, the submission assumed all combination dose packs (15 mg + 45 mg, 30 mg + 60 mg, 30 mg + 90 mg) were sufficient for 28 days of therapy. A year of full therapy compliance would require 13.04 packs.

Additionally, the submission presented three alternative estimates based on more restricted populations:

- excluding patients with well-preserved renal function (CKD Stage 1)
- excluding patients with less rapidly progressing disease (Mayo class 1C),
- excluding patients with both well-preserved renal function (CKD Stage 1) and less rapidly progressing disease (Mayo class 1C)

The submission was considered by DUSC. DUSC considered the estimates presented to be underestimated and identified the following issues:

- Given the uncertainty and potential variability in the prevalence of ADPKD, the prevalent population may be larger than estimated.
- The Mayo classification system may not be appropriate and there may be difficulties effectively implementing it into practice to identify the eligible patient population in Australia.
- The expected initiation rates (■% in first year, ■% in later years) may be underestimated as tolvaptan is the first disease-modifying therapy for ADPKD.
- The potential for use outside the requested restriction in patients with slow disease progression or early stage disease.

⁸ Willey C.J, Blais J.D, Hall A.K, Krasa H.B, Makin A.J, Czerwiec F.S. Prevalence of autosomal dominant polycystic kidney disease in the European Union. *Nephrol Dial Transplant* 2017. 32: 1356-1363

⁹ Irazabal M.V, Rangel L.J, Bergstralh E.J, Osborn S.L, Harmon A.J, Sundsbak J.L. Imaging classification of autosomal dominant polycystic kidney disease: A simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015. 26:160-172

- There were no stopping criteria, and it was uncertain if patients would cease treatment if they progressed to CKD stage 4 or if the rate of disease progression decreased.
- There was no age restriction in the requested PBS restriction, while the financial estimates only included patients aged 18 to 60 years inclusive.
- There was no accounting for wastage.
- The submission estimated a small additional cost to government due to increased liver function testing with tolvaptan treatment. DUSC advised that the MBS costs would be higher than expected if the number of treated patients per year was higher than estimated.
- The submission also presented the anticipated cost savings associated with avoiding or delaying dialysis and kidney transplant over the lifetime of patients who initiate tolvaptan treatment in the first five years of listing. DUSC agreed with the commentary that any cost saving to government from the avoidance of dialysis would not likely be realised within the five year forward estimates.

March 2018 PBAC Meeting

The resubmission used an epidemiological approach, similar to that used in the March 2017 submission. The resubmission retained the prevalence of 356 per million and the prevalence approach where prevalence remains constant over time, disregarding initiating patients and death or progression onto ESRD which were assumed to cancel each other out.

The Mayo classification was removed from the proposed eligibility criteria. The eligibility criteria was revised to include an absolute rate of eGFR change per year (loss of 2.5 mL/min/1.73m² or greater). The PBS restriction was amended and restricted to patients aged 18 to 60 years inclusive. The submission estimated 18.5% of ADPKD patients would meet the PBS eligibility criteria. The revised eligibility criteria were:

- For patients aged 18-50 years, patients must have:
 - a. eGFR of 89 to 30 mL/min/1.73 m² after initiation of tolvaptan therapy
 - b. Annualised eGFR loss of 2.5 mL/min/1.73m² or greater.
- For patients aged 51-55 years, patients must have:
 - a. eGFR of 65 to 30 mL/min/1.73 m² after initiation of tolvaptan therapy
 - b. Annualised eGFR loss of 2.5 mL/min/1.73m² or greater.
- For patients aged 56-65 years, patients must have:
 - a. eGFR of 44 to 30 mL/min/1.73 m² after initiation of tolvaptan therapy
 - b. Annualised eGFR loss of 2.5 mL/min/1.73m² or greater.

Uptake rates increased from ■% in Year 1 to ■% in Year 5 to ■% in Year 1 and ■% in Year 5. Cost savings due to avoidance or delay of RRT were not considered in the estimates.

The resubmission was not considered by DUSC.

July 2018 PBAC Meeting

The minor resubmission included a revised PBS restriction and revised price and financial terms.

The minor resubmission revised the eGFR change criteria in the restriction to 5 mL/min/1.73m² in one year or 2.5 mL/min/1.73m² over 5 years or greater. The proportion of ADPKD patients eligible for tolvaptan PBS treatment eligibility rate was revised from 18.5% to 15%.



Table 2: Revised usage and financial estimates proposed in the July 2018 submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent ADPKD population (356 per million)						
ADPKD patients where a 'hard cap' is set to ensure cost-effectiveness (15%)						
Tolvaptan estimated initiation rates						
Patients initiating treatment						
Treatment persistence for each year of therapy	100%	84.7%	80.8%	77.1%	73.5%	70.2%
Number of patients remaining on tolvaptan at the beginning of each year among those initiated in:						
Year 1						
Year 2	-					
Year 3	-	-				
Year 4	-	-	-			
Year 5	-	-	-	-		
Year 6	-	-	-	-	-	
Total patients on therapy						

Total patient years on therapy (half-cycle corrected)						
Total tolvaptan packs dispensed (13.04/patient)						
- 15 mg + 45 mg dose pack						
- 30 mg + 60 mg dose pack						
- 30 mg + 90 mg dose pack						
Cost with effective DPMQ (\$)						
Cost of tolvaptan	\$	\$	\$	\$	\$	\$
Patient copay (mean \$25.06)	\$	\$	\$	\$	\$	\$
Net cost to the PBS/RPBS	\$	\$	\$	\$	\$	\$
LFT cost to MBS (12 tests per year, \$11.65 per test)	\$	\$	\$	\$	\$	\$
Net cost to government	\$	\$	\$	\$	\$	\$

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; DPMQ, dispensed price for maximum quantity; Δ eGFR, change in estimated glomerular filtration rate; LFT, liver function test; PBS, Pharmaceutical Benefits Scheme; pop'n, population; RPBS, Repatriation Pharmaceutical Benefits Scheme.

