Cost-effectiveness of tolvaptan (Jinarc®) for the treatment of autosomal dominant polycystic kidney disease (ADPKD)

The NCPE has issued a recommendation regarding the cost-effectiveness of tolvaptan (Jinarc®). Following assessment of the applicant's submission, the NCPE recommends that tolvaptan (Jinarc®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Otsuka) economic dossier on the cost effectiveness of tolvaptan (Jinarc®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics
The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics   **September 2018**

Summary

In February 2018, Otsuka submitted a dossier to examine the cost-effectiveness of tolvaptan (Jinarc®) under the High Tech Drug Arrangements for Autosomal Dominant Polycystic Kidney Disease (APKD). ADPKD is an inherited form of kidney disease characterised by the progressive development of numerous renal cysts. As they enlarge, functional tissue is destroyed and replaced by fibrosis which leads to renal function decline. There is a high degree of inter and intra familial variability in disease course. Approximately 70% of patients will eventually progress to end stage renal disease (ESRD).

Tolvaptan is a vasopressin 2 receptor antagonist. Vasopressin continuously promotes cellular proliferation and fluid accumulation into cysts and is a dominant factor controlling the rate of cyst and kidney enlargement in ADPKD. At the time of submission, tolvaptan was licensed for rapidly progressing patients with autosomal dominant polycystic kidney disease for initiation of therapy in chronic kidney disease (CKD) stage 1-3 only. Since then, the license was extended to include treatment initiation in CKD stage 4. In their submission, the applicant has only applied for reimbursement for a subgroup of the licensed population – initiation of therapy in rapidly progressing patients with ADPKD in CKD stage 2 or 3 only. Tolvaptan is available in 15mg, 30mg, 45mg, 60mg and 90mg tablets. The starting dose is 45mg am +15mg pm. Patients are titrated up to 60mg am + 30mg pm and finally 90mg am + 30mg pm if tolerated with at least weekly intervals between titrations. The initial dose is administered orally 30 minutes before breakfast and the second dose 8 hours later with or without food.

1. Comparative effectiveness of tolvaptan

Design and Methods

The principal evidence base for tolvaptan in ADPKD comes from TEMPO 3:4 and REPRISE - two phase three, double blind, multicentre randomised controlled trials. In TEMPO 3:4 eligibility criteria included thresholds for age, creatinine clearance and total kidney volume. REPRISE eligibility criteria defined estimated glomerular filtration rate (eGFR) eligibility thresholds stratified by age. Both sets of inclusion criteria were designed to enrich the population for rapidly progressing disease. Renal function criteria in TEMPO 3:4 approximately equates to CKD stage 1-3a (3% of patients in TEMPO 3:4 were in stage 3b). The eGFR criteria in REPRISE included patients in late CKD stage 2 to CKD stage 4.

Unlike TEMPO 3:4, REPRISE included a run in period before the treatment phase designed to identify patients who could tolerate tolvaptan and to minimise withdrawal in the randomised phase. Patients in both trials were randomised to tolvaptan or placebo. The treatment phase was 36 months for TEMPO 3:4 and 12 months for REPRISE.

Results

In TEMPO 3:4, 961 patients were randomised to tolvaptan and 484 to placebo. Baseline characteristics were balanced. Over the three year period, total kidney volume increased by 2.8% per year (95% Confidence Interval (CI), 2.5 to 3.1) with tolvaptan versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo (Primary Endpoint). The treatment difference was -2.7 percentage points per year (95% CI,-3.3 to -2.1, p < 0.0001)

In REPRISE, 683 patients were randomised to tolvaptan and 687 to placebo. The mean change in eGFR at 1 year with adjustment for the duration of the trial for each patient and interpolated to 1 year was -2.34 ml/min/1.73m^2 (95% CI, -2.81 to -1.87) in the tolvaptan group as compared with -3.61 ml/min/1.73m^2 (95% CI, -4.08 to -3.14) in the placebo group. Tolvaptan resulted in a slower decline than placebo in the eGFR at one year (Primary Endpoint: difference 1.27ml/min/1.73m^2; 95% CI, 0.86 to 1.68). The Review Group calculate that this equates to a percentage reduction of 35% in the rate of eGFR decline.

Results of selected secondary endpoints is presented in Table 1.

