February 2016

Drug	Tolvaptan (Jinarc)
Indication	To slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD)
Listing Request	As per indication
Dosage Form	45 + 15 mg, 60 + 30 mg, and 90 + 30 mg tablets
NOC Date	February 25, 2015
Manufacturer	Otsuka Canada Pharmaceutical Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

ADPKD	autosomal dominant polycystic kidney disease
CI	confidence interval
CKD	chronic kidney disease
CUA	cost-utility analysis
ESRD	end-stage renal disease
GFR	glomerular filtration rate
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Tolvaptan (Jinarc)
Study Question	"To evaluate the long-term cost-effectiveness of JINARC (tolvaptan) to slow the progression of kidney enlargement in patients with ADPKD compared to the current standard of care."
Type of Economic Evaluation	CEA and CUA
Target Population	Patients with autosomal dominant polycystic kidney disease (ADPKD)
Treatment	Tolvaptan twice daily in split-dose regimens of 60 mg, 90 mg, or 120 mg
Outcomes	QALYs Life-years
Comparator	Standard of care (monitoring and palliative care/symptom management)
Perspective	Canadian Ministry of Health
Time Horizon	Lifetime (50 years)
Results for Base Case	For tolvaptan compared with standard of care: • $244,402 per QALY • $2.3 million per life-year
Key Limitations	• Three-year trial data (baseline and relative risk of outcomes) extrapolated over a lifetime, with unknown durability of treatment effectiveness over time • The model is informed by surrogate outcomes (GFR) and this is used to predict clinically important outcomes that occur over a very long time frame • Uncertainty in impact of kidney pain on utility, utility in ADPKD patients at various stages of CKD, and true costs of care in the Canadian setting • Considers patients that are in general at high risk of progression of disease, but may not represent all patients that may be considered for treatment
CDR Estimates	• Exploration of uncertainty in rate of disease progression and relative treatment efficacy using manufacturer's reference case highlights some of the uncertainty: ○ 95% CI on relative efficacy on progression: ICUR ranges from $136,000 to $419,000 per QALY ○ Use in a cohort with slower disease progression: ICUR ranges from $301,000 to $363,000 per QALY • A plausible reference case using Canadian costs, higher ESRD utility, and shorter kidney pain duration, ICUR is $387,000 per QALY ○ 95% CI on relative efficacy on progression: ICUR ranges from $203,000 to $852,000 per QALY ○ Use in a patient cohort with slower disease progression: ICUR is $473,000 per QALY

ADPKD = autosomal dominant polycystic kidney disease; CEA = cost-effectiveness analysis; CI = confidence interval; CKD = chronic kidney disease; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ESRD = end-stage renal disease; GFR = glomerular filtration rate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Tolvaptan (Jinarc) is indicated to slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD).[1] The dosage is 45 + 15 mg, 60 + 30 mg, or 90 + 30 mg and is administered orally as a split dose twice daily. [redacted]

The manufacturer submitted a cost-utility analysis comparing tolvaptan with standard of care (monitoring of renal function, blood pressure control, and symptom management) in adult patients with ADPKD over a lifetime time horizon (50 years) from the perspective of the Canadian health care payer.[2] Disease progression in terms of chronic kidney disease (CKD) stages and relative efficacy with tolvaptan were obtained from the three-year TEMPO 3:4 trial.[3] Other inputs such as costs and quality of life were obtained from published literature.

Summary of Identified Limitations and Key Results

The manufacturer modelled disease progression by estimating decline in kidney function over time using observed changes in kidney function from the TEMPO 3:4 trial.[3] However, while change in glomerular filtration rate (GFR) is a correlate, its relationship with clinically important outcomes (such as end-stage renal disease [ESRD]) is not clearly defined, particularly in ADPKD patients where decline over time may not be linear. Use of a surrogate, with consequences on clinically important outcomes over a very long time frame, introduces significant uncertainty. Further, the manufacturer assumed that differences in loss of kidney function observed in a fairly short-term randomized controlled trial (RCT) (three years in terms of kidney function decline) could be extrapolated to a lifetime time horizon. If efficacy attenuates over time, the incremental cost-utility ratio (ICUR) may be underestimated; however, an open-label, two-year extension trial suggested continued efficacy in the surrogate end point.[4]

The relative efficacy of tolvaptan versus standard of care was assumed to be constant across all CKD stages in the model. However, evidence from TEMPO 3:4 suggested that the treatment effect may vary by kidney volume and different patient characteristics. Further, ADPKD patients may have increased kidney volume but have less severe disease, with a lower risk of progression and reaching ESRD (for example, polycystic kidney disease 1 gene [PKD1] non-truncating mutation and polycystic kidney disease 2 gene [PKD2]). Patients in the TEMPO 3:4 study were in general at high risk. Use of tolvaptan in lower-risk patients would likely result in a higher ICUR.