Source: table 4.2, p20 of the minor submission

Table 3: Stepped-wise presentation of the proposed revisions to the Section 4 estimates – net costs to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
March 2018 estimates	\$	\$	\$	\$	\$	\$
Price reduction ()	\$	\$	\$	\$	\$	\$
Revised eligible population size – base case estimates for the current minor submission	\$	\$	\$	\$	\$	\$

Source: table 4-3, p21 minor submission.

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

November 2016 PBAC Meeting

The PBAC deferred consideration of the submission from the November 2016 PBAC agenda (item 5.15) to the March 2017 PBAC agenda (item 4.01). Accordingly, the submission did not proceed to the Economics or Drug Utilisation Sub-committee (DUSC) meetings in the November 2016 cycle, but was considered by ESC and DUSC in the March 2017 cycle.

March 2017 PBAC Meeting

The submission requested a Section 85 Authority Required (Written) PBS listing for tolvaptan for the treatment of ADPKD.

The PBAC did not recommend the listing of tolvaptan for the treatment of ADPKD, on the basis that it was uncertain about the long-term clinical benefit of tolvaptan in the treatment of ADPKD and that it was concerned about the potential for substantial liver toxicity associated with the use of this drug.

The PBAC's concern with the proposed restriction was in line with DUSC's advice regarding the utilisation and financial estimates, where the use of the Mayo classification may not be practical for identifying the eligible patient population in Australia and the uptake of tolvaptan may be broader than intended. The PBAC agreed with DUSC that the uptake would be higher as tolvaptan is the first disease modifying therapy for ADPKD and may be used in patients with slower disease progression or early stage disease in an attempt to preserve maximum kidney function.

For further details refer to the [Public Summary Document](#) from the March 2017 PBAC meeting.

March 2018 PBAC Meeting

The PBAC deferred making a decision regarding the listing of tolvaptan for ADPKD. The PBAC accepted the high clinical need for effective therapy to treat ADPKD, however it was considered the clinical benefit of tolvaptan treatment was uncertain and at best very small. No new trial data is anticipated to resolve this issue. Treatment was also expected to be long-term, over 40-50 years.

The PBAC considered the estimated eligible population to be highly uncertain and the utilisation and financial implications presented in the submission were most likely underestimated. The PBAC advised the uncertainty around utilisation was unlikely to be mitigated by the proposed RSA in the resubmission. There was residual uncertainty about the treatment effect and the most likely population to respond to therapy will require a more targeted population estimated with 100% rebate over an agreed estimated utilisation.

Differences between the March 2017 submission and resubmission's estimates include proposed price reduction, narrower PBS population and higher uptake rates in the

submission. The PBAC considered the estimated utilisation and financial implications were substantially underestimated in the resubmission.

- The assumption that prevalence of ADPKD will remain constant due to the approximate equivalence of the incident and discontinuing populations was not adequately justified and the prevalent ADPKD population was most likely underestimated.
- The resubmission acknowledged that the estimated utilisation of tolvaptan based on the UK THIN database was most likely underestimated. Given the lack of applicable epidemiological data, the proportion of Australian ADPKD patients who would be eligible for tolvaptan treatment under the requested listing was highly uncertain.
- The increased uptake of tolvaptan compared with the previous submission may be reasonable, given tolvaptan is the first disease-modifying therapy for ADPKD. However, uptake rates remained uncertain.
- There remained potential for use outside the requested restriction to patients with slower disease progression or early stage disease.
- The assumption of no wastage during the initial titration of tolvaptan was unlikely to be realised in clinical practice and most likely underestimate tolvaptan utilisation.

For further details refer to the [Public Summary Document](#) from the March 2018 PBAC meeting.

July 2018 PBAC Meeting

The PBAC recommended the PBS listing of tolvaptan as Section 85 Authority Required (Written) for initiation and an Authority Required (Streamlined) listing for continuing treatment of ADPKD. The PBAC was satisfied that for some patients, tolvaptan provides a small benefit although its effect on end stage kidney disease (ESKD) is uncertain.

The PBAC advised that the PBS listing for tolvaptan should be restricted to prescribing by nephrologists for initiation and in consultation with a nephrologist for continuing treatment. The PBAC noted the tolvaptan Product Information provided a special warning and precaution for use regarding tolvaptan- associated liver injury and that continued monitoring for hepatotoxicity during tolvaptan treatment was required.

The PBAC considered the hard cap set at ■■■ of the prevalent population was acceptable, noting that assumed high persistence with treatment (between 100% - 73.5% over the first five years of listing) may be optimistic, but was internally consistent with modelled assumptions.

For further details refer to the [Public Summary Document](#) from the July 2018 PBAC meeting.

