

**4.01 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 Pharmaceutical Australia Pty Ltd**

The PBAC deferred consideration of this 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 (ESC) or Drug Utilisation Sub-Committee (DUSC) meetings in the November 2016 cycle, but was considered by ESC and DUSC in the March 2017 cycle.

1 Purpose of Application

1.1 The submission requested a Section 85 Authority required (in writing) PBS listing for tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD).

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price (effective price)	Max. Qty.	Proprietary Name and Manufacturer
TOLVAPTAN					
15mg, oral tablets	28	1	\$ [REDACTED] (\$ [REDACTED])		Jinarc [®] Otsuka Australia Pharmaceutical P/L
30mg, oral tablets	28	1	\$ [REDACTED] (\$ [REDACTED])		
15mg + 45mg, oral tablets	56	5	\$ [REDACTED] (\$ [REDACTED])		
30mg + 60mg, oral tablets	56	5	\$ [REDACTED] (\$ [REDACTED])		
30mg + 90mg, oral tablets	56	5	\$ [REDACTED] (\$ [REDACTED])		
Condition	Autosomal dominant polycystic kidney disease (ADPKD)				
Category	General schedule				
Restriction	Authority Required - In Writing				
Prescriber type	Medical Practitioners				
Treatment phase	Initial and continuing				
Episodicity	Chronic				
PBS indication	Autosomal dominant polycystic kidney disease (ADPKD)				
Treatment criteria	Must be treated by a specialist who has undergone tolvaptan prescriber training				
Clinical criteria	<ul style="list-style-type: none"> • The condition must be a confirmed diagnosis of ADPKD, CKD stages 1-3; <u>AND</u> • Patient must have evidence of rapid disease progression, or predicted rapid disease progression, defined as: <ul style="list-style-type: none"> • a confirmed annual eGFR decline ≥ 5.0 mL/min/1.73 m² in 1 year, <u>and/or</u> ≥ 2.5 mL/min/1.73 m² per year over a period of 5 years; <u>OR</u> • htTKV compatible with Mayo classes 1C–1E disease (corresponding to a predicted eGFR decrease ≥ 2.5 mL/min/1.73 m² per year) 				

Definitions	<p><u>Mayo classification System</u> The Mayo classification system, described by Irazabal et al (2014) stratifies ADPKD cases from two registries (Mayo Clinic Translational Polycystic Kidney Disease Centre [MTPC] and Consortium of Renal Imaging Studies in Polycystic Kidney Disease [CRISP]) into five subclasses (1A–1E) based on TKV and age. These categories reflect estimated kidney growth rates, measured as yearly percentage increase:</p> <ul style="list-style-type: none"> • <1.5% (class 1A) • 1.5%–3% (class 1B) • 3%–4.5% (class 1C) • 4.5%–6% (class 1D) • >6% (class 1E)
Prescriber instructions	<p><u>Details of tolvaptan prescriber training requirements</u> Otsuka has committed to ensuring that in Australia all the Jinarc® prescribers are educated on the use of the drug and that a liver function monitoring program is implemented to minimise the risk of hepatic injury. The Jinarc® Registry, a web-based platform, will be set up to host the training material and prescriber certification and to support long-term liver monitoring and safety. All prescribers and patients must take part in the Jinarc® Registry in order to prescribe/receive Jinarc® in Australia.</p>
Cautions	<p><u>Recommendations for the management of potential hepatic toxicity</u> To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of Jinarc®, continuing monthly for 18 months and at regular 3 monthly intervals thereafter. Concurrent monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice) is recommended.</p>

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CRISP, Consortium of Renal Imaging Studies in Polycystic Kidney Disease ; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; MTPC, Mayo Clinic Translational Polycystic Kidney Disease Centre

- 2.1 Listing was requested on a cost-effectiveness basis compared to placebo.
- 2.2 The recommended dose regimen for tolvaptan is 120mg daily, given as a split-dose regimen of 90mg in the morning (taken at least 30 minutes before the morning meal) and 30mg eight hours later (taken with or without food). The differential split-dose regimen is recommended to prevent excessive urine production during sleep and reduce nocturia, while maintaining maximum efficacy.
- 2.3 The requested restriction includes patients with evidence of rapid disease progression (based on estimated Glomerular Filtration Rate (eGFR)) or predicted rapid disease progression (based on the novel Mayo classification system).
- 2.4 In addition to the above requested listing (referred to as “Scenario 1”), the submission presented three alternative listing scenarios (Scenarios 2-4) based on more restricted populations, excluding patients with either well-preserved renal function (chronic kidney disease (CKD) stage 1) or less rapidly progressing disease (Mayo class 1C), or both. The exclusion of these patients improved the cost effectiveness of tolvaptan but it is uncertain whether these restrictions could be effectively implemented in practice. There is potential for leakage outside the more restrictive scenarios, given tolvaptan would be the first disease-modifying therapy for ADPKD and physicians may opt to treat patients earlier in order to preserve maximum kidney function. In addition, the Mayo classification system is only applicable to the subset of typical ADPKD patients and is not recommended for use

in clinical practice (<http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754>). The Pre-PBAC Response stated that the sponsor was willing to have patient selection determined solely on the basis of eGFR changes, without relying on the Mayo classification.

- 2.5 The submission requested that tolvaptan be prescribed only by specialist medical practitioners who have undergone tolvaptan prescriber training.
- 2.6 Scenarios 3 and 4 are largely non-informative as many of the Mayo class 1C patients would still be able to access treatment under the eGFR criterion of the proposed restriction. The Pre-Sub-Committee Response (PSCR) acknowledged this, and suggested that should one of these scenarios be recommended by the PBAC, the minimal required eGFR decline values should be removed, or altered to match the Mayo-based eligibility. The PSCR also acknowledged that patients with atypical disease are excluded from the Mayo classification as they tend to have slowly progressive disease (which does not warrant tolvaptan), and expressed willingness to specifically exclude these patients from the PBS listing.
- 2.7 The Pre-PBAC Response stated that to address uncertainties regarding the applicability of the trial population to the PBS population (see 'Clinical trials'), the sponsor was willing to limit the use of tolvaptan to patients with Mayo Classes 1D and 1E only. The PBAC considered that the requested restriction would be difficult to implement in practice.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** The ACM Outcome from 2-3 February 2017 was available at the time of the PBAC meeting. The ACM agreed with the TGA Delegate and considered that tolvaptan had an overall positive benefit-risk profile for slowing 'the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stage 1 to 3A at initiation of treatment with evidence of rapidly progressing disease.' The proposed indication was for CKD stages 1-3.
- 3.2 The TGA first round clinical evaluator recommended rejection of the application on the grounds that the modest efficacy benefits (some preservation of renal function and a small decrease in the incidence of severe renal pain events) were outweighed by the risk of severe drug-induced liver injury. The evaluator noted that the FDA had requested an additional efficacy study (156-13-210 or NCT02160145), to be conducted in ADPKD subjects with late Stage 2 to early Stage 4 chronic kidney disease. The benefits of tolvaptan may be greater in such a population and the sponsor was requested to provide details of the progress of this study to the TGA.
- 3.3 The TGA second round clinical evaluator recommended authorisation for the sponsor's proposed indication, subject to updates to the PI, provision of results from 156-13-210 (NCT02160145), provision of clinically relevant information from the ongoing studies in the pharmacovigilance plan, and the finalisation of an agreed risk management plan.
- 3.4 The TGA delegate asked the ACM to provide advice on the following specific issues:
 1. Is the reduction in total kidney volume (TKV) increase clinically significant?