The CADTH Common Drug Review (CDR) noted limitations with a number of model inputs:

- US cost data were used to inform direct medical costs in the model, as Canadian-specific costing studies were not identified. Although the values were adjusted to estimate the lower cost in Canada, it might not truly reflect the cost of care in Canada.
- Tolvaptan results in a reduction in "clinically important episodes" of kidney pain.[3] Kidney pain in ADPKD may be acute or chronic. In the model, kidney pain is represented by assuming a continuous, lifelong (50 years) reduction in utility due to pain (i.e., chronic pain); however, the trial-assessed outcome implies acute or self-limited episodes of pain. The modelled approach may overestimate benefits of reducing acute kidney pain episodes.

- A utility score from the general dialysis and CKD population was used; however, patients with ADPKD tend to be healthier and younger than other patients with ESRD. Overestimating the disutility of ESRD may favour tolvaptan — underestimating the ICUR.

An alternate scenario using plausible, appropriate inputs — Canadian costs, higher ESRD utility (0.65), and shorter kidney pain episode duration (one month) — led to an ICUR when comparing tolvaptan with standard of care of $386,700 (incremental cost of tolvaptan was $178,992; incremental quality-adjusted life-years [QALYs] were 0.47). Additional sensitivity analyses were considered, varying the annual GFR decline for milder patients and considering the confidence interval (CI) bounds for the relative reduction in GFR decline for tolvaptan, which resulted in an ICUR ranging from $203,344 to $851,892 per QALY for tolvaptan compared with standard of care. The uncertainty with the use of a surrogate end point (GFR) and the relative efficacy of tolvaptan across CKD stages could not be addressed in reanalyses.

Conclusions

The manufacturer's base case suggests tolvaptan results in an additional 0.66 QALYs compared with standard of care, but is $161,955 more costly, driven primarily by drug acquisition costs ($216,460), resulting in an ICUR of $244,402 per QALY.

The ICUR in a plausible CDR reference case increase when Canadian costs, greater ESRD utility, and shorter kidney pain duration are assumed in the model, leading to an ICUR of $387,000 per QALY. The ICUR further increases if used in a patient group with overall slower progression of disease ($473,000 per QALY), or if drug efficacy is lower ($851,000 per QALY with lower CI).

There is significant uncertainty (regardless of what reference case is used) given the use of a surrogate outcome, and the very long time frame over which clinical benefits are captured.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) comparing tolvaptan with standard of care (monitoring, blood pressure control, and symptom management) in a cohort of patients with autosomal dominant polycystic kidney disease (ADPKD)[2] based on characteristics of participants in the TEMPO 3:4 trial.[3] The time horizon was patient lifetime (50 years), and the model used the Canadian public payer perspective. All patients in the model started in a health state reflecting categories of kidney function (by glomerular filtration rate [GFR] and chronic kidney disease [CKD] stage) according to the distribution observed in the TEMPO 3:4 trial, and over time could either remain in the same stage or experience worsening of kidney function and transition to the subsequent CKD stage, including end-stage renal disease (ESRD) where patients initiate dialysis. Patients in the ESRD state have a probability of obtaining a kidney transplant. All health states have a mortality risk that differs by patient age and CKD stage.

Since ADPKD mortality rates were not available, the mortality odd ratios observed in the general CKD population were used as a proxy,[5] and were combined to the mortality rate by age from the Statistics Canada life tables. As patients with ADPKD may be healthier than other patients with renal disease, the risk of mortality in ESRD was adjusted downward using data from ESRD ADPKD patients.[6] Probability of receiving a kidney transplant was based on actual transplant rates observed in the Canadian ADPKD patient population by age group.[7] Transition probabilities were estimated based on the renal function decline rate (–3.81 mg/mL per year) observed in the placebo group of the TEMPO 3:4 trial.[3] Validation was provided against a published cost-effectiveness analysis and an observational study (CRISP).[8,9] The tolvaptan treatment effect was incorporated by using a lower observed decline in renal function (–2.61 mg/mL per year), resulting in a lower probability of transitioning to worse kidney function (lower GFR) and more advanced CKD stage.

As ADPKD-specific utility values by CKD stage and ESRD are not available, utilities obtained from the general CKD population were used as a proxy.[10] Utilities for ESRD/dialysis and post-transplant were obtained from two Canadian studies that were not specific for ADPKD as a cause of renal failure.[11,12] An additional disutility of [redacted] was assigned to the adverse event of renal pain.[13] Drug costs were from the manufacturer based on an average cost of three different strength combinations (45 + 15 mg, 60 + 30 mg and 90 + 30 mg) [redacted]. An 8% wholesale/pharmacy markup and $9 dispensing fee were also added to the drug cost. The prescription cost was adjusted with a compliance rate of 90% reflecting the average compliance rate observed in the TEMPO 3:4 trial. A liver monitoring cost of $120 per year was also included for monthly liver function tests to monitor for hepatotoxicity. Direct medical costs by CKD stage and ESRD were obtained from a US ADPKD-specific study,[14] and costs were adjusted by a cost ratio of [redacted] to account for the lower cost of care in Canada.[15] The costs of a renal transplant and post-transplant were obtained from a Canadian study.[16]