November 2019 PBAC Meeting

The PBAC recommended the listing of tolvaptan, in the form of tablet 15 mg and tablet 30 mg, for the treatment of ADPKD, under the same conditions for which tolvaptan was

currently listed. The PBAC considered single-dose packs will improve dose flexibility for patients who require dose modification.

The PBAC also recommended the initial treatment phase for tolvaptan to be changed from Authority Required (Written) to Authority Required (Telephone/Electronic). The PBAC considered 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 was relatively low.

For further details refer to the [Public Summary Document](#) from the November 2019 PBAC meeting.

Methods

Data extracted from the PBS claims database maintained by the Department of Health and processed by Services Australia were used for the analyses. Prescription data were extracted from when tolvaptan was PBS listed 1 January 2019 up to and including 30 June 2021. Data were extracted on 5 August 2021.

These data were used to determine the number of incident and prevalent patients, number of prescriptions supplied, prescriber type and to analyse patient demographics such as age and gender. Initiating and prevalent patients were counted by quarter of supply. An initiating patient was defined based on their first date of supply of tolvaptan.

The Kaplan-Meier method was used to analyse treatment duration with tolvaptan, censoring patients that were still continuing treatment at the analysis end date. Patients were followed until 30 June 2021. The median standard treatment days was 29 days. Patients were censored if they received a supply within three sets of standard treatment days before the analysis end date.

A dose and strength sequence analysis was conducted to examine the titration patterns in patients. Patients were followed from PBS list date 1 January 2019 to 30 June 2021. The first prescribed dose was recorded and if patients were subsequently up-titrated or down-titrated, these were noted to form the patient's chronological titration sequence.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.¹⁰

Data manipulation was undertaken using SAS.

¹⁰ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

Overall utilisation

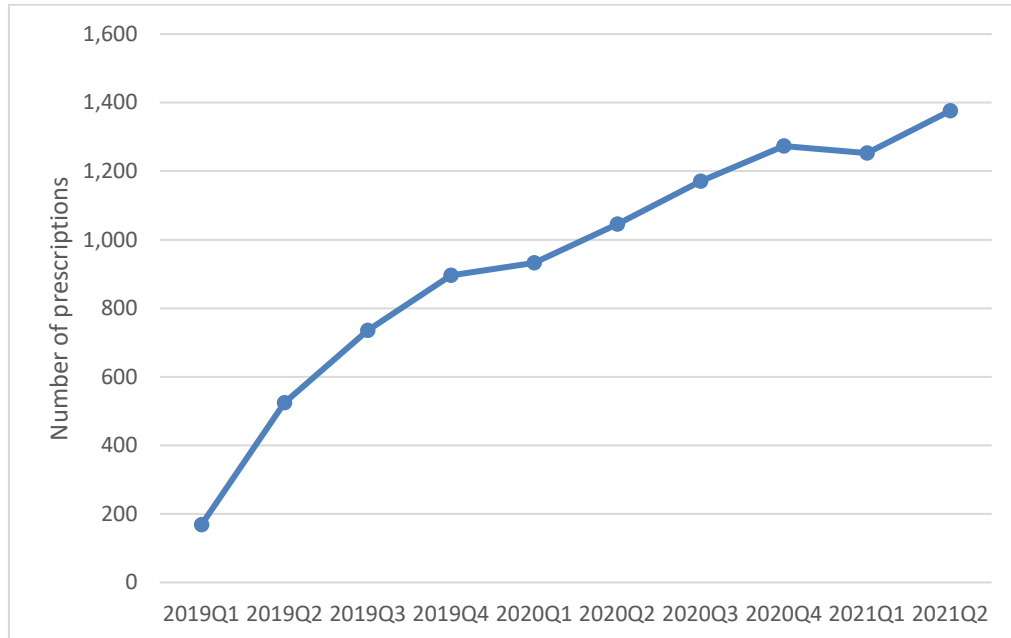


Figure 1: Number of tolcapton prescriptions supplied according to supply quarter

From Figure 1, the overall trend of tolcapton prescriptions supplied since PBS listing is increasing, with an average of approximately 1,106 prescriptions per supply quarter in 2020.