Table 1 Summary of Tolvaptan Randomised Controlled Trial results

	TEMPO 3:4		REPRISE	
	Description	Result	Description	Result
Key Secondary Endpoint	Composite of time to clinical progression	HR, 0.87; (95% CI 0.78-0.97, p=0.01)	Mean Slope of the changes in the eGFR that was derived from individual slopes for each patient, with adjustment for the duration of the observations and with interpolation to 1 year.	Difference 1.01ml/min/1.73m^2 (95% CI 0.62 to 1.40), P<0.001 Percentage Treatment Effect :24%*
Secondary Endpoint	Effect of tolvaptan vs. placebo on renal function decline from end of dose titration to month 36 measured using 1/SCr	Absolute Treatment Effect: 1.20 [mg/ml]$^{-1}$ (95% CI 0.62,1.78 p<0.0001) Percentage Treatment effect: 31.6% (95% CI Not reported)		
CI, Confidence Interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; m, metre; min, minute; ml, millilitre; SCr, Serum Creatinine.				
* Calculated by Review Group				

The Review Group identified a number of limitations in the clinical evidence presented. Discontinuation rates in TEMPO 3:4 were high and imbalanced with only 77% of patients in the tolvaptan arm and 86.2% of patients in the placebo group completing the trial. Therefore treatment effects were biased for tolvaptan as adjustments were not made for the length of time patients were in the trial. The focus of this assessment is the subgroup of

the population in CKD stage 2 to 3 but the trial was not powered for the assessment of treatment effect in subgroups. The clinical evidence shows that tolvaptan slows the rate of kidney function decline, however the precise magnitude of the results varied considerably depending on the kidney function measure used and the statistical measures employed. Therefore the precise magnitude of the treatment effect is associated with uncertainty.

2. Safety of tolvaptan

Safety information presented by the applicant focused on the TEMPO 3:4 trial**.** Adverse events led to more discontinuations in the tolvaptan group than in the placebo group. Rates of adverse events in TEMPO 3:4 (97.9% tolvaptan, 97.1% placebo) were similar in both arms although the adverse event profile differed. The most common adverse events observed with tolvaptan were thirst, polyuria, nocturia, pollakiuria, dry mouth and polydipsia. For serious treatment–emergent adverse effects, the incidence was similar for patients treated with tolvaptan or placebo (18.4% vs 19.7%). No patient died during trial participation.

A greater proportion of patients who received tolvaptan had elevations of liver enzyme levels. Two patients on tolvaptan in TEMPO 3:4 (0.2%), met the definition of a Hy's law case. In TEMPO 3:4, liver function monitoring was only conducted every 4 months. In REPRISE, liver function monitoring was conducted monthly and tolvaptan was interrupted/discontinued if liver function abnormalities were seen. There were no Hy's law cases seen in the REPRISE study. The applicant proposed that this may be due to the more frequent liver function monitoring regimen adopted. At the time of applicant submission, a risk management plan for tolvaptan was in the process of being agreed between the applicant and the HPRA which includes monthly liver function tests. Detailed advice is provided in the Summary of Product Characteristics. A post-authorisation safety study (PASS) is underway to characterise and quantify the risk of idiosyncratic liver injury in patients with ADPKD who are treated with tolvaptan in clinical practice.

3. Cost effectiveness of tolvaptan

Methods

A cost-utility analysis comparing tolvaptan versus standard of care (corresponding to the placebo arm of TEMPO 3:4) was conducted under the HSE perspective. A societal perspective was considered in scenario analysis. An individual patient level simulation model was presented in Microsoft Excel®. Stochastic uncertainty was modelled in the base-case and parameter uncertainty was modelled in probabilistic sensitivity analysis. The Review Group were concerned that patient heterogeneity was not modelled given that the

model was built as a patient level simulation model.

The model was divided into two distinct modules: ADPKD progression module and ESRD module. In the ADPKD progression module, disease progression was measured using eGFR. Rate of progression were predicted from regression equations from the placebo arm of TEMPO 3:4. Health states corresponding to CKD stage 2, 3, and 4 were retrofitted to the predicted eGFR values. On reaching the eGFR threshold for ESRD, patients entered the ESRD module to the CKD stage 5 pre-renal replacement therapy health state. As eGFR declined further, patients were modelled to receive conservative care, dialysis and transplant. Patient transitions to death were possible from all health states.