The ACM advised that the reduction in total kidney volume was statistically significant, and though the clinical benefit to the patient was small it was useful.

2. Does tolvaptan have a clinically significant effect on renal function in ADPKD patients? ACM advised that there was a high withdrawal rate with the studies submitted, however the effects and measures were significant.
3. Should the indication include patients with CKD Stage 3? The ACM advised that the indication should include patients with Chronic Kidney Disease (CKD) stage 3 and especially stage 3A.
4. Is the proposed risk mitigation strategy sufficient to mitigate the risk of severe liver injury? In particular, should routine liver function monitoring be mandated? The ACM noted that the appearance of liver injury in trial subjects indicates that there is likely to be a higher level of liver toxicity in general treatment populations. The ACM advised that regular monitoring of liver function made reversal of liver toxicity possible and while the proposed monitoring is adequate the ACM advised that baseline liver function testing should be conducted.

3.5 The PBAC has not previously considered tolvaptan for ADPKD.

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

4 Clinical place for the proposed therapy

4.1 ADPKD is a late-onset multisystem disorder characterised by bilateral renal cysts, cysts in other organs (e.g. liver, seminal vesicles, pancreas, arachnoid membrane), vascular abnormalities (e.g. intracranial aneurysms, dilatation of the aortic root, thoracic aortic dissection), mitral valve prolapse and abdominal hernias. Approximately 50% of patients diagnosed with ADPKD will progress to end-stage kidney disease (ESKD) by 60 years of age.¹

4.2 The submission claimed that tolvaptan would provide a treatment option for patients with a confirmed diagnosis of ADPKD, with chronic kidney disease stages 1-3 (CKD) at the initiation of treatment, and evidence of rapidly progressing disease or predicted rapid disease progression. There is currently no other disease modifying treatment available for patients with ADPKD. Current management of ADPKD is supportive care with no active treatment.

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

5 Comparator

5.1 The submissions nominated a comparator of best supportive care (placebo). ESC agreed this was an appropriate comparator. Best supportive care was defined in the submission as "treatments to control symptoms and complications associated with ADPKD". In practice, tolvaptan would be prescribed in addition to best supportive care.

¹ Taylor M., Johnson A.M., Tison M., Fain P. and Schrier R. Earlier diagnosis of autosomal dominant polycystic kidney disease: importance of family history and implications for cardiovascular and renal complications. American Journal of Kidney Disease 2005; 46:415–423.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the clinical place in therapy, emphasising that tolvaptan should be used in patients with evidence of rapidly progressing disease and that both the use of eGFR changes and Mayo classification could identify these patients. The clinician also described the clinical significance of the tolvaptan outcomes from TEMPO 3:4, explaining that renal function can remain stable for many years in patients with ADPKD, but that small changes in renal function decline can translate to large impacts on outcomes such as death/end-stage renal disease (ESRD)/doubling of serum creatinine over time (based on the RENAAL, IDNT and AASK trials). In addition, the clinician discussed the relationship between changes in TKV and eGFR, explaining that:
- TKV is the most commonly cited prognostic indicator in the published ADPKD literature.
 - CRISP trial data support the use of TKV and age (via the Mayo scoring system) to identify those patients who are most likely to benefit from treatment with tolvaptan; and
 - CRISP trial data also show that although glomerular filtration rate (GFR) can remain stable for decades, renal enlargement progresses significantly in the early stages of the disease. Thus for early intervention, TKV may be a more reliable marker than GFR.

The PBAC considered that the hearing was reflective of the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (8) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of anticipated benefits of treatment with tolvaptan including slowing disease progression, prolonging life, and avoidance of dialysis and transplantation. The comments noted the lack of treatment options currently available for this genetic condition, which affects multiple generations of families.
- 6.3 The PBAC noted the advice received from Kidney Health Australia supporting subsidised access to tolvaptan for ADPKD patients in Australia. The organisation stated that at present there is no cure or specific treatment available for ADPKD patients in Australia, and that tolvaptan is currently the only treatment specifically for ADPKD. The organisation stated that it slows the rate of change of kidney volume, a measure of disease progression in ADPKD. Tolvaptan may therefore delay long-term progression of the disease. The organisation also noted that tolvaptan has been approved for use in ADPKD by regulatory agencies in Japan, Canada, and Western Europe.
- 6.4 The PBAC noted the clinical evidence was not fully supportive of the long-term benefits suggested by the consumer comments.

Clinical trials

6.5 The submission was based on one head-to-head trial comparing tolvaptan to placebo in patients with ADPKD (TEMPO 3:4).

6.6 Details of the trial presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised placebo controlled trial		
TEMPO 3:4	A phase 3, multi-center, double-blind, placebo-controlled, parallel-arm trial to determine long-term safety and efficacy of oral tolvaptan tablet regimens in adult subjects with autosomal dominant polycystic kidney disease (156-04-251). Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. Perrone RD, Coons SJ, Cavanaugh K, Finkelstein F, Meyer KB. Patient-reported outcomes in clinical trials of CKD-related therapies: report of a symposium sponsored by the National Kidney Foundation and the U.S. Food and Drug Administration. Muto S, Kawano H, Higashihara E, et al. The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial.	Clinical Study Report: 14 Feb 2013. <i>New England Journal of Medicine</i> 2012; 367(25):2407-2418. <i>American Journal of Kidney Diseases</i> Dec 2013; 62(6):1046-1057. <i>Clinical and Experimental Nephrology</i> 2015a: 19(5):867-877.

Source: Table 23, pp.36-37 of the submission.

6.7 The key features of the direct randomised trial are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
Tolvaptan vs. placebo						
TEMPO 3:4	1445	R, DB, PC, PA, MC, superiority 36 months + 14-42 day follow up	Low	Adults 18-50 yrs ADPKD + baseline TKV \geq 750mL (MRI) CrCl \geq 60mL/min	Annualised rate of change in TKV; eGFR; reciprocal serum CrCl	Change in eGFR used in sensitivity analysis
TEMPO 3:4 CKD subgroup	1272	Post hoc subgroup analysis	High	Subgroup limited to patients with CKD 1-3 ^a	Annualised rate of change in TKV; eGFR	Change in eGFR used in base case
TEMPO 3:4 Mayo subgroup	1181	Post hoc subgroup analysis	High	Subgroup limited to patients with Mayo class 1C-1E ^b	Annualised rate of change in TKV; eGFR	Change in eGFR used in sensitivity analysis

Source: Table 28, p.46 of the submission.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CrCl, creatinine clearance; DB, double blind; MC, multi-centre; MRI, magnetic resonance scanning; PA, parallel arm; PC, placebo controlled; R, randomised; TKV, total kidney volume; yrs, years.