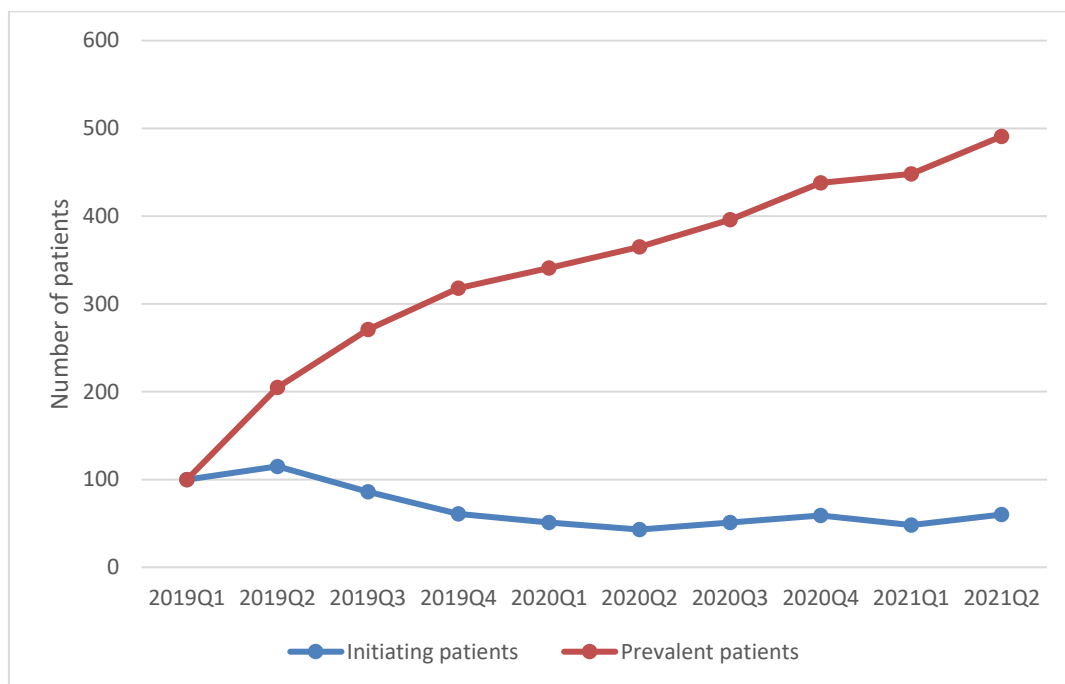


Figure 2: Number of incident and prevalent tolcapitan patients according to supply quarter

Figure 2 shows that the number of patients initiating tolcapitan treatment remained stable, with an average of approximately 68 patients initiating treatment per supply quarter. There was an average of approximately 338 patients treated with tolcapitan per supply quarter.

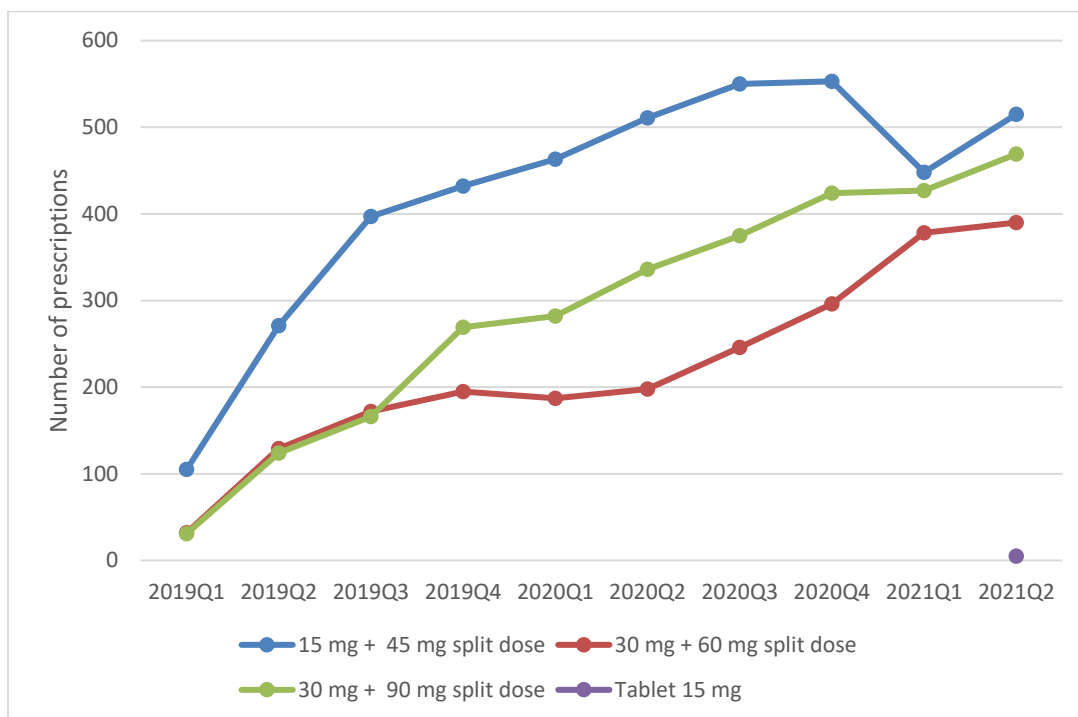


Figure 3: Number of prescriptions supplied according to strength and supply quarter

Note: Where the prescription count is between 1 and 4 (inclusive), a figure data point is set to 5 to protect patient confidentiality.

From Figure 3, an increasing trend is observed in all strengths of tolvaptan. The most common tolvaptan strength dispensed was the lowest strength split dose tablet, 15 mg + 45 mg. Tablet strengths 15 mg and 30 mg were PBS listed June 2021. A small number of 15 mg tablets were supplied. No 30 mg tablets were supplied by analysis end date.