2. MANUFACTURER'S BASE CASE

In the reference case, the manufacturer reported that tolvaptan compared with standard of care is associated with an additional 0.07 life-years and an additional 0.66 quality-adjusted life-years (QALYs). Treatment with tolvaptan resulted in additional costs from drug acquisition, but lower health care costs (Table 2), with a total incremental cost of $161,955. The cost per QALY is $244,402, and the cost per life-year is $2,318,302.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Tolvaptan	Standard of Care	Difference
Life-years	16.98	16.91	0.07
QALYs	13.87	13.21	0.66
Cost ($)			
Tolvaptan cost	217,460	0	217,460
Direct health care cost	303,644	359,149	–55,505
Total cost	521,104	359,149	161,955
ICER ($/life-year)			2,318,302
ICUR ($/QALY)			244,402

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

2.1 Summary of Manufacturer's Sensitivity Analyses

The reference case result for tolvaptan versus standard of care is $244,402 per QALY. The following parameters increased/decreased the incremental cost per QALY gained by more than 20%:

- Tolvaptan reduces kidney function decline compared with standard of care by 20% (versus base case 31.6%): cost per QALY $354,000
- Discount rates 3% cost and 0% benefit (versus 5% for both): cost per QALY $118,000
- Generic at year 5 at 70% of brand price (versus no generic): cost per QALY $173,000
- Kidney function decline –2.81 mg/mL per year (versus –3.81 mg/mL per year): cost per QALY $301,000
- Starting cohort 30 years, 100% in CKD1 (versus 40 years, CKD distribution from TEMPO 3:4): cost per QALY $294,000
- Starting age 40 years, 50% CKD Stage 3a, 50% CKD Stage 3b (versus 40 years, CKD distribution from TEMPO 3:4): cost per QALY $183,000.

The manufacturer also provided a CUA from the societal perspective by including productivity and travel costs; incremental cost-utility ratio (ICUR) = $213,000 per QALY.

According to the cost acceptability curve from the probabilistic sensitivity analyses, 0% of the incremental cost-effectiveness ratios (ICERs) would fall below a $100,000 per QALY threshold and 18% of the ICERs would fall below a $200,000 per QALY threshold.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Uncertainty in modelling natural history of disease.**
  The manufacturer models disease progression by estimating decline in kidney function over time using observed changes in kidney function from the TEMPO 3:4 trial. However, while change in GFR is a correlate, its relationship with clinically important outcomes (such as ESRD) is not clearly defined, particularly in ADPKD patients where decline over time may not be linear. The manufacturer claimed "projecting ADPKD patient cohorts over time based strictly on the TEMPO 3:4 horizon provides a conservative estimate of the long-term decline in kidney function and the number of patients reaching ESRD"; however, it is not clear that this is a conservative estimate, as the trial included patients at varying points in disease trajectory.

- **Uncertainty in long-term efficacy.**
  The model assumes that differences in loss of kidney function observed in a fairly short-term randomized controlled trial (RCT) (three years in terms of kidney function decline) can be extrapolated to a lifetime time horizon. If efficacy attenuates over time, the ICUR may be underestimated; however, an open-label two-year extension trial[4] suggested continued efficacy in the surrogate end point.

- **Patient heterogeneity.**
  The relative efficacy of tolvaptan is assumed to be constant across all CKD stages in the model. However, evidence from TEMPO 3:4 suggests that the treatment effect may vary by kidney volume and different patient characteristics. There are many ADPKD patients who may have increased kidney volume (polycystic kidney disease 1 gene [PKD1] non-truncating mutation and polycystic kidney disease 2 gene [PKD2]) but have less severe disease with a lower risk of progression and reaching ESRD, and as such absolute risk of ESRD (absolute benefit of treatment) may be lower in such patients.

- **CKD costs based on US data.**
  US cost data are used to inform direct medical cost in the model, as Canadian-specific costing studies are not identified. Although the values are adjusted to estimate the lower cost in Canada, it might not truly reflect the cost of care in Canada.

- **Impact on kidney pain.**
  The model incorporates a reduction in kidney pain (and less disutility from this) and applies this for the entire model duration (50 years). However, the trial outcome was defined as clinically important "episodes" of kidney pain, implying that the reduction was in acute (versus chronic) pain associated with this disease. Applying a constant lifelong disutility may overestimate the impact of episodes of kidney pain (and overestimate benefit of decreasing its frequency).

- **Utility for ESRD.**
  A utility score from the general dialysis and CKD population was used; however, as noted in other sections of the report, patients with ADPKD tend to be healthier and younger than other patients with ESRD, and may have a higher utility than other ESRD patients. Overestimating the disutility of ESRD may favour tolvaptan.

3.1 CADTH Common Drug Review Analyses

The CADTH Common Drug Review (CDR) considered the following analyses to address the limitations identified earlier:

1. **Episodic kidney pain.**
   When the duration of kidney pain is shortened to one month (manufacturer stated a disutility of [redacted] but applied to one month = [redacted]), incremental cost = $161,955 and incremental QALYs = 0.50, ICUR = $321,347 per QALY. If episodes of pain are one or two weeks, the ICURs = $328,604 per QALY and $326,399 per QALY, respectively.

2. **Greater utility score for ESRD on dialysis.**
   If a numerically greater utility estimate for patients on dialysis is used (0.65 versus base case 0.57) from another Canadian study (weighted average of in-centre hemodialysis and home nocturnal dialysis),[17] incremental cost = $161,955 and incremental QALYs = 0.63, ICUR = $260,571 per QALY.