^a CKD 1: eGFR \geq 90 mL/min/1.73m²; CKD 2: eGFR 60-89 mL/min/1.73m²; CKD 3: eGFR 30-59 mL/min/1.73m²

^b Height adjusted TKV by age used to categorise patients into predicted kidney growth rates (Mayo class): 1C: 3.0-4.5%; 1D: 4.5-6.0%; 1E: >6.0%

6.8 The ESC advised that although the TEMPO 3:4 trial was blinded, the treatment assignment could have been unblinded due to the effects of tolvaptan on increased urination, dehydration and fluid intake. Adverse events were consistent with this action with higher levels of hyponatraemia and sodium increase.

- 6.9 The primary outcome of TEMPO 3:4 was the difference between tolvaptan and placebo in rate of change in TKV from baseline to 12, 24 and 36 months. The key secondary composite outcome events were worsening renal function, renal pain, hypertension and albuminuria. For worsening renal pain, hypertension and albuminuria, events were collected from baseline to 36 months (or last visit). However, for worsening renal function, events were defined with completion of the three week titration phase as baseline, making interpretation of the composite outcome difficult.
- 6.10 The outcomes used in the modelled economic evaluation were based on a post hoc analysis stratified by CKD stage (base case) and Mayo class (sensitivity analysis). The source of the analysis of Mayo sub-classes was not provided in the submission.
- 6.11 There were differences in diagnostic criteria, measures of CKD and definition of rapidly progressing disease between the trial population and the proposed PBS population. The TEMPO 3:4 trial is likely to reflect only a subset of the Australian population eligible for treatment with tolvaptan under the requested restriction; i.e. younger patients with better preserved kidney function but more rapidly progressing disease (defined as elevated TKV at baseline), more likely to experience benefits from delayed ADPKD progression.
- 6.12 In addition, it was unclear whether estimates of TKV by MRI or CT scans are comparable to abdominal sonography (the preferred first-line diagnostic tool in Australian clinical practice). The PSCR highlighted a validation study by Bhutani, 2015 has concluded ultrasound to be reliable in patient risk stratification for disease progression, and that ultrasound is expected to remain the preferred imaging tool for TKV assessment in Australia (Rangan and Nakivell, 2014). The evaluation had noted that Bhutani et al. (2015) selected a small non-representative sample of young patients (age 15–46 years) from CRISP with eGFR values over 70mL/min/1.73m², and demonstrated that ultrasound determined kidney length over 16.5cm predicted the onset of chronic kidney disease stage 3 within the subsequent 8 years. The evaluation also noted that Bhutani et al. (2015) also found that ultrasound was inferior to MRI in terms of measuring TKV, and systematically overestimated TKV compared to MRI based estimates. The PBAC noted the sponsor hearing agreed that 3D ultrasound was inferior to MRI, but MRIs are generally used in research but not in clinical practice.
- 6.13 Thus patients with ADPKD included in TEMPO 3:4 may not be comparable to the Australian population who would be eligible for treatment with tolvaptan should it be PBS listed.
- 6.14 The ESC advised that the open label tolvaptan extension study (TEMPO 4:4) has been completed, and this may provide data on longer term adverse events, but was not fully presented in the submission. Other ongoing trials may also be relevant to decision making; these include an RCT for stage 2–4 CKD due to ADPKD, for which recruitment is completed (REPRISE, NCT02160145 (alternate ID: 156-13-210)) and a trial of tolvaptan in children and adolescents with ADPKD (NCT02964273), which is still recruiting.
- 6.15 The PSCR stated that “The interim results from TEMPO 4:4 showed the benefits of an additional 3 years of treatment were maintained in the early-treated group (those

on tolvaptan in the double blind phase; i.e., treated over 5 years), with a mean eGFR reduction of 16.77 mL/min/1.73m² from baseline, compared with 19.92 mL/min/1.73m² for those crossed over from placebo (p=0.0003).”

Comparative effectiveness

- 6.16 The rate of change in total kidney volume with tolvaptan and placebo is summarised in Table 3 below.

Table 3: Results of change in TKV over 36 months (observed cases, CKD stages 1-3), TEMPO 3:4

Treatment	n	Mean annualised TKV growth rate ^a % (SD)	Estimated slope ^b	Rate difference ^c (95% CI)	Slope reduction %	Ratio of geometric mean ^d (95% CI)	p-value
Tolvaptan	819	2.777 (5.659)	0.0280	-2.708 (-3.269, -2.147)	49.2	0.974 (0.969, 0.980)	<0.0001
Placebo	458	5.608 (5.330)	0.0551				

Source: Table 34, p.61 of the submission.

Abbreviations: SD, standard deviation; TKV, total kidney volume.

^a Derived by linear mixed effect model fitted to log(10) transformed TKV repeated measures data, time ((MRI date - baseline MRI date)/365.25) as a continuous variable.

^b Slope estimated as [geometric mean of annualised growth rate – 1].

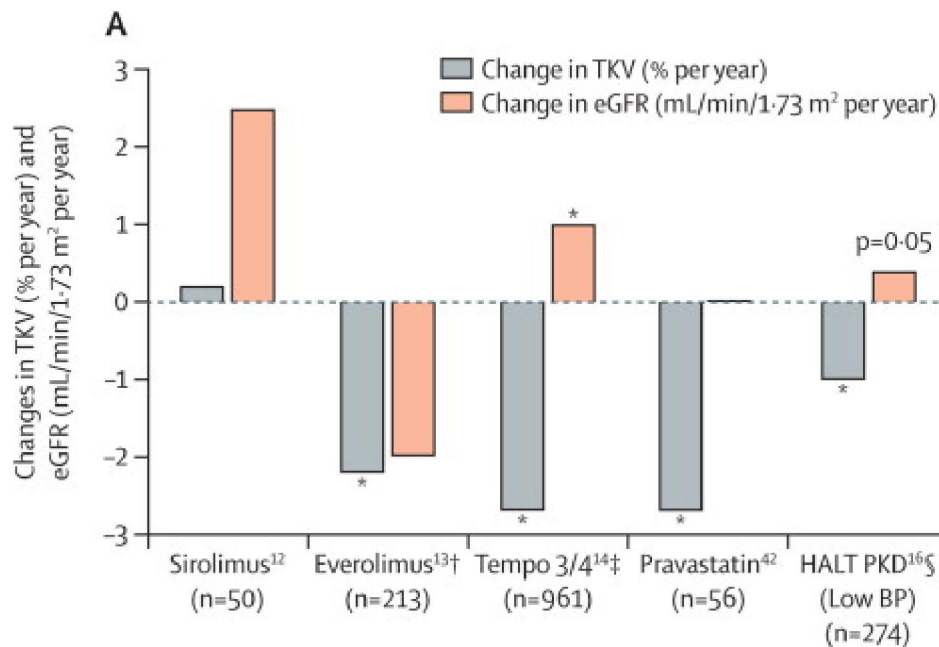
^c Derived *post hoc* from delta method assuming independence between estimates of the slope between treatments.

