Technology Guidance

Tolvaptan

for treating autosomal dominant polycystic kidney disease

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended tolvaptan for inclusion on the MOH List of Subsidised Drugs for treating autosomal dominant polycystic kidney disease (ADPKD). The decision was based on the uncertain extent of clinical benefit, and because tolvaptan was unlikely to represent a cost-effective use of healthcare resources for treating ADPKD.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of tolvaptan for treating autosomal dominant polycystic kidney disease (ADPKD). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions (PHIs) and patient experts from local patient and voluntary organisations. Published clinical and economic evidence for tolvaptan was considered in line with its registered indication.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. The Committee noted that ADPKD is a hereditary condition characterised by renal cyst formation, kidney enlargement, hypertension, and renal function impairment. Around 50% of patients with ADPKD progress to end-stage renal disease (ESRD) by the age of 50 to 60 years.

2.2. Tolvaptan is a vasopressin antagonist that slows the development of renal cysts and renal insufficiency in patients with ADPKD. In local clinical practice, blood pressure control with renin-angiotensin-aldosterone system (RAAS) inhibitors represents the current standard management for ADPKD. Tolvaptan would be used in addition to RAAS inhibitors.

2.3. The Committee considered 33 testimonials from local patients and carers about their lived experiences with polycystic kidney disease and the treatments they had received. The Committee acknowledged that people with polycystic kidney disease tired easily and experienced symptoms that often led to anxiety, disturbed sleep, and a poorer quality of life. Many patients were undergoing haemodialysis treatment which they found effective and with manageable side effects. However, they noted

that the long treatment times and frequent sessions significantly impacted daily activities, relationships, work, and ability to travel overseas.

2.4. The Committee noted that while most respondents surveyed were not familiar with tolvaptan, they considered that any new treatments should be more affordable, enable them to perform daily activities, maintain kidney function, provide them with enough energy to travel overseas, and delay or prevent progression to haemodialysis.

Clinical effectiveness and safety

3.1. The Committee reviewed published clinical evidence from two randomised controlled trials comparing tolvaptan with placebo, as an addition to standard management, in patients with ADPKD and either CKD stages 1 to 3 (TEMPO 3:4 trial) or CKD stages 2 to 4 (REPRISE trial) at baseline.

3.2. In both trials, tolvaptan demonstrated statistically significant reductions in the rate of estimated glomerular filtration rate (eGFR) decline compared to placebo. In the TEMPO 3:4 trial, tolvaptan also demonstrated benefits on a composite outcome of clinical progression compared to placebo. These benefits were driven by effects on kidney function decline and kidney pain.

3.3. Nonetheless, the Committee acknowledged that the extent of long-term clinical benefit from tolvaptan treatment was uncertain, given the lack of data on disease progression to ESRD. They also considered that the generalisability of trial results to the local setting was unclear, given variability in trial populations. Specifically, patients recruited in the REPRISE and TEMPO 3:4 trials differed significantly in terms of baseline CKD stage and definition of rapidly progressing disease.

3.4. The Committee noted that, compared to placebo, tolvaptan was associated with a higher incidence of adverse events due to increased aquaresis (polyuria, polydipsia, nocturia, and urinary frequency) and a higher risk of idiosyncratic hepatotoxicity. They considered that tolvaptan was inferior in safety compared to current standard management.

Cost effectiveness

4.1. No local cost-effectiveness studies were identified for tolvaptan in patients with ADPKD. The Committee reviewed economic evaluations from overseas HTA agencies which considered that the cost-effectiveness of tolvaptan compared to standard of care was highly uncertain due to limitations in clinical evidence, and a price reduction was required to ensure cost-effectiveness.

4.2. The Committee concluded that tolvaptan was unlikely to represent a cost-effective

use of healthcare resources in Singapore, given that the price of tolvaptan was higher than prices in overseas reference jurisdictions.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first 5 years of listing tolvaptan on the MOH List of Subsidised Drugs for treating ADPKD.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing tolvaptan on the MOH List of Subsidised Drugs for treating ADPKD. The decision was based on the uncertain extent of clinical benefit, and because tolvaptan was unlikely to represent a cost-effective use of healthcare resources for treating ADPKD.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

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The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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