3. **Canadian cost of care.**
   When direct medical cost from more recent Canadian sources is used[18] with a CKD cost of $16,742 and an ESRD cost of $58,847 (inflated to 2014 Canadian dollars), incremental cost = $178,991 and incremental QALYs = 0.66, ICUR = $270,112 per QALY. Note, however, that these data are from general CKD/ ESRD patients, and not specific for ADPKD patients.

4. **Administration in cohort with less severe disease progression.**
   Change annual GFR decline from 3.81 mg/mL to 2.81 mg/mL to simulate patients with less progressive disease, incremental cost = $189,715 and incremental QALYs = 0.64, ICUR = $300,559 per QALY. Assessed in another way, if all patients start in CKD Stage 1 (earlier stage of disease), incremental cost = $223,693 and incremental QALYs = 0.61, ICUR = $362,673 per QALY.

5. **Exploration of uncertainty in relative efficacy.**
   Change the annual GFR decline from 3.81 mg/mL to 3.70 mg/mL to reflect trial ITT placebo population and change relative reduction with tolvaptan to upper and lower bounds of trial CI.{31,9} For lower CI (treatment effect 0.597, i.e., –16.1% relative reduction with tolvaptan), incremental cost = $177,686 and incremental QALYs = 0.42, ICUR = $418,938 per QALY. For upper CI (treatment effect 1.357, i.e., –52.8% relative reduction with tolvaptan), incremental cost = $143,247 and incremental QALYs = 1.05, ICUR = $135,999 per QALY.

6. **Reduced drug cost for low-dose patients.**
   As the 90 + 30 mg pills can be split in half for the 45 + 15 mg dose patients (18.6% from the TEMPO 3:4 trial), reducing cost of tolvaptan by 50% for these patients (thus with a weighted cost of [redacted]), incremental cost = $142,019 and incremental QALYs = 0.66, ICUR = $214,318 per QALY.

7. **Short time horizon.**
   To assess the timing of accrual of benefits and costs, shorter time horizons were explored. Note that in the reference case, incremental QALYs = 0.66.

   - 1 year: Incremental cost = $15,780 and incremental QALYs = 0.01; ICUR = $1,389,430
   - 5 years: Incremental cost = $69,273 and incremental QALYs = 0.0728; ICUR = $1,072,959
   - 10 years: Incremental cost = $112,135 and incremental QALYs = 0.17; ICUR = $ 677,649.

8. **Plausible CDR reference case.**
   A new plausible reference case with Canadian costs, higher ESRD utility (0.65), and shorter kidney pain duration (one month with a disutility of [redacted]) is considered. Incremental cost = $178,992 and incremental QALYs = 0.47; ICUR = $386,700 per QALY.
   - Change annual GFR decline from 3.81 mg/mL to 2.81 mg/mL for milder patients, incremental cost = $205,376 and incremental QALYs = 0.43, ICUR = $473,107 per QALY
   - For lower CI (treatment effect 0.597, i.e., –16.1% relative reduction with tolvaptan), incremental cost = $185,329 and incremental QALYs = 0.22, ICUR = $851,892 per QALY
   - For upper CI (treatment effect 1.357, i.e., –52.8% relative reduction with tolvaptan), incremental cost = $175,176 and incremental QALYs = 0.86, ICUR = $203,344 per QALY.

The impact of price reduction both on the manufacturer's submitted base case and the CDR reference case (the aforementioned scenario 8) is provided in Table 3.

TABLE 3: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

	ICURs of Submitted Drug Versus Comparator	
Price	Base-case Analysis Submitted by Manufacturer	Reanalysis by CDR Based on Canadian Costs, Higher ESRD Utility, and Shorter Kidney Pain Duration
Submitted	244,402	386,700
10% reduction	212,053	340,388
20% reduction	179,705	294,077
30% reduction	147,356	247,765
40% reduction	115,007	201,454
50% reduction	82,658	155,142
60% reduction	50,309	108,831
70% reduction	17,961	62,519
80% reduction	Dominant	16,208

CDR = CADTH Common Drug Review; ESRD = end-stage renal disease; ICUR = incremental cost-utility ratio.

Based on the CDR reference case, a 60% price reduction would be required to achieve an ICUR of approximately $100,000 per QALY, and a greater than 73% price reduction for an ICUR of approximately $50,000 per QALY.

4. ISSUES FOR CONSIDERATION

The patent for tolvaptan is currently due to expire in 2019. The possibility of a generic launch at year 5 would reduce the drug cost.

The possibility of splitting the 90 + 30 mg pills for patients on 45 + 15 mg (in 18.6% of patients of TEMPO 3:4) might further reduce the cost of the drug (see CDR reanalysis scenario 6).

There is a spectrum of disease severity regarding risk of progression of renal function to ESRD. The TEMPO 3:4 study included patients who in general would be deemed higher risk. There are no well-defined criteria to identify high- versus low-risk patients, and some tests (such as magnetic resonance imaging [MRI] for total kidney volume [TKV]) are costly and are not standard of care.