^d Estimated ratio of geometric mean of annualised growth rate of tolvaptan and placebo.

- 6.17 Patients with baseline CKD stages 1-3 treated with tolvaptan reported a mean annualised growth in TKV of 2.78% per year over three years, compared with 5.61% for patients taking placebo, a statistically significant difference of –2.71% per year (95% CI -3.27, -2.15) over three years.
- 6.18 In the ITT population, patients treated with tolvaptan appeared to experience a decreased rate of disease progression in terms of increasing TKV over three years of therapy compared to placebo. While differences in disease progression were small but statistically significant compared to placebo (best supportive care) the clinical importance of these differences over long term therapy was not supported and differences in quality of life were not explored.
- 6.19 TKV and height-adjusted TKV (htTKV) are direct and clinically important relative measures of ADPKD progression consistent with aetiology and mechanism of injury (Fick-Brosnahan et al. 2002, Chapman et al. 2012, King et al. 2000, Grantham et al. 2010 and 2012). However, there is no validated correlation between TKV or htTKV and rate of progression in patients with ADPKD in terms of kidney function; i.e. rate of decline in eGFR or creatinine clearance, rise in serum creatinine or time to ESKD. The PBAC has not previously considered this outcome in this therapeutic area or accepted the relevance of TKV as a surrogate outcome for kidney disease progression.
- 6.20 The ESC was particularly concerned that the rate of change of TKV from baseline had uncertain clinical significance as it may not be a valid surrogate endpoint for eGFR decline nor time to ESKD. Although baseline TKV is correlated with long-term renal function decline (i.e. future decline in renal function is predicted by baseline TKV), the ESC was concerned that there is no validated correlation between growth in TKV and rate of decline of eGFR, or time to ESKD, and that there is even some evidence to suggest dissociation between these outcomes. As explained in a review of the clinical management of ASPKD, Ong et al. (2015), TKV “probably captures other risk factors for rapid disease progression” and that “[a]lthough most biomarkers

correlated with eGFR, whether these markers can predict disease progression more accurately than serial serum creatinine measurements is unknown” (p1999).² The ESC noted the figure below, which suggests that everolimus reduced TKV growth in patients with ADPKD but failed to slow decline in renal function.

Figure 1: Changes in TKV and improvement of renal function of clinical trials involving 100 or more patients with ADPKD^a



^aReductions in TKV and changes in eGFR that were significantly different from baseline values are denoted by an asterisk (p<0.05).

Source: Ong ACM, Devuyst O, Knebelmann B & Walz G (2015) “Autosomal dominant polycystic kidney disease: the changing face of clinical management” *The Lancet*, 385, p 1998.

- 6.21 It was therefore unclear how the effect of tolvaptan on TKV growth would predict the effect of tolvaptan on renal function. Moreover, the ESC noted that the relationship between baseline TKV and future decline in renal function becomes evident only with longer follow-up time (likely greater than five years as per the CRISP results)³. Even if it was accepted that the TKV growth rate is an appropriate surrogate for change in renal function over the long term, the 3-year TEMPO 3:4 trial does not provide adequate data to support this relationship (see 6.22-6.24).
- 6.22 The decline in renal function was a more valid endpoint for interpreting the effect of tolvaptan on slowing the progression of ADPKD. However, the small differences in the rate of decline in eGFR over three years compared to placebo may not represent clinically important differences for patients treated with tolvaptan.

² Ong ACM, Devuyst O, Knebelmann B & Walz G (2015) “Autosomal dominant polycystic kidney disease: the changing face of clinical management” *The Lancet*, 385: 1993–2002

³Chapman AB, Bost JE, Torres VE, et al., (2012). Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. Mar 2012;7(3):479-486.

- 6.23 The secondary outcome of rate of change in renal function by reciprocal serum creatinine or eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation; CKD-EPI) also showed statistically significant differences compared to placebo favouring tolvaptan, see table below.

Table 4: Rate of change in renal function 1/serum creatinine or eGFR (CKD-EPI equation; week 3 to 36 months)

Measure of renal function	Tolvaptan			Placebo			Difference in mean rate of change per year (95% CI)
	n	Mean rate of change per year ^a	Estimated slope ^b	n	Mean rate of change per year ^a	Estimated slope ^b	
1/ serum creatinine	842	-2.555	-2.609	464	-3.682	-3.812	1.203 (0.622, 1.783)
eGFR (CKD-EPI)	842	-2.680	-2.723	464	-3.568	-3.700	0.977 (0.597, 1.357)

^aSummary statistics were based on slope of change, obtained by regressing renal function data (Week 3/EOT and beyond) against time by subject. Time variable used in the regression was equal to (observation date - Week 3/EOT date)/365.25.

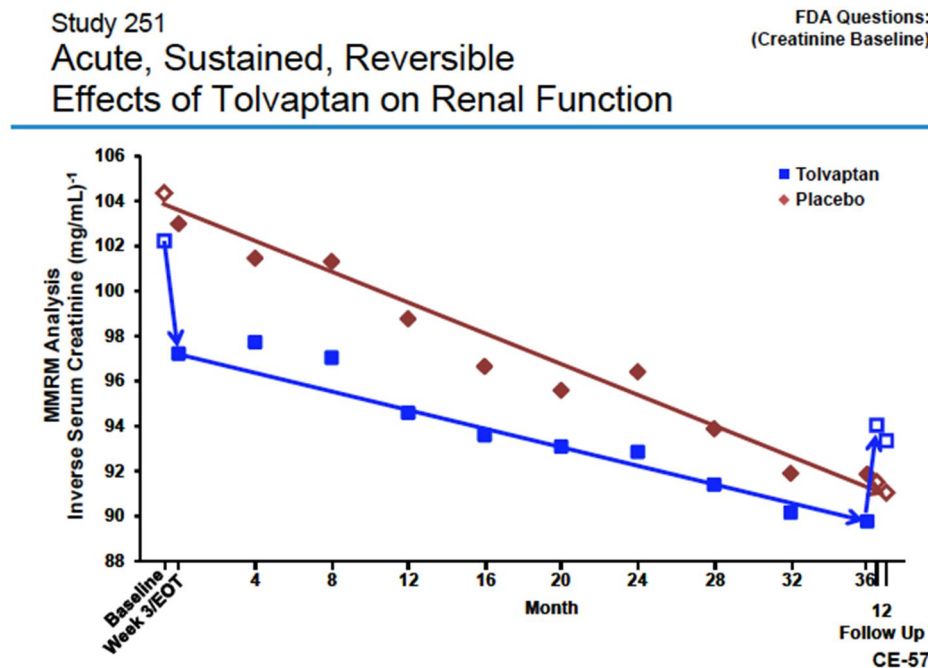
^bDerived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

Source: Table 38, p.67 of the submission.

Abbreviations: CKD-EPI, Chronic Kidney Disease - Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate.