Utilisation by relevant sub-populations/regions or patient level analysis

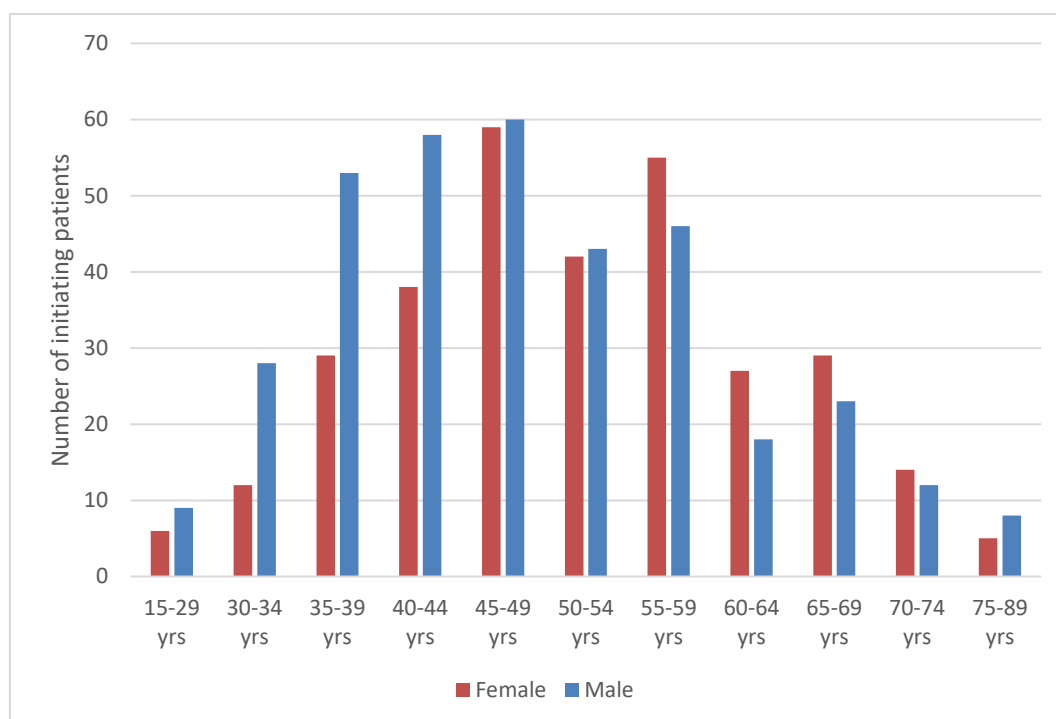


Figure 4: Age and gender distribution of initiating tollevantan patients

Figure 4 shows the age and gender distribution of patients at initiation of tollevantan. The most common age group initiating tollevantan treatment are those aged between 45 to 49 years (17.7%) for both males and females.

The age of initiating tollevantan patients ranged from 18 to 88 years, with a median age of 49 years.

In those aged 44 years and less, males accounted for a higher proportion of initiating patients than females. In patients aged 55 years and over, females accounted for a greater proportion of initiating compared to males.

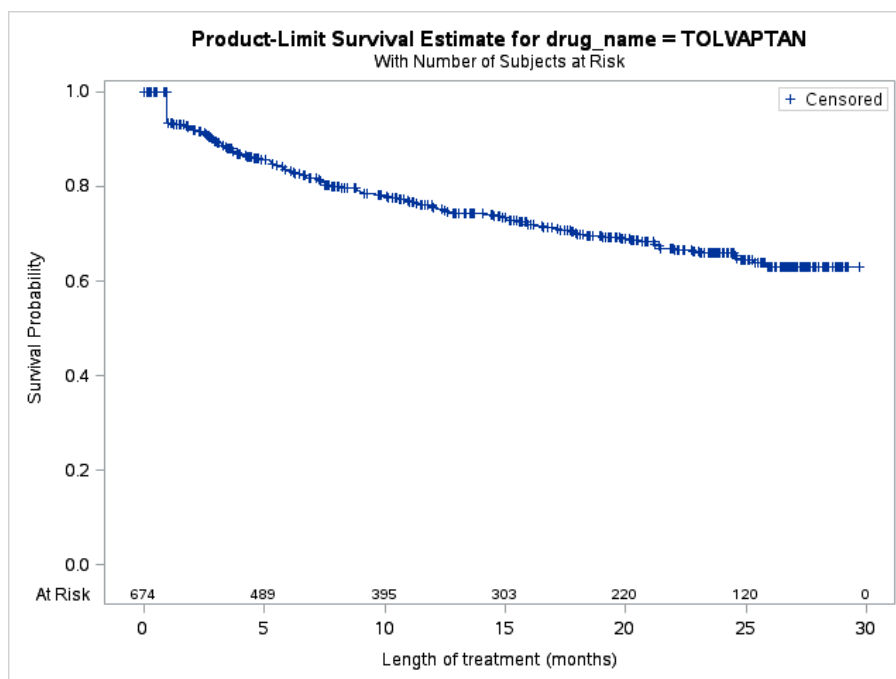


Figure 5: Kaplan Meier curve of tolvaptan treatment duration (months) in patients who are followed to 30 June 2021

The data were too immature to fully analyse the time on tolvaptan, with a median time on therapy not being reached within 30 months from first listing. Of the 674 patients who initiated tolvaptan between 1 January 2019 and 30 June 2021, 72.7% of patients were censored at analysis end date.

