CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

TOLVAPTAN
(Jinarc — Otsuka Canada Pharmaceutical Inc.)
Indication: Autosomal Dominant Polycystic Kidney Disease

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tolvaptan not be listed to slow the progression of kidney enlargement in patients with autosomal dominant polycystic kidney disease (ADPKD).

Reasons for the Recommendation:

1. In one randomized, double-blind study (TEMPO 3:4, N = 1,445), the annual percentage change in total kidney volume (TKV) for patients with ADPKD was statistically significantly less with tolvaptan compared with placebo (2.8% versus 5.5%). However, the relationship between this finding and outcomes of clinical importance, including the need for dialysis and renal replacement therapy, and the extent to which these changes are maintained over the lifetime of the patient are uncertain.
2. The use of tolvaptan in patients with ADPKD is associated with important safety issues including liver injury, hypernatremia, increases in uric acid and gout, polyuria and thirst, [redacted], and skin cancers.

Of Note:

- Patient groups noted that there is an unmet need for an ADPKD treatment that will delay the need for dialysis and kidney transplantation and improve the quality of life of patients. CDEC considered the patient group input and acknowledged their unmet need; however, there is insufficient evidence to demonstrate that treatment with tolvaptan will lead to improvements in the endpoints of greatest importance to patients.

Background:
Tolvaptan is a selective vasopressin V2 receptor antagonist indicated to slow the progression of kidney enlargement in patients with ADPKD. Tolvaptan is available as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg tablets. Tolvaptan should be administered in two daily doses approximately eight hours apart: 45 mg + 15 mg (60 mg per day), 60 mg + 30 mg (90 mg per day), or 90 mg + 30 mg (120 mg per day).

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials and pivotal studies of tolvaptan in patients with ADPKD, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients with ADPKD.

Patient Input Information
One patient group, the Polycystic Kidney Disease Foundation of Canada, responded to the CDR call for patient input. Information was obtained through personal knowledge, patient telephone interviews, and an online survey. The following is a summary of information that was received:

- ADPKD affects every aspect of patients' lives and can prevent them from participating in normal daily activities. Patients report suffering from fatigue, anxiety, high blood pressure, abdominal distension, back pain, abdominal pain, and liver cysts. In addition, respondents identified additional key issues associated with polycystic kidney disease (PKD), including having to wrap bandages around their abdomens daily to prevent pain and/or hernias, limitations on physical tasks, social stigma, and the emotional consequences of the way they look.
- Caregivers of those with PKD are faced with a number of challenges, including financial hardships, intimacy issues, changes in lifestyle, physical challenges, and fear of the consequences that this condition may have on their loved one.
- Patient input emphasized the importance of having treatments that delay the progression of PKD and/or prevent it from developing in the first place and stressed that no therapies other than tolvaptan are approved for the treatment of ADPKD.
- Patients expect tolvaptan will delay the need for dialysis and kidney transplantation, prolong their lives, and improve their quality of life. They also noted the challenges of using tolvaptan, which requires a very large daily intake of fluids and results in increased urination, dry mouth, thirst, and other adverse effects.

Clinical Trials
The CDR systematic review included one phase 3, randomized, double-blind, placebo-controlled trial. TEMPO 3:4 (N = 1,445) was a pivotal trial that evaluated the efficacy and safety of tolvaptan for ADPKD. Adult patients with ADPKD were randomized (2:1) to receive tolvaptan or placebo. Tolvaptan was administered in a split-dose morning and afternoon regimen starting at 45 mg + 15 mg. The dose was increased weekly based on patient tolerability to 60 mg + 30 mg and then to 90 mg + 30 mg. Patients continued on the highest tolerable dose for up to 36 months.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- TKV — change from baseline assessed by magnetic resonance imaging (MRI) at months 12, 24, and within two weeks before or after 36 months.
- Time to clinical progression — defined as worsening kidney function based on a 25% reduction in the reciprocal of serum creatinine (SCr); clinically significant kidney pain that required medical leave, pharmacologic treatment, or invasive intervention; worsening hypertension; or worsening albuminuria.