- 6.24 In terms of the clinical significance of small changes in TKV and eGFR, the PSCR claimed that “[a]part from its eGFR links, a substantially enlarged kidney has direct QoL impacts, e.g., a 29% reduction with tolvaptan in clinically significant renal pain (p=0.007)”. In terms of the rate of decline of eGFR, the PSCR provided a meta-analysis: “Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality” (Coresh et al., 2015, JAMA) to support its claim that even a small rate of decline in eGFR corresponds to a lowered risk of progression to End Stage Renal Disease. The PSCR noted that Gansevoort, 2016 stated about tolvaptan that: “Provided that this effect was maintained, it would translate into every 4 years of treatment delaying the incidence of ESRD by approximately one additional year.”
- 6.25 The use of relative reductions in slope compared to placebo as measures of treatment effect in the primary and key secondary outcomes was not adequately justified and is difficult to interpret, and may not represent patient-relevant outcomes. Similar differences in slope in each CKD stage reflect substantially different measures of preserved kidney function in terms of eGFR; and large relative reductions in slope may reflect small differences in preserved kidney function, particularly in CKD stages 3 and 4.
- 6.26 Moreover, the ESC was concerned that the use of inverse serum creatinine post-titration at week 3 rather than at randomisation, as the starting point for the slope calculation, made interpretation of results challenging. If the baseline inverse serum creatinine levels were used as the starting points for slope calculation, there may not be a treatment effect. The ESC noted that this concern was shared by the FDA Cardiovascular and Renal Drugs Advisory Committee. Although the analysis was not presented in the submission to the PBAC, the ESC noted that a response had been prepared for the FDA Committee, based on the same trial data, which included the figure below.

Figure 2: Acute, sustained, reversible effects of tolvaptan on renal function



Source: Otsuka presentation to FDA Cardiovascular and Renal Drugs Advisory Committee, 5 August 2013; available via: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm364581.htm>

- 6.27 The sponsor presentation explained that use of week 3 as baseline was pre-specified in the 2007 protocol: “baselines for the Composite Secondary Efficacy endpoint will be defined as the value obtained at Week 3 (or End of Titration) visit because some shifts of serum creatinine level are expected with tolvaptan administration and with placebo administration in the context of a prescribed fluid regimen”. The same baseline was to be used for renal function slope. Further, in the FDA Briefing Document (p58), it was noted that “in 2009, the sponsor was advised to add post-therapy follow-up visits to assess effects on endpoints that might be susceptible to potential ‘hemodynamic effects’, and the change from baselines to the post-therapy period when any potential ‘hemodynamic effect’ had worn off”.
- 6.28 The ESC considered the impact of hydration on the treatment effect made interpretation of the benefit problematic. Inverse serum creatinine levels were affected by levels of hydration at baseline compared to week 3; and likewise it may be hypothesised that improvements post-treatment (at week 36) were affected by the continuing habit of higher levels of hydration.
- 6.29 The exploratory post hoc analysis of change in eGFR by baseline CKD stage or Mayo class is summarised in Table 5.

Table 5: Post hoc analysis of mean annualised rate of change in eGFR (CKD-EPI equation) by baseline CKD stages 1-3 or Mayo subclasses 1C-1E (ITT; end of week 3 titration to 36 months); TEMPO 3:4

Treatment	n	Mean annualised rate of change in eGFR slope ^a %	Relative slope reduction %	p-value	
ITT population (CKD stage 1-3)					
CKD stages 1-3	Tolvaptan	842	-2.7	27.0	<0.0001
	Placebo	464	-3.6		
Post hoc subgroup analysis (CKD stages 1-3)					
CKD stage 1 (eGFR≥90mL/min/1.73m ²)	Tolvaptan	267	-2.2	15.5	0.2324
	Placebo	158	-2.6		
CKD stage 2 (60-89mL/min/1.73m ²)	Tolvaptan	402	-2.7	29.1	<0.0001
	Placebo	214	-3.9		
CKD stage 3 (30-59mL/min/1.73m ²)	Tolvaptan	147	-3.7	31.0	<0.0001
	Placebo	84	-5.3		
Post hoc subgroup analysis (Mayo sub-classes 1C-1E)					
Class 1C 3.0-4.5% incr TKV/year	Tolvaptan	187	-3.59	35.4	<0.0001
	Placebo	304	-2.32		
Class 1D 4.5-6.0% incr TKV/year	Tolvaptan	152	-3.89	23.1	0.007
	Placebo	299	-2.99		
Class 1E >6.0% incr TKV/year	Tolvaptan	78	-4.93	29.8	0.002
	Placebo	161	-3.46		

Source: Table 63, p.111; Table 66, p.113 of the submission; Figure 3, Torres et al. (2016).

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; TKV, total kidney volume.

^a Annualised rate of change in eGFR for CKD stages from Figure 3, Torres et al (2016); Source for Mayo sub-class analysis not provided.

- 6.30 Mean annualised rate of change in eGFR for patients treated with tolvaptan was statistically significantly smaller in patients with baseline CKD stages 2-3 compared with placebo. There was no statistically significant difference between patients with baseline CKD stage 1 disease treated with tolvaptan compared to similar patients given placebo (p=0.2324).
- 6.31 In the post hoc subgroup analysis by Mayo sub-classes 1C-1E, there were statistically significant differences in mean annualised rate of change in eGFR between treatment arms in each sub-class. The Mayo subgroup analysis was not provided in the submission and could not be verified during the evaluation.
- 6.32 The results of the post-hoc subgroup analyses were not reliable (particularly for the Mayo sub-class subgroups), and should be interpreted with caution.

Comparative harms

- 6.33 Statistically significantly larger proportions of patients taking tolvaptan reported adverse events compared with placebo. The most frequently reported adverse events in patients treated with tolvaptan were related to its aquaretic effect (e.g. thirst, polyuria, nocturia, pollakiuria, polydipsia) and fatigue.
- 6.34 There was a statistically significantly larger proportion of discontinuations due to adverse events in patients treated with tolvaptan compared with placebo (approximately 3.5 times).