As this is the first specific disease-modifying drug for ADPKD, and the side effect profile does not include frequent and/or severe adverse reactions, there is likely to be high demand by both patients and practitioners for this drug.

4.1 Patient Input

Patients report that the most important aspects in the management of polycystic kidney disease (PKD) are to control high blood pressure, kidney function, and to slow the progression of cyst development and growth on both the liver and kidneys. Patients also report the significant impact PKD has on their quality of life and activities of daily living. Quality of life in terms of kidney function is incorporated into the economic model. Patients also report the impact on primary caregivers, as well as travel time and discomfort related to clinic visits, what is assessed via a societal perspective in the submission. The adverse effects caused by tolvaptan include liver monitoring, large fluid intake and frequent urination, tiredness, dry mouth, thirst, and dizziness.

5. CONCLUSIONS

The manufacturer base case suggests tolvaptan results in an additional 0.66 QALYs compared with standard of care, but is $161,955 more costly, driven primarily by drug acquisition costs ($216,460). The manufacturer-stated ICUR is $244,402 per QALY.

The ICUR in a plausible CDR reference case increases when Canadian costs, greater ESRD utility, and shorter kidney pain duration are assumed in the model ($387,000 per QALY). The ICUR further increases if used in a patient group with overall slower progression of disease ($473,000 per QALY), or if drug efficacy is lower ($851,000 per QALY with lower CI).

There is significant uncertainty (regardless of what reference case is used), given the use of a surrogate outcome and the very long time frame over which clinical benefits are estimated.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures.

TABLE 4: COST COMPARISON TABLE FOR TOLVAPTAN

Drug/ Comparator	Strength	Dosage Form	Price[a] ($)	Recommended Use	Average Cost per Year ($)
Tolvaptan (Jinarc)[b]	45 + 15 mg 60 + 30 mg 90 + 30 mg	Tab	[redacted]	Administered twice daily in split-dose regimens of 45 + 15 mg, 60 + 30 mg, or 90 + 30 mg[c]	[redacted]

[a] Price includes cost of 2 tablets of each strength.
[b] Manufacturer's confidential submitted price.
[c] According to these split-dose regimens, the total daily tolvaptan doses are 60, 90, or 120 mg, respectively.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS TOLVAPTAN RELATIVE TO THE STANDARD OF CARE?

Tolvaptan Versus Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$244,402 per QALY $2,318,302 per life-year					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments *Reviewer to provide comments if checking "no"*	None		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 7: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of global model/Canadian model done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

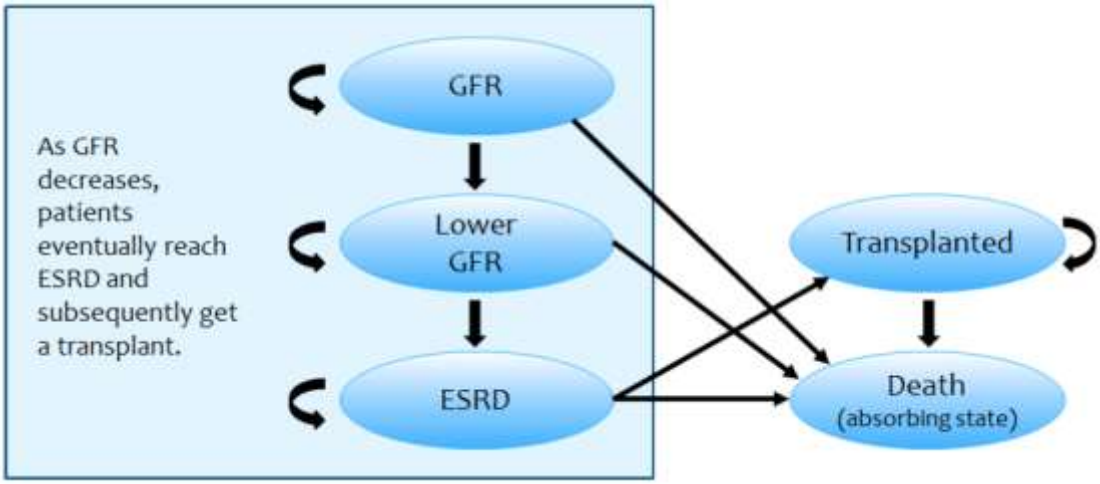
CDR = CADTH Common Drug Review.

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

In the Markov model with annual cycle, patients with autosomal dominant polycystic kidney disease (ADPKD) enter at different chronic kidney disease (CKD) stages (expressed as a glomerular filtration rate [GFR] interval),[2] with the distribution of patients in each CKD health state based on the TEMPO 3:4 trial.[3] Within each Markov cycle, patients can either remain in the same CKD stage or transit to the next one (Figure 1). Some patients will also either obtain a kidney transplant based on the number of patients in the end-stage renal disease (ESRD) stage, or die based on the mortality risk driven by age and CKD stage.

FIGURE 1: HEALTH STATES IN MANUFACTURER MODEL



ESRD = end-stage renal disease; GFR = glomerular filtration rate.
Source: Manufacturer's pharmacoeconomic submission.[2]

Transition probabilities were estimated based on the renal function decline rate observed in the placebo group of the pivotal TEMPO 3:4 trial. Model validation was conducted by comparing the disease progression with a published cost-effectiveness analysis [8] and the CRISP observational study.