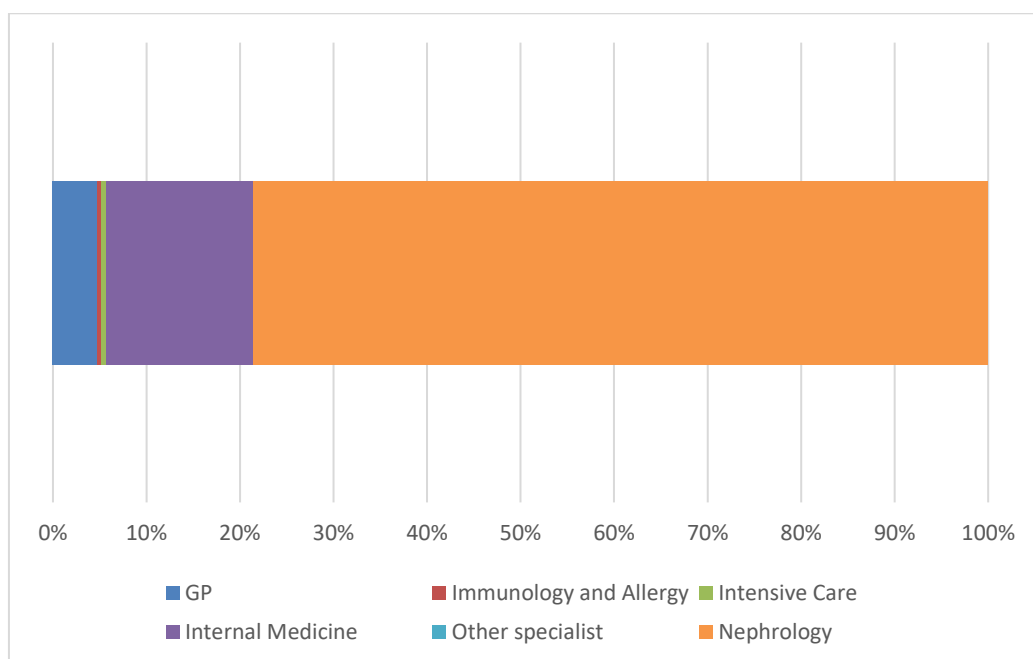


Figure 6: Prescriptions by prescriber

Note: "Other specialist" defined as including oncology, neurology, obstetrics and gynaecology, and surgery
 Note: "GP" defined as including non-vocationally registered GP, vocationally registered GP, trainee GP and GP with unclassified registration status.

Note: 4.9% of prescriptions had an unknown prescriber.

From Figure 6, nephrologists accounted for the majority (78.5%) of tolvaptan prescriptions prescribed.

Table 4: Tolvaptan dose sequence analysis

Sequence	Number of patients	Percentage
15 mg + 45 mg	295	43.8%
15 mg + 45 mg>30 mg + 60 mg	136	20.2%
15 mg + 45 mg>30 mg + 60 mg>30 mg + 90 mg	115	17.1%
30 mg + 90 mg	38	5.6%
15 mg + 45 mg>30 mg + 60 mg> 15 mg + 45 mg	15	2.2%
Rare (<2%) dosing sequences	75	11.1%
Total	674	

Note: Rare dosing sequences defined as sequences that account for which less than 2% of all tolvaptan dose sequences.

From Table 4, approximately 83% of patients followed the suggested dosing schedule published in the Tolvaptan Product Information, initiating treatment with the lowest strength dose and up-titrating.⁷ Patients only supplied the lowest split dose 45 mg + 15 mg tablets accounted for the most common dosing regimen (43.8%). Approximately 37% of patients up titrated to higher strength doses, 30 mg + 60 mg (20.2%) and 30 mg + 90 mg (17%).

Analysis of actual versus predicted utilisation

Table 5: Tolvaptan actual versus predicted utilisation

Tolvaptan listing years		Year 1	Year 2	Year 3
		January 2019 – December 2019	January 2020 – December 2020	January 2021- December 2021
Patients	Predicted	██████████	██████████	██████████
	Actual	362	500	516
	Difference	██████████	██████████	██████████
Prescriptions	Predicted	██████████	██████████	██████████
	Actual	2,323	4,421	2,629
	Difference	██████████	██████████	██████████

Note: Year 3 predicted numbers are for the full year, actual numbers are six months of data (January 2021 to June 2021 inclusive).

From Table 5, actual patient and prescription figures were lower than estimated. The number of patients in the first and second year of tolvaptan listing were lower by █████ and █████, respectively.

The number of prescriptions in the first and second year of tolvaptan listing were lower by █████ and █████, respectively.

Overall, there was a greater decrease in the number of prescriptions compared to the number of patients predicted.

Discussion

Despite the increased utilisation trend, overall utilisation of tolvaptan was lower than predicted. The submission estimated ADPKD prevalence to be 365 per million based on an unpublished European systematic review.⁸ Since the submission, Australian ADPKD prevalence estimates continue to be limited, with publications reporting prevalence of 1 in 1,000 (1,000 per million).^{11,12} This estimate was based on a study by Dalgaard (1956)¹³ and substantially higher than what was estimated in the submission. However, Dalgaard had estimated morbid risk, the theoretical risk of being ill from ADPKD during a lifetime of 80 years duration, which has been incorrectly cited and misinterpreted as ADPKD prevalence.^{8,14}

Although there were limited Australian literature to inform ADPKD prevalence, a number of recent sources could be indicative of Australian ADPKD prevalence. Recent systematic reviews conducted in Europe and the United States reported ADPKD prevalence to be 2.7 per 10,000 (270 per million) and 4.3 per 10,000 (430 per million), respectively.^{14,15} The average (350 per million) of these recent prevalence estimates is similar to the ADPKD prevalence used in the submission.

The precautionary details described in the boxed warning could have contributed to low tolvaptan uptake. The boxed warning states: “Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations in bilirubin-total (BT). To help mitigate the risk of liver injury, blood injury for hepatic transaminases is required prior to initiation and continued monthly for 18 months, then every 3 months thereafter.”⁷ Although this boxed warning was published in the Product Information at the time of submission, the mandatory requirements for prescriber education and certification on the risk of liver injury and the importance of liver monitoring through the sponsor’s IMADJIN® program was not described at the time of submission.