- 6.35 The most commonly reported serious adverse event in patients treated with tolvaptan was elevated levels of liver enzymes (alanine aminotransferase and aspartate aminotransferase). Three Hy's Law cases (i.e. cases of hepatocellular injury sufficient to suggest a high risk of a fatal drug-induced liver injury with continued general use) were identified as likely or highly likely to be related to tolvaptan in TEMPO 3:4. All three patients returned to normal liver function with no long term liver injury after cessation of tolvaptan.
- 6.36 The PSCR reiterated a claim of inferior comparative safety. However, it argued that the risk of hepatic toxicity was small (2/819 patients) and harms were reported reversible, typically within one to four months. The PSCR also stated that the risk of hepatic toxicity will be managed with adequate prescriber training and "mandatory liver function tests". Restricting prescribing to specialists only is also expected to manage this risk. Overall, the PSCR contended that the proposed listing targets a subgroup in which the risk benefit ratio is favourable – the safety profile is partially balanced by a reduced incidence of disease-related events, offering highly patient-relevant benefits; i.e. [reduction in] haematuria ($p < 0.001$), renal pain and urinary tract infections ($p < 0.05$).
- 6.37 The ESC considered the long-term safety profile of tolvaptan was unknown and raised concerns regarding the accumulated events (particularly hepatic impairment) over time (the benefits of tolvaptan are based on very long treatment durations). The ESC noted that hepatic impairment was more common in the 3-year TEMPO 3:4 trial (1.8% in treatment group vs 0.2% in placebo group), and that the FDA has only approved tolvaptan for hypervolemic and euvolemic hyponatremia (but not ADPKD), and has limited treatment duration to 30 days due to hepatotoxicity. In line with the FDA approval, the ESC also noted that tolvaptan (Samsca®) is currently TGA registered for the treatment of clinically significant hypervolemic or euvolemic hyponatremia, with administration for more than 30 days not recommended due to the risk of hepatotoxicity.
- 6.38 The Pre-PBAC Response argued that Samsca® has a different indication and "a very different risk benefit profile", and that the 30 day precaution did not exist in the EU. The PBAC noted that the caution applied to Samsca® was in response to results from the TEMPO 3:4 trial in ADPKD⁴, and that it was consistent with the Australian registration.
- 6.39 The ESC considered that TEMPO 4:4 and other ongoing studies (see 'Clinical trials') may provide additional data relevant to the longer benefit/harm assessment of tolvaptan.

Benefits/harms

- 6.40 A summary of the comparative benefits and harms for tolvaptan versus placebo is presented in the table below.

⁴ FDA Drug Safety Communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death (30 April 2013), accessed via: <https://www.fda.gov/Drugs/DrugSafety/ucm350062.htm>

Table 6: Summary of comparative benefits and harms for tolvaptan and placebo (36 months duration of follow-up)

Benefits	Tolvaptan	Placebo	Treatment difference	Relative difference
Mean TKV growth rate per year: % (SD)	2.78 (5.66)	5.61 (5.33)	-2.83%	50.5%
Mean rate of change per year (eGFR): %	-2.680	-3.568	0.89	24.9%
Harms	Tolvaptan	Placebo	Event rate per 100 patients	
			Tolvaptan	Placebo
Thirst	531/961	99/483	55.3	20.5
Nocturia	280/961	63/483	29.1	13.0
Renal pain	260/961	171/483	27.1	35.4
Decreased appetite	69/961	5/483	7.2	1.0
Polydipsia	100/961	17/483	10.4	3.5
Hypernatraemia	27/961	5/483	2.8	1.0
Hepatic enzyme increased	17/961	1/483	1.8	0.2
Blood sodium increased	14/961	1/483	1.5	0.2

Source: Table 34, p.61; Table 46, pp.74-76 of the submission
Abbreviations: SD, standard deviation; TKV, total kidney volume

- 6.41 On the basis of the direct evidence presented in the submission, treatment with tolvaptan compared with placebo (best supportive care) resulted in statistically significant slower growth in total kidney volume (difference in growth rate per year of 2.83%) over 3 years, but this may not represent a clinically important difference given the uncertainty about the relationship between eGFR and TKV.
- 6.42 On the basis of the direct evidence presented in the submission, treatment with tolvaptan compared with placebo (best supportive care) resulted in statistically significant slower decline in eGFR (difference in average decline per year of 0.89%) over 3 years. The validity of this treatment effect is uncertain. The starting point for the calculation of this treatment benefit was post-titration at week 3. If randomisation (or “week 0”) was taken as the starting point for calculation, there may not have been a treatment effect.
- 6.43 On the basis of the direct evidence presented in the submission, for every 100 patients treated with tolvaptan compared with placebo (best supportive care) over 3 years, approximately:
- 16 additional patients would experience nocturia
 - 8 fewer patients would experience renal pain
 - 2 additional patients would experience hypernatraemia
 - 2 additional patients would experience an increase in hepatic enzymes
 - 1 additional patient would experience increased blood sodium.

Clinical claim

- 6.44 The submission described tolvaptan as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. The ESC agreed with the safety claim, but considered that the efficacy of tolvaptan remained uncertain.
- 6.45 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.

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

Economic analysis

6.47 The submission presented a modelled cost-effectiveness/cost-utility analysis comparing tolvaptan to best supportive care (placebo) for the treatment of patients with ADPKD.

6.48 A summary of the model structure and rationale is presented in Table 7.

Table 7: Summary of model structure and rationale

Methods used to generate results	Two module Markov cohort expected value analysis (270 risk profile permutations)
Time horizon	Lifetime (maximum patient age 100 years)
Cycle length	1 year; half-cycle correction
Treatments	Tolvaptan, placebo
Health states	CKD stage 1, CKD stage 2, CKD stage 3, CKD stage 4, CKD stage 5 (pre-dialysis), CKD stage 5 (dialysis), post-transplantation, death
Outcomes	Reciprocal serum creatinine levels, eGFR, quality-adjusted life years
Transition probabilities	Based on the predicted decline in eGFR levels by gender, age and Mayo class based on the Mayo model of kidney decline in ADPKD patients. Target populations synthesised from the Mayo ADPKD study. Treatment effects based on <i>post hoc</i> analysis of treatment efficacy by CKD stages in the TEMPO 4:3 trial. Dialysis and transplantation probabilities based on ANZDATA reports.
Discount rate	5% for costs and outcomes
Software package	Excel 2013

Source: constructed during the evaluation.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CKD, chronic kidney disease.

6.49 The economic model implemented each of 270 risk profiles as separate population cohorts and generated weighted aggregate costs and QALYs. The model describes annual changes in the population mean eGFR of each cohort for the intervention and comparator groups and then each cohort is moved to the corresponding CKD state. This overly complicated approach increases the uncertainty of the model outputs.

6.50 All cohorts start in CKD states 1-3 (dependent on their risk profile). After reaching the dialysis health state, the transition probabilities are no longer dependent on eGFR levels. Patients on dialysis may continue with dialysis therapy, have kidney transplantation or die in each model cycle. Patients with a kidney transplant may continue in their current state, have a graft rejection (and return to dialysis state) or die in each model cycle.

6.51 The model is essentially a patient-level state transition model in which a single patient is run through the model for each of the 270 defined patient groups. So the model represents variation in the characteristics of the target population, but assumes all patients within each of the 270 groups experience the same disease pathway. In reality, disease progression varies between patients, which impacts on the timing of quality of life effects and the incurrance of treatment costs. It also impacts on the modelled impact of competing risks, primarily death, i.e. patients with reduced disease progression are more likely to die before reaching ESKD. The impact of assuming no variation in disease progression increases with increasing skew in the distribution of disease progression.