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	In the TEMPO 3:4 trial, the tolvaptan group was associated with an average decrease of 2.61 mg/mL per year versus 3.81 mg/mL per year with placebo, a relative treatment effect of 31.6% ($P < 0.001$).	Reasonable. However, a surrogate for hard clinical end points, and uncertain whether efficacy attenuates over time.
Natural history	It was estimated based on the renal function decline rate observed in the placebo group of the pivotal TEMPO 3:4 trial.	Uncertain as the TEMPO 3:4 trial lasts only 3 years. Population treated may differ from population studied.

Data Input	Description of Data Source	Comment
Utilities	As ADPKD-specific utility values are not available, utilities obtained from published studies conducted on CKD in general were used as a proxy.	May overestimate the disutility of more advanced CKD, especially ESRD on dialysis.
AEs	Not modelled except reduced kidney pain.	Thirst and polyuria mentioned from the patient input were not modelled. This might favour tolvaptan.
Kidney transplant	Kidney transplant rate based on actual transplant rates observed in the Canadian ADPKD patient population by age group.	Appropriate.
Mortality	Mortality rates observed in the general CKD population are used as a proxy. The mortality odds ratio observed from the US Renal Data System is combined with the mortality rate by age found in Statistics Canada life tables.	Reasonable assumption.
Costs		
Drug	Cost per day from manufacturer.	
Administration	A wholesale/pharmacy markup of 8% and a dispensing fee of $9.00 were added to the drug cost.	Appropriate.
AEs	A liver monitoring cost of $120 per year was added to the cost of tolvaptan.	Appropriate.
Health state	Direct medical costs for each CKD stage were obtained from an ADPKD-specific study conducted by Knight et al. (2015)[14] on health insurance claims in the United States. These figures were subsequently annualized and adjusted to account for the lower cost of care in Canada. The costs of a renal transplant and post-transplant were obtained from a Canadian study.	Uncertainty in converting US costs to Canadian costs.

ADPKD = autosomal dominant polycystic kidney disease; AE = adverse event; CKD = chronic kidney disease; ESRD = end-stage renal disease.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Treatment effect was assumed to remain constant over the 50-year model horizon.	Uncertain.
Mortality rates and utilities observed in the general CKD population were used as proxies for ADPKD patients.	Uncertain.
Disease progression for ADPKD patients can be captured by CKD stage rather than total kidney volume.	Neither are validated surrogates for hard clinical outcomes such as ESRD. Ascertainment of clinically relevant outcomes would require a much longer trial.

ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; ESRD = end-stage renal disease.

Manufacturer's Results

TABLE 10: TOLVAPTAN ADPKD COST-UTILITY MODEL, BASELINE RESULTS

Discounted Results per Patient Over 50 Years	Tolvaptan	Standard of Care	Difference
Benefits			
Life-years	16.98	16.91	0.07
QALYs	13.87	13.21	0.66
Costs			
Tolvaptan cost	$217,460		
Direct health care cost	$303,644	$0	$217,460
Productivity and travel cost		$359,149	$55,505
Over-unemployment	Not included	Not included	Not included
Travel cost	Not included	Not included	Not included
Total cost	**$521,104**	**$359,149**	**$161,955**
Cost-effectiveness			
ICER life-years			$2,318,302
ICER QALYs			$244,402

ADPKD = autosomal dominant polycystic kidney disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using Monte Carlo simulations and one-way deterministic sensitivity analyses that varied model parameters by using alternative values. A series of one-way sensitivity analyses was conducted by the manufacturer, including: societal perspective (productivity and travel costs); efficacy (20% to 40%); discount rates (2%, 3%, and 0%); 100% treatment compliance; shorter time horizon (25 years); transplant rate (± ~25%); generic launch (70% of drug cost); kidney function decline (95% confidence interval [CI]); mortality odds ratio in ESRD (3.0 to 5.0, base case 3.8649); utility for ESRD (0.5 to 0.65); starting age and CKD stage distribution.

The reference case result for tolvaptan versus standard of care is $244,402 per quality-adjusted life-year (QALY). The following parameters increased/decreased the incremental cost per QALY gained by more than 20%:

- Tolvaptan reduces kidney function decline compared with standard of care by 20% (versus 31.6%): cost per QALY $354,000
- Discount rates 3% cost and 0% benefit: cost per QALY $118,000
- Generic at year 5 at 70% of brand price: cost per QALY $173,000
- Kidney function decline –2.81 mg/mL per year: cost per QALY $301,000
- Starting cohort 30 years, 100% in CKD Stage 1: cost per QALY $294,000
- Starting age 40 years, 50% CKD Stage 3a, 50% CKD Stage 3b: cost per QALY $183,000.

The manufacturer also provided a cost-utility analysis (CUA) from the societal perspective by including productivity and travel costs; incremental cost-utility ratio (ICUR) = $213,000 per QALY.