- Kidney function — change in the slope of kidney function from post-dose baseline to last on-drug trial visit, ascertained by the reciprocal of SCr. Exploratory analyses were also conducted using the estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD-EPI}$) equation and the Modification of Diet in Renal Disease ($eGFR_{MDRD}$) equation, and estimated creatinine clearance (eCrCl) with the Cockcroft-Gault equation.
- Blood pressure:
  - For patients who were non-hypertensive at baseline, change from baseline in mean arterial pressure and time to progression to high prehypertension (systolic blood pressure [SBP] > 129 mm Hg and/or diastolic blood pressure [DBP] > 84 mm Hg), hypertension (SBP > 139 mm Hg and/or DBP > 89 mm Hg), or requiring antihypertensive therapy.
  - For patients taking antihypertensive therapy at baseline, percentage with clinically sustained decrease in blood pressure leading to sustained reduction in antihypertensive therapy compared with baseline.
- Change from baseline in kidney pain as assessed with a Likert scale of 0 to 10, with 0 representing no pain (recall period: four months) in patients not taking pain medications at baseline.

The primary outcome was the percentage annual rate of change in TKV.

Efficacy

- Treatment with tolvaptan statistically significantly delayed the time to the composite outcome of clinical progression compared with placebo (incidence rate 43.94 versus 50.04 events per 100 person-years). This result was driven by fewer events of kidney function decline and clinically relevant episodes of kidney pain with tolvaptan. Hazard ratios for time to these events were:
  - Clinical progression: 0.87 (95% confidence interval [CI], 0.78 to 0.97)
  - Kidney function decline: 0.39 (95% CI, 0.26 to 0.57)
  - Worsening kidney pain: 0.64 (95% CI, 0.47 to 0.89)
  - Worsening hypertension: 0.94 (95% CI, 0.81 to 1.09)
  - Worsening albuminuria: 1.04 (95% CI, 0.84 to 1.28).
- Compared with placebo, the annual percentage increase in TKV was statistically significantly lower with tolvaptan (2.8% versus 5.5%, 49.2% reduction in growth rate). The difference in slope was −2.7% per year (95% CI, −3.3 to −2.1).
- There was statistically significantly less decline in kidney function with tolvaptan compared with placebo, as measured by the slope of reciprocal of SCr, $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and eCrCl. The mean differences for tolvaptan and placebo for these end points were:
  - Reciprocal of SCr: 1.20 mg/mL^{-1} per year (95% CI, 0.62 to 1.78)
  - $eGFR_{CKD-EPI}$: 0.98 mL/min/1.73 m^2 per year (95% CI, 0.60 to 1.36)
  - $eGFR_{MDRD}$: [redacted]
  - eCrCl: [redacted]
- There was no statistically significant difference in mean change from baseline in kidney pain scores between tolvaptan and placebo in patients not taking pain medication at baseline (mean difference −0.08; 95% CI, −0.20 to 0.03).

Harms (Safety and Tolerability)

- Serious adverse events were experienced by 18.4% of patients in the tolvaptan group and 19.7% of patients in the placebo group. More patients in the tolvaptan group experienced serious adverse events related to elevations in liver enzymes (2.2% versus 0.8%), chest pain (0.8% versus 0.4%), and headache (0.5% versus 0). Basal cell carcinoma was more frequent in the tolvaptan group (0.8% versus 0.2%).
- Nearly all patients experienced at least one adverse event (97.9% in tolvaptan group and 97.1% in placebo group). More patients in the tolvaptan group experienced alanine aminotransferase and aspartate aminotransferase elevation greater than 2.5 times the upper limit of normal (4.9% versus 1.2% and 3.2% versus 0.8%, respectively). Hypernatremia (serum sodium > 150 mmol/L) occurred in 4% of patients receiving tolvaptan and 1.4% of patients receiving placebo. The following adverse events were more commonly reported for patients receiving tolvaptan compared with placebo: clinically significant increases in uric acid (6.2% versus 1.7%), gout (2.9% versus 1.4%), polyuria (38.3% versus 17.2%), and thirst (55.3% versus 20.5%).
- More patients receiving tolvaptan withdrew from the trial due to adverse events (15.4% versus 5.0%). The most common adverse event leading to withdrawal of tolvaptan was polyuria ([redacted]), followed by pollakiuria ([redacted]), nocturia ([redacted]), thirst ([redacted]), abnormal liver function ([redacted]), and fatigue ([redacted]).