- 6.52 The ESC advised that the model could be improved by either:
- estimating transition probabilities between and beyond the CKD states rather than applying the same eGFR reduction to each of the full cohorts, or
 - analysing larger numbers of individual patients for each of the 270 patient groups, representing variation in eGFR progression within each group.
- The validity of the cost-effectiveness model could also be assessed in relation to external data describing the age at onset of ESKD.
- 6.53 A lifetime time horizon for the economic model appeared to be appropriate given the chronic, prolonged disease course of ADPKD. However, the extrapolation of treatment effects from three years in the pivotal clinical trial to a maximum of 30 years in the economic model is highly uncertain.
- 6.54 Additionally, the Mayo model of renal function decline is used to predict the natural history of ADPKD patients treated with tolvaptan or best supportive care over long timespans (up to 80 years in model). The accuracy of the Mayo classification of kidney function decline decreases over 40-80 years, potentially resulting in further uncertainty.
- 6.55 Key drivers with the economic model are summarised in Table 8.

Table 8: Key drivers with of the economic model

Extrapolation of treatment effect	The model extrapolation of treatment effects from 3 years in the pivotal clinical trial to a maximum of 30 years in the economic model. There are limited long term data to support continuing treatment effect over time.	High, favours tolvaptan
Treatment effect in CKD4	The model assumes treatment efficacy in CKD4 is the same as reported for the post hoc subgroup analysis results for CKD3. It is unclear whether this is reasonable as there are no clinical data to support treatment effect in CKD4 patients.	High, favours tolvaptan
Treatment effect with disease progression	The model assumes that the treatment efficacy of tolvaptan increases over time as patients experience disease progression. This assumption has a major impact on the economic analysis and is poorly justified in the submission.	High, favours tolvaptan
Utilities applied to dialysis and transplant health states	The disutility associated with dialysis (-0.13) may have been overestimated and the utility gain associated with successful transplant (+0.08) underestimated in the submission, when compared with estimates from OVERTURE, an international, multicentre, longitudinal, observational study in ADPKD patients.	High, favours tolvaptan.
Handling of discontinuations	Treatment discontinuations were applied as a proportional reduction in treatment efficacy rather than as a probability of no treatment. This approach may accelerate the cohort's progression through CKD states but at an individual-patient level it allows all treatment benefits accrued while patients are on treatment to be maintained after discontinuation (as their rate of decline is never worse than placebo).	Moderate, favours tolvaptan
Mayo model of renal function decline	The Mayo model of kidney function decline is extrapolated over the duration of the model. This is not adequately justified in the submission.	Uncertain impact
Threshold effects	The model applies mean changes in eGFR rather than transition probabilities between CKD states. The entire cohort moves through the model at the same time. There are anomalies in the cost effectiveness of tolvaptan across risk profile cohorts are due to small differences in the natural history which result in cohorts crossing thresholds into different categories. These threshold effects have a major impact on the individual cost-effectiveness estimates for patient cohorts.	Uncertain impact

Source: compiled during the evaluation

6.56 The results of the economic model are summarised in Table 9.

Table 9: Results of the economic evaluation

Scenario	Tolvaptan	Placebo	Increment
Scenario 1: TGA eligibility population, lifetime duration [base case]			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	13.5293	12.8535	0.6758
Incremental cost per QALY gained			\$ [REDACTED]
Scenario 2: no CKD Stage 1 patients, lifetime duration			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	12.6870	11.9885	0.6985
Incremental cost per QALY gained			\$ [REDACTED]
Scenario 3: no Mayo class 1C patients, lifetime duration			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	12.8950	12.2142	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Scenario 4: no CKD Stage 1 patients and no Mayo class 1C patients, lifetime duration			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	12.0871	11.4513	0.6359
Incremental cost per QALY gained			\$ [REDACTED]

Source: Table 123, p.185 of the submission.

Abbreviations: QALY, quality adjusted life year; TGA, Therapeutic Goods Administration.

The redacted table shows ICERs in the range of \$45,000/QALY – \$200,000/QALY.

- 6.57 Based on the economic model, treatment with tolvaptan compared to placebo was associated with a cost per QALY gained ranging from \$105,000/QALY – \$200,000/QALY (Scenario 1) to \$45,000/QALY – \$75,000/QALY (Scenario 4). Scenarios 3 and 4 are largely non-informative as many of the Mayo class 1C patients would still be able to access treatment under the eGFR criterion of the proposed restriction.
- 6.58 The economic model was most sensitive to time horizon, discount rate, treatment efficacy estimates, the modelled decline in eGFR, the costs and disutility associated with dialysis, and transplantation rates.

Drug cost/patient/year: \$ [REDACTED].

- 6.59 The annual cost for tolvaptan split dose packs was \$ [REDACTED] (effective price), based on 13.04 scripts per year (=365 days per year/28 days' per pack). This is a [REDACTED]% reduction off the requested published price; an annual cost of \$ [REDACTED]. [REDACTED]

Estimated PBS usage & financial implications

- 6.60 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of tolvaptan for the treatment of ADPKD.
- 6.61 The DUSC considered that the net cost to Government was 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 slower disease progression or early stage disease.
- 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.

Table 10: Estimated utilisation and cost to the PBS in the first five years of listing tolvaptan for ADPKD

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 1: TGA/PBS eligibility population					
Australian population	24,781,121	25,201,317	25,619,895	26,037,356	26,452,147
Adult ADPKD patients [CKD 1-3 & Mayo 1C-1E]	█	█	█	█	█
Tolvaptan initiation rates	█	█	█	█	█
Patients initiating treatment	█	█	█	█	█
Patients continuing year 2 (84.7%)	-	█	█	█	█
Patients continuing year 3 (79.2%)	-	-	█	█	█
Patients continuing year 4 (76.9%)	-	-	-	█	█
Patients continuing year 5 (76.5%)	-	-	-	-	█
Total patients on therapy	█	█	█	█	█
Total persistent patient years on therapy (with half-cycle correction)	█	█	█	█	█
Total tolvaptan packs dispensed (13.04 per patient)	█	█	█	█	█
Cost of tolvaptan (effective DPMQ \$█)	\$█	\$█	\$█	\$█	\$█
Patient co-payments (mean \$24.34)	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost to the PBS/RPBS	\$█	\$█	\$█	\$█	\$█
MBS cost of liver function testing (12 tests per year, \$11.65 per test)	\$█	\$█	\$█	\$█	\$█
Net cost to government	\$█	\$█	\$█	\$█	\$█

Source: Table 130, p.202; Table 131, p.203; Table 132, p.204; Table 133, p.205; Table 134, p.206; Table 135, p.206; Table 139, p.210; Table 142, p.212; Table 143, p.213 of the submission.

Abbreviations: ADPKD, Autosomal Dominant Polycystic Kidney Disease; CKD, chronic kidney disease; DPMQ, dispensed price for maximum quantity; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 – \$20 million.

6.62 The net cost of listing tolvaptan on the PBS for treatment of patients with ADPKD was estimated to be up to \$10 – \$20 million in the fifth year of listing. The estimated cumulative net cost over five years was \$60 – \$100 million. The submission estimated a small additional cost to government due to increased liver function testing with tolvaptan treatment (cumulative cost of less than \$10 million over five years). The DUSC advised that the MBS costs would be higher than expected if the number of treated patients per year was higher than estimated.