According to the cost acceptability curve from the probabilistic sensitivity analyses, 0% of ICURs would fall below a $100,000 per QALY threshold and 18% of ICURs would fall below a $200,000 per QALY threshold.

CADTH Common Drug Review Reanalysis

The CADTH Common Drug Review (CDR) considered the following analyses to address the limitations identified earlier as described in section 3.1 of this report, summarized in Table 5.

TABLE 11: SUMMARY OF CADTH COMMON DRUG REVIEW ANALYSES

Scenario		Assumption	Tolvaptan vs. Standard Care		
			Change in Cost	Change in QALYs	ICUR
1	Episodic kidney pain	Manufacturer stated a disutility of [redacted] but applied to 1 month = [redacted]	$161,955	0.50	$321,347
		Episodes of pain are 1 or 2 weeks (disutility [redacted] or [redacted])			$326,399 to $328,604
2	Greater utility score for ESRD on dialysis	Numerically greater utility estimate for patients on dialysis (0.65 vs. base case 0.57[17])	$161,955	0.63	$260,571
3	Canadian cost of care	Direct medical cost from more recent Canadian sources is used[18] with a CKD cost of $16,742 and an ESRD cost of $58,847 (inflated to 2014 Canadian dollars); note, however, that these data are not from ADPKD patients	$178,991	0.66	$270,112
4	Administration in cohort with less severe disease progression	Change annual GFR decline from 3.81 mg/mL to 2.81 mg/mL to simulate patients with less progressive disease	$189,715	0.64	$300,559
		If all patients start in CKD Stage 1 (earlier stage of disease)	$223,693	0.61	$362,673
5	Exploration of uncertainty in relative efficacy	Lower CI: treatment effect 0.597, i.e., –16.1% relative reduction with tolvaptan	$177,686	0.42	$418,938
		Upper CI: treatment effect 1.357, i.e., –52.8% relative reduction with tolvaptan	$143,247	1.05	$135,999
6	Reduced drug cost for low-dose patients	90 + 30 mg pills can be split in half for the 45 + 15 mg dose patients (18.6% from the TEMPO 3:4 trial), reduces cost of tolvaptan by 50% for these patients (thus a weighted cost of [redacted])	$142,019	0.66	$214,318
7	Short time horizon	To assess the timing of accrual of benefits and costs, shorter time horizons were explored: 1 year 5 years 10 years	 $15,780 $69,273 $112,135	 0.01 0.07 0.17	 $1,389,430 $1,072,959 $677,649
8	Plausible CDR reference case	Canadian costs, higher ESRD utility (0.65) and shorter kidney pain duration (1 month with a disutility of [redacted]) — Scenarios 1a, 2, 3	$178,992	0.47	$386,700

ADPKD = autosomal dominant polycystic kidney disease; CDR = CADTH Common Drug Review; CI = confidence interval; CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

APPENDIX 5: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUGS

The draft assessment report from the Evidence Review Group (ERG) of the National Institute for Health and Care Excellence (NICE) assessing tolvaptan (Jinarc) for the treatment of autosomal dominant polycystic kidney disease (ADPKD) is currently available and summarized here. It should be emphasized that this report is the draft version, currently at the public consultation phase. The final report is expected to be published in September 2015.

TABLE 12: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE (May 2015)[19]
Treatment	Tolvaptan (Jinarc) for the treatment of ADPKD.
Price	The cost of tolvaptan in the UK is estimated to be £15,761 (C$32,894[a]) per patient per annum, based on a daily cost of £43.15 (C$90.06[a]) per patient (flat price). The company (Otsuka Pharmaceuticals) has agreed to a patient access scheme with the Department of Health in England. If tolvaptan is recommended, this scheme would provide a simple discount to the list price of tolvaptan.
Similarities with CDR submission	• A lifetime time horizon cost-utility analysis with a cycle length of 1 year and assessing the health care system perspective was submitted, comparing tolvaptan with standard of care. • The model considers 2 main periods, the first capturing disease progression and the second being ESRD encountering dialysis and renal transplant. • The disease evolution and the effect of tolvaptan treatment was based on 3-year trial data (TEMPO 3:4 trial), which were extrapolated to a lifetime. • Utility scores were not available for ADPKD-specific stages, so chronic kidney disease stages were applied for the modelled disease health states, with disutility applied for kidney pain. • Treatment adverse events were not specifically modelled.
Differences from CDR submission	This was a patient-level simulation model (versus a Markov one submitted to CDR) using UK cost estimates. Additional disutility was applied for dialysis complications.
Manufacturer's results	Incremental cost (tolvaptan – standard care): £31,838 (C$66,449[a]); incremental QALYs: 0.92; ICUR: £34,733 (C$72,491[a]) per QALY gained.
Issues noted by the review group	• The population included in the TEMPO 3:4 trial may be limitedly generalizable to the UK patient population that may be prescribed tolvaptan. • The applications of disease evolution and of the effect of tolvaptan treatment in the model are not conservative and are favouring tolvaptan. • The application of treatment discontinuation for tolvaptan is not conservative and is favouring tolvaptan. • The utility scores used for the disease health states are highly uncertain for ADPKD-specific stages; the application of some disutility weights is likely to be associated with double-counting favouring tolvaptan. • A trial sponsored by the manufacturer is currently ongoing (OUVERTURE) with interim results collected. This trial is collecting EQ-5D data in patients with ADPKD, and the use of this data for utility scores could increase the credibility of the cost-utility results. • Treatment adverse events were not specifically modelled; this is an important omission, especially considering the hepatotoxicity cases reported from the tolvaptan clinical program.