¹¹ PKD Australia. ADPKD: PKD Australia. Accessed 26 August 2021 < <https://pkdaustralia.org/adpkd/> >

¹² Rangan G.K, Tchan M.C, Tong A, Wong A.T.Y, Nankivell B.J. Recent advances in autosomal-dominant polycystic kidney disease. Royal Australasian College of Physicians Internal Medicine Journal. 2016. 46(8):883-892.

¹³ Dalgaard O.Z. Bilateral polycystic disease of the kidneys; a follow-up of two hundred and eighty-four patients and their families. Acta Med Scand Suppl. 1956; 328:1-255

¹⁴ Solazzo A, Testa F, Giovanella S, Busutti M, Furci L, Carrera P. The prevalence of autosomal dominant polycystic kidney disease (ADPKD): A meta-analysis of European literature and prevalence evaluation in the Italian province of Modena suggest that ADPKD is a rare and underdiagnosed condition. PLOS One, 2018. Accessed from: <<https://doi.org/10.1371/journal.pone.0190430>>

¹⁵ Willey C, Kamat S, Stellhorn R, Blais J. Analysis of Nationwide Data to Determine the Incidence and Diagnosed Prevalence of Autosomal Dominant Polycystic Kidney Disease in the USA: 2013-2015. Kidney Diseases 2019;5: 107-117

Additionally, the requirements for patients to commit to lifestyle modifications whilst receiving tolvaptan treatment could have further contributed to its low uptake.¹⁶ Tolvaptan is administered twice daily in split-dose regimens following a stringent dosing and meal schedule, requiring patients to plan accordingly to ensure adequate dosing. Furthermore, tolvaptan is associated with a number of side effects. As tolvaptan increases urine production, patients are required to drink plenty of water throughout the day and before bedtime regardless of perceived thirst levels. Serious side effects requiring urgent medical attention include difficulty urinating, allergic reaction symptoms (such as face swelling and breathlessness) and signs of electrolytes imbalances (such as dizziness and seizures)^{16,17} Additional measures are required for long term treatment including regular monitoring of electrolytes.⁷

Despite new single dose packs of 15 mg and 30 mg being PBS listed on 1 June 2021, they would unlikely increase future tolvaptan utilisation. Based on European marketing data, the submission estimated single doses would account for approximately 1 to 5% of total utilisation. The single dose packs were anticipated to be used by patients who require a reduced dose if concomitantly taking medicines that inhibit CYP3A liver enzymes and in patients who require a temporary dose reduction.

DUSC consideration

DUSC considered the boxed warning, mandatory prescriber education, lifestyle modifications and the treatment associated side effects as possible reasons for low tolvaptan utilisation. DUSC noted that clinical input was sought from nephrologists to explore possible reasons for low tolvaptan utilisation.

DUSC noted the restriction requires patients to have rapidly progressing disease (defined as a decline in EGFR of greater than or equal to 5 ml/min/1.73 m² within one year or an average decline in EGFR of greater than or equal to 2.5ml/min/1.73m² per year over a five year period). Furthermore, DUSC noted the restriction change in April 2020, where the initial treatment phase was changed from Authority Required (Written) to Authority Required (Telephone/Electronic). DUSC considered clinical input which described many ADPKD patients were not eligible as they had stable renal function and did not have a decline in eGFR. However, DUSC considered that the eligibility criteria should remain as the clinical benefit of tolvaptan treatment for these patients is unclear. Further clinical input considered the burden of the previous initial paper based authorisation process may have contributed to low utilisation.

¹⁶ Sans-Atxer L, Joly D. Tolvaptan in the treatment of autosomal dominant polycystic kidney disease: patient selection and special considerations. *International Journal of Nephrology and Renovascular Disease* 2018(11): 41-51

¹⁷ Jinarc (tolvaptan). Australian Approved Consumer Medicine Information. Chatswood: Otsuka Australia Pharmaceutical Pty Ltd. Approved 24 March 2017. Available from <<https://www.tga.gov.au/consumer-medicines-information-cmi>>

DUSC noted tolvaptan is taken in split doses of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The TGA Product Information describes the up-titration process where patients are recommended to be maintained on the highest tolerable dose. DUSC noted the most common dosing regimen were patients only supplied the lowest split dose of 45 mg + 15 mg tablets. DUSC considered clinician input which described the urine osmolality goal of <200 mOsm/L could be achieved with the lowest tolvaptan dose in conjunction with increased fluid intake.

DUSC noted as data were too immature to analyse the time on tolvaptan treatment, the median treatment duration was not reached by the analysis end date 30 June 2021. DUSC considered clinician input which described that approximately 22% of patients who initiate tolvaptan treatment stop for a variety of reasons including hepatic adverse events (abnormal alanine aminotransferase [ALT], aspartate aminotransferase [AST] and/or bilirubin), aquaretic tolerability, disease progression and acute renal impairment.¹⁸

DUSC noted the requirements for patients to commit to lifestyle modifications whilst receiving tolvaptan treatment. Tolvaptan is administered twice daily in split-dose regimens following a stringent dosing and meal schedule. Furthermore, tolvaptan is associated with a number of side effects such as increased urine production, and as such patients are required to increase fluid intake. There can be serious side effects requiring urgent medical attention including difficulty urinating, allergic reaction symptoms (such as face swelling and breathlessness) and signs of electrolytes imbalances (such as dizziness and seizures). There are also additional measures required for long term treatment including regular monitoring of electrolytes. DUSC considered clinical input which described patient's reluctance to initiate treatment was due to polyuria, potential liver toxicity and the requirement for monthly liver function tests. Further clinical input described Stage 1 and 2 ADPKD patients were often reluctant to initiate treatment due to the rare liver associated side effects.