- 6.63 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. The submission estimated a cumulative lifetime cost saving of \$60 – \$100 million . The commentary considered that these cost savings are highly uncertain as they are projected over the lifetime of patients (up to 80 years from initiation) and incorporate all main issues of concern with the economic model. 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.
- 6.64 The estimated financial implications were uncertain, given the assumed low initiation rates for tolvaptan, the first disease modifying therapy available for ADPKD; the uncertainty regarding whether the Mayo classification system can be effectively implemented in practice to identify the eligible patient population; and the potential for use outside of the proposed restriction.
- 6.65 Overall, the net cost of listing tolvaptan on the PBS/RPBS for the treatment of ADPKD has the potential to exceed \$20 – \$30 million per year .

Quality Use of Medicines

- 6.66 The sponsor has committed to ensuring that all tolvaptan prescribers are educated on the use of the drug and that a liver function monitoring program is implemented to minimise the risk of hepatic injury. The Jinarc[®] Registry, a web-based platform, will be set up to host the training material; prescriber certification and to support long-term liver monitoring and safety. The requested restriction states that all prescribers and patients must take part in the Jinarc[®] Registry in order to prescribe/receive Jinarc[®] in Australia. In the PSCR the sponsor elaborated that along with the prescriber training initiative, it would set up a patient registry within which patients' eligibility for initiating and continuing tolvaptan, including adherence to the liver tests requirements, would be monitored. This registry would also monitor dispensing of tolvaptan. DUSC had concerns that prescriber and patient participation in a sponsor-managed registry was included in the requested restriction as a condition of PBS prescribing and supply. The PBAC noted the Pre-PBAC Response stated that the registry proposed in the submission "has been reviewed by the TGA and accepted as a key element of the risk management plan". The PBAC noted that the inclusion of a sponsor-managed registry in the PBS restriction was not itself problematic, but that the proposed restriction wording would need to be further developed in consultation with the Department, should tolvaptan be recommended for PBS listing in future.

Financial Management – Risk Sharing Arrangements

- 6.67 The sponsor indicated a willingness to enter into a risk-sharing arrangement to address the financial uncertainty associated with the PBS listing of tolvaptan.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the listing of tolvaptan for the treatment of autosomal dominant polycystic kidney disease (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. In this context, the PBAC considered that the incremental cost-effectiveness was very high and unclear and the likelihood of high overall costs to government was unacceptable.
- 7.2 The PBAC agreed that Best Supportive Care (BSC) was the appropriate comparator. BSC was defined in the submission as “treatments to control symptoms and complications associated with ADPKD”. The PBAC agreed that, in practice, tolvaptan would be prescribed in addition to BSC.
- 7.3 The PBAC noted that the requested listing scenarios included patients with evidence of rapid disease progression (based on eGFR) or predicted rapid disease progression (based on the novel Mayo classification system). The PBAC considered that the requested restriction would be difficult to implement in practice as:
- measurement of TKV requires magnetic resonance imaging which may be problematic for prescribers given the cost and availability of testing equipment; it is not part of routine clinical care and has not been validated for use in routine clinical practice. The alternative, ultrasonography has uncertain diagnostic and prognostic properties in this setting; and
 - other sources of variability in eGFR, apart than disease progression, may result in broader use than intended.
- 7.4 The PBAC’s concern with the restriction was in line with the DUSC’s advice regarding the utilisation and financial estimates – that the use of the Mayo classification may not be practical for identifying the eligible patient population in Australia, and that the uptake of tolvaptan may be broader than intended. The PBAC agreed with the DUSC’s concern 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.
- 7.5 In reaching its view of the uncertain clinical benefit of tolvaptan, the PBAC considered that the pivotal trial TEMPO 3:4 did not provide adequate data to support a conclusion that tolvaptan had superior efficacy to placebo in the treatment of ADPKD. The PBAC noted that the primary outcome of the trial was the difference in the rate of change in TKV from baseline, with key secondary composite outcome events of worsening renal function, renal pain, hypertension and albuminuria. In relation to treatment of ADPKD, the PBAC was of the view that the outcome of greatest clinical importance was prevention of ESKD, but accepted that eGFR may be a reasonable surrogate (albeit not validated in this setting) and agreed with the PSCR that pain and hypertension were also clinically important outcomes. With this in mind, the PBAC agreed with the ESC that whilst TEMPO 3:4 showed a very small decrease in the rate of TKV growth from baseline, this was of uncertain clinical importance and not a validated surrogate outcome for ESKD in this or other settings. The PBAC also agreed with the ESC that the data provided in the submission suggested little or no difference in terms of renal function as measured by inverse serum creatinine. In particular, the PBAC agreed with the ESC that the use of inverse

serum creatinine post-titration at week 3 rather than at randomisation, as the starting point for the slope calculation, made interpretation of results challenging. Adding to the difficulty of interpretation was that although TEMPO 3:4 was a blinded trial, the treatment assignment could have been unblinded due to the effects of tolvaptan on increased urination, dehydration and fluid intake.

- 7.6 At the same time as the PBAC was uncertain about the clinical benefits of tolvaptan, it was concerned about the significantly inferior safety compared with placebo. Specifically, it noted that there was a statistically significantly larger proportion of discontinuations due to adverse events in patients treated with tolvaptan compared with placebo (approximately 3.5 times), and that hepatic impairment was more common (1.8% in treatment group vs 0.2% in placebo group). The PBAC also noted that based on the results of the TEMPO 3:4 trial, the FDA had limited tolvaptan to a treatment duration to 30 days due to hepatotoxicity (for its approved indication of hypervolemic and euvolemic hyponatremia). Overall, the PBAC considered that the short-term safety of tolvaptan compared to placebo was inferior, and the long-term safety unknown.
- 7.7 The PBAC noted the ESC's advice that the open label tolvaptan extension study (TEMPO 4:4) has been completed, and this may provide data on longer term adverse events, but was not fully presented in the submission. Other ongoing trials may also be relevant to decision making; these include an RCT for stage 2–4 CKD due to ADPKD, for which recruitment is completed (REPRISE, NCT02160145 (alternate ID: 156-13-210)) and a trial of tolvaptan in children and adolescents with ADPKD (NCT02964273), which is still recruiting. The PBAC noted the PSCR and Pre-PBAC Response's statements that early results from TEMPO 4:4 support longer-term efficacy. The PBAC considered that this trial and others mentioned may be relevant to its decision-making and may assist to lessen its uncertainty regarding the clinical benefits and long-term harms of tolvaptan.
- 7.8 The PBAC agreed with the evaluation and ESC comments regarding the economic analysis in the submission (paragraphs 6.42-57). It considered that in the context of uncertain clinical benefit and long-term safety, the resulting ICERs were also uncertain and unacceptably high.
- 7.9 The PBAC considered that a resubmission would need to be a major submission to allow for the evaluation of updated clinical data and economic modelling.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

Otsuka Australia Pharmaceutical is committed to providing additional evidence and work with the PBAC to ensure tolvaptan is PBS listed and available to patients with ADPKD as soon as possible.