	NICE (May 2015)[19]
	• The mortality estimates and some cost components used are not conservative and are favouring tolvaptan.
Results of reanalyses by the review group (if any)	• ERG preferred base case including variation of disease progression, and variation of some utilities, some costs, and the probability values for kidney pain = incremental cost (tolvaptan – standard care): £37,956 (C$79,218[a]); incremental QALYs: 0.59; ICUR: £64,515 (C$134,649[a]) per QALY gained. • ERG worst-case scenario (most conservative case against tolvaptan) = incremental cost (tolvaptan – standard care): £32,095 (C$66,985[a]); incremental QALYs: 0.44; ICUR: £73,705 (C$153,830[a]) per QALY gained.
Recommendation	"Tolvaptan is not recommended within its marketing authorization for treating autosomal dominant polycystic kidney disease to slow the progression of cyst development and renal insufficiency in adults who have chronic kidney disease Stages 1 to 3 at the start of treatment and evidence of rapidly progressing disease."

ADPKD = autosomal dominant polycystic kidney disease; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions Questionnaire; ERG = Evidence Review Group; ESRD = end-stage renal disease; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year.
[a] Exchange rate from UK pound sterling to Canadian dollar (25 August 2015): 2.0871 (http://www.bankofcanada.ca/rates/exchange/daily-converter/).

APPENDIX 6: SUMMARY OF OTHER PUBLISHED ECONOMIC EVALUATIONS

A cost-effectiveness analysis comparing tolvaptan with placebo in patients with early autosomal dominant polycystic kidney disease (ADPKD) (defined by an estimated glomerular filtration rate [eGFR] of 80 mL/min/1.73 m^2) was published in 2013 by Erickson et al.[8] at Stanford University, funded by National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ). The study used a similar model as the one in the manufacturer's submission. Table 13 summarizes the similarities and differences between the two models.

TABLE 13: COMPARISON BETWEEN ERICKSON ET AL. AND MANUFACTURER'S SUBMITTED MODEL

	Erickson et al.	Manufacturer
Model	Markov model with 3-month cycle, with patients progressing from CKD Stages 2 to 5	Markov model with annual cycle, with patients progressing from CKD Stages 1 to 5
Discount rate	3%	5%
Setting	US	Canada
Starting age	40	40
Kidney transplant modelled	No	Yes CIHI/CORR and costing from Canadian study (Barnieh 2011)[16]
Benefits and side effects modelled	Liver monitoring costs twice a year	Monthly liver monitoring costs and reduction of kidney pain (improvement in QALY)
Efficacy	TEMPO 3:4	TEMPO 3:4
Mortality	CKD Stage-specific mortality (Go 2004[20]) and US life table	CKD Stage-specific mortality (US Renal Data System 2013)[5] and Canadian life table
Drug cost	Tolvaptan costs included medication, laboratory, and clinical follow-up. Liver enzyme levels were monitored twice a year (annual cost of $62.8 [C$82.8[a]]). A factor of 0.64 to convert average wholesale prices to lowest prices (monthly cost of $5,760 [C$7,591[a]], translates to a daily cost of $192 [C$253[a]]).	[redacted] per day with 8% markup and $9 dispensing fee. A liver-monitoring cost of $120 per year was added to the cost of tolvaptan.
Compliance rate	84.6%	90%
Direct medical costs	No cost associated with Stage 2, cost obtained from study on CKD patients (Smith 2007[21])	Costs obtained from ADPKD-specific study (US) (Knight 2005),[14] and converted to Canadian dollars (Tousignant 2013)[15]

	Erickson et al.	Manufacturer
QALY	Obtained from study on CKD patients (Gorodetskaya 2005)[10]	Obtained from study on CKD (Gorodetskaya 2005),[10] ESRD patients (McFarlane 2006), and patients with kidney transplant (Laupacis 1996)[12]
Results	US$744,100 (C$980,649[a])/QALY (2010 $) Subgroup analyses: Men $769,500 (C$1,014,124[a])/QALY Women $720,600 (C$949,679[a])/QALY	C$244,402/QALY (2014 $)

ADPKD = autosomal dominant polycystic kidney disease; CIHI = Canadian Institute for Health Information; CKD = chronic kidney disease; CORR = Canadian Organ Replacement Register; ESRD = end-stage renal disease; QALY = quality-adjusted life-year.
[a] Exchange rate from US to Canadian dollar (1 September 2015): 1.3179 (http://www.bankofcanada.ca/rates/exchange/daily-converter/).
Note: Differences in results between the published report and the manufacturer model may be due to differences in drug acquisition cost. When the cost used in the reference case for Erickson (US$192, approximately C$250) and same discount rates (3%) are used in the manufacturer model, the ICUR is C$1.5M per QALY (compared with $744,100/QALY in 2010 US dollars).

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