In line with the licensed indication for tolvaptan, patients were modelled to receive tolvaptan or standard of care until the CKD stage 5 pre renal replacement health state was reached. Patients who discontinued treatment were modelled to no longer accrue the costs or benefits of therapy. The applicant applied eGFR declines directly from TEMPO 3:4 for years 1-3. After year 3, the applicant applied a percentage relative treatment effect in annual eGFR decline versus placebo of 30% derived from eGFR (measured using the CKD Epidemiology Collaboration equation) from patients in CKD stage 2 or 3 in TEMPO 3:4

The Review Group had a number of concerns regarding the economic model including the derivation and application of regression equations used to predict progression and the treatment and extrapolation of survival data for patients on renal replacement therapy.

Cost data applied was based on data obtained from systematic literature review, HSE Ready Reckoner and the National Renal Office. Health Related Quality of Life was not measured in the pivotal clinical trials. The applicant sourced utility values from a systematic literature review. The Review Group were concerned that ESRD utility values were not ADPKD specific and may be capturing co-morbidities associated with CKD which may be more likely to occur with non-inherited forms of CKD.

Results

The Review Group made a number of changes to the model parameters in their preferred base case, including adjusting modelled patient characteristics, adjusting background costs in post-transplant patients, adjusting haemodialysis access costs, applying a disutility value to account for the adverse effects associated with tolvaptan, adjusting mortality rates in the pre-ESRD states, adjusting the annual cost of treatment for different pack sizes and applying an excess cost in year 1 to account for the extra costs associated with dose titration. Under the NCPE preferred base case, the Review Group estimated the ICER of tolvaptan versus standard of care as €253,287/QALY (Incremental costs, €147,749, Incremental QALYS 0.58). In the final applicant base case, the ICER was €223,527/QALY

(Incremental Costs €121,506, Incremental QALYs, 0.54). Under NCPE and applicant assumptions, tolvaptan is not cost effective at thresholds of €20,000/QALY or €45,000/QALY.

Under applicant assumptions, tolvaptan is modelled to delay the time to ESRD by 2.3 years and lead to a reduction of 2 months in the length of time spent on dialysis (as compared to standard of care.).

Sensitivity analysis

Probabilistic ICERS versus standard of care were marginally lower than the deterministic ICERs presented above: €244,766/QALY and €220,267/QALY under the NCPE and applicant preferred assumptions respectively. Under applicant and NCPE assumptions, the probability of cost-effectiveness at thresholds of €20,000/QALY and €45,000/QALY is zero. Under the NCPE preferred assumptions, decreasing and increasing the treatment effect of tolvaptan (across the expected 95% confidence intervals) results in an increase in the ICER by 48% and a decrease in the ICER by 21% respectively.

4. Budget impact of tolvaptan

The applicant has proposed five different presentations of tolvaptan for reimbursement including 56 tablet packs (containing 90mg+30mg tablets or 60mg+30mg tablets or 45mg+15mg tablets); each pack equating to 28 days supply. Also, 7 tablet packs (containing 30mg or 15mg tablets) are intended for dose titration and dose adjustment. The 56 tablet packs are approximately flat priced. The proposed price to wholesaler of the 60mg+30mg x 56 tablet pack is €1,489. The Review Group applied a weighted average cost of the 56 tablet packs (based on usage patterns in TEMPO 3:4) in the NCPE base case. The updated average annual cost per-patient is €20,681.21 (including 8% wholesale mark-up, mandatory rebate and patient care fee).The Review Group calculate an annual cost of €22,099.77 in year 1 which includes plausible extra costs associated with dose titration.

Under the NCPE preferred assumptions, the NCPE project a gross drug budget impact of €2.0 million in year 1 rising to €4.1 million in year 5 for a five year cumulative gross drug budget impact of €17.8 million. The net drug budget impact is expected to be equivalent to the gross drug budget impact.

5. Patient Submissions
No patient submissions were received.

6. Conclusion

The applicant has applied for reimbursement in a subgroup of the licensed population – initiation of therapy in rapidly progressing patients with ADPKD in CKD stage 2 or 3. The clinical evidence has demonstrated the ability of tolvaptan to reduce the rate of renal function decline. Therefore tolvaptan is expected to delay rather than remove the need for renal replacement therapy. However the precise magnitude of benefit is uncertain as the measurement of treatment effect varied depending on the measurement of renal function employed and the statistical methods used to analyse the data. There is a very low probability of cost-effectiveness and a high probability that the ICER far exceeds the cost-effectiveness thresholds for existing treatments. The NCPE recommends that tolvaptan not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Goods) Act 2013.