DUSC considered clinical input on other reasons that could have contributed to low utilisation of tolvaptan. This included:

- ADPKD can be managed through other factors such as maintaining blood pressure, hydration, smoking cessation. During the early stages of the disease, increased fluid intake is sufficient to manage the condition.
- Therapeutic inertia.
- Prescriber reluctance due to the lack of data regarding the long term benefits of treatment.

DUSC noted the Pre-Sub-Committee Response described the, "need to recognise the importance of making such medication widely available to Australian patients who otherwise would have no other disease modifying treatment with proven efficacy."

¹⁸ Thomas M, Gois P.H.F, Butcher B.E, Ta M, Wyk G.V. All-cause discontinuation of tolvaptan in patients with autosomal dominant polycystic kidney disease (ADPKD): A secondary use of data analysis of patients in the IMADJIN dataset. Australian and New Zealand Society of Nephrology: The Nephrology and Transplantation Update Course and Annual Scientific Meeting. Accessed 13 October 2021: <https://anzsnasm.com/11038>

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Otsuka Australia Pharmaceutical Pty. Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

References

Chapman A.B, Guay-Woodford L.M, Grantham J.J, Torres V.E, Bae K.T, Baumgarten D.A et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney International* 2003 (64): 1035-1045

Dalgaard O.Z. Bilateral polycystic disease of the kidneys; a follow-up of two hundred and eighty-four patients and their families. *Acta Med Scand Suppl.* 1956; 328:1-255

Gabow P.A, Autosomal Dominant Polycystic Kidney Disease. *The New England Journal of Medicine* 1993, 329 (5): 332-342

Gonzalez-Perrett S, Kim K, Ibarra C, Damiano A.E, Zotta E, Batelli M. Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca^{2+} -permeable nonselective cation channel. *PNAS* 2001, 98(3): 1182-1187

Hateboer N, v Dijk M.A, Bogdanova N, Coto E, Saggar-Malik A.K, San Millan J.L et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. *The Lancet* 1999 (353): 103-107

Irazabal M.V, Rangel L.J, Bergstralh E.J, Osborn S.L, Harmon A.J, Sundsbak J.L. Imaging classification of autosomal dominant polycystic kidney disease: A simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015. 26:160-172

Jinarc (tolvaptan). Australian Approved Consumer Medicine Information. Chatswood: Otsuka Australia Pharmaceutical Pty Ltd. Approved 24 March 2017. Available from <<https://www.tga.gov.au/consumer-medicines-information-cmi>>

Jinarc (tolvaptan). Australian Approved Product Information. Chatswood: Otsuka Australia Pharmaceutical Pty Ltd. Approved 24 March 2017, updated 26 June 2020. Available from <<https://www.tga.gov.au/product-information-pi>>

Kidney Health Australia. Factsheet Polycystic Kidney Disease 2019. Accessed 30 July 2021: <https://kidney.org.au/resources/factsheets-and-photosheets/polycystic-kidney-disease-factsheet>

PKD Australia. ADPKD: PKD Australia. Accessed 26 August 2021 <<https://pkdaustralia.org/adpkd/>>

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

Rangan G.K, Tchan M.C, Tong A, Wong A.T.Y, Nankivell B.J. Recent advances in autosomal-dominant polycystic kidney disease. *Royal Australasian College of Physicians Internal Medicine Journal.* 2016. 46(8):883-892.

Sans-Atxer L, Joly D. Tolvaptan in the treatment of autosomal dominant polycystic kidney disease: patient selection and special considerations. *International Journal of Nephrology and Renovascular Disease* 2018(11): 41-51

Solazzo A, Testa F, Giovanella S, Busutti M, Furci L, Carrera P. The prevalence of autosomal dominant polycystic kidney disease (ADPKD): A meta-analysis of European literature and prevalence evaluation in the Italian province of Modena suggest that ADPKD is a rare and underdiagnosed condition. *PLOS One*, 2018. Accessed from:
<https://doi.org/10.1371/journal.pone.0190430>

Spithoven E, Kramer A, Meijer E, Orskov B, Wanner C, Abad J.M et al. Renal replacement therapy for autosomal dominant kidney disease (ADPKD) in Europe: prevalence and survival – an analysis of data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2014, 29: 15-25

Willey C.J, Blais J.D, Hall A.K, Krasa H.B, Makin A.J, Czerwiec F.S. Prevalence of autosomal dominant polycystic kidney disease in the European Union. *Nephrol Dial Transplant* 2017. 32: 1356-1363

Willey C, Kamat S, Stellhorn R, Blais J. Analysis of Nationwide Data to Determine the Incidence and Diagnosed Prevalence of Autosomal Dominant Polycystic Kidney Disease in the USA: 2013-2015. *Kidney Diseases* 2019; 5: 107-117