Cost and Cost-Effectiveness

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 public payer. Disease progression in terms of chronic kidney disease (CKD) stages and relative efficacy with tolvaptan were obtained from the TEMPO 3:4 trial. Other inputs, such as costs and quality of life, were obtained from published literature.

CDR identified a number of limitations with the manufacturer's pharmacoeconomic submission:

- Disease progression was modelled by estimating the decline in kidney function over time using observed changes in kidney function from TEMPO 3:4. While change in eGFR is a correlate, its relationship with clinically important outcomes (such as the time to end-stage renal disease [ESRD]) is not clearly defined.
- The model assumes that differences in loss of kidney function observed in the three-year TEMPO 3:4 trial can be extrapolated to a lifetime time horizon. If efficacy attenuates over time, the incremental cost-utility ratio (ICUR) may be underestimated.
- The relative efficacy of tolvaptan is assumed to be constant across all CKD stages in the model. Evidence from TEMPO 3:4 suggests that the treatment effect may vary by kidney volume and different patient characteristics.
- US cost data were used to inform direct medical costs in the model. Although the values are adjusted to estimate the lower cost in Canada, it may not truly reflect the cost of care in Canada.
- The model incorporates a reduction in kidney pain and applies this for the entire model duration (i.e., 50 years). The trial outcome was defined as clinically important "episodes" of kidney pain, implying that the reduction was acute pain, as opposed to chronic pain, associated with ADPKD. Applying a constant lifelong disutility may overestimate the impact of episodes of kidney pain and overestimate the benefit of decreasing its frequency.

- 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, and may have a higher utility than other ESRD patients. Overestimating the disutility of ESRD may favour tolvaptan.

The manufacturer suggests in its base case that tolvaptan is associated with an ICUR of $244,402 per quality-adjusted life-year (QALY) when compared with standard of care. When CDR considered Canadian costs, a greater ESRD utility, and a shorter duration of kidney pain in the model, it resulted in an ICUR of $387,000 per QALY. The ICUR further increased when considering a patient group with overall slower progression of disease ($473,000 per QALY), or if drug efficacy was assumed to be lower ($851,000 per QALY).

[redacted].

Other Discussion Points:

CDEC noted the following:

- The product monograph states that, to help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of tolvaptan, then continued monthly for 18 months, every three months for the next 12 months, and then every three to six months thereafter during treatment with tolvaptan.
- CDEC noted that TKV, the primary endpoint of TEMPO, was not adjusted for the height and age of the patient. This is an important limitation of the study design and limited the ability of CDEC to interpret the clinical relevance of this endpoint.
- The open-label extension study, TEMPO 4:4, reported sustained reduction in eGFR slope in patients continuing on tolvaptan and decelerated slope in patients switched to tolvaptan over an additional two year period. However, serious limitations for the findings of the extension study include the non-randomized and open-label design, the small and highly selected population, and only data from an interim analysis were available for review, therefore, the conclusion that treatment effect persists seems premature and highly uncertain.
- CDEC noted that the National Institute for Health and Care Excellence (NICE) recommended tolvaptan as a possible treatment for ADPKD, for patients with the following clinical criteria: they have chronic kidney disease stage 2 or 3 at the start of treatment and there is evidence of rapidly progressing disease. CDEC noted that there is currently no standard definition of rapidly progressing ADPKD; therefore, the committee discussed published criteria (Irazabal et al., 2014) for identifying patients with rapidly progressing ADPKD with a clinical expert. It was acknowledged that, at present, there would be practical challenges with applying these criteria to identify patients who should receive tolvaptan in clinical practice. CDEC concluded that a recommendation based on the identification of rapidly progressing patients would create challenges for the jurisdictions to consistently implement. In addition, the relative cost-effectiveness of tolvaptan in such a patient population could not be evaluated based on the available data.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- Long-term clinically relevant outcomes in the context of a disease that evolves slowly over many years are not yet available. The relationship between the primary trial outcome of TKV and long-term outcomes such as ESRD and renal replacement is not clear.
- Data for clinically important outcomes such as mortality, delaying dialysis, disease complications, quality of life, hospitalization, extra-renal complications, and infections are not yet available.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets:
October 21, 2015: Three CDEC members were unable to attend this portion of the meeting.
February 16, 2016: Four CDEC members were unable to attend this portion of the meeting.

Conflicts of Interest:
None.

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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