



Cost-effectiveness of patiromer (Veltassa®) for the treatment of hyperkalaemia

The NCPE has issued a recommendation regarding the cost-effectiveness of patiromer (Veltassa®). Following assessment of the applicant's submission, the NCPE recommends that patiromer (Veltassa®) not be considered for reimbursement. 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 (Vifor) economic dossier on the cost effectiveness of patiromer (Veltassa®). 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.

Summary

In April 2018, Vifor submitted a dossier to examine the cost-effectiveness of patiromer (Veltassa®) under the community drug schemes. Patiromer is licensed for the treatment of hyperkalaemia in adults. There is no universal consensus definition of what serum potassium level constitutes hyperkalaemia. Various arbitrary cut-offs such as >5, >5.5 or >6 mmol/L are used to denote different levels of severity.

Patiromer (Veltassa®) is a non-absorbed, cation exchange polymer that contains a calcium sorbitol counter ion. It increases faecal potassium excretion through binding of potassium in the gastrointestinal tract in exchange for calcium. This results in a reduction in the concentration of free potassium in the gastrointestinal tract and leads a reduction of serum potassium levels.

While the license for patiromer is broad, the applicant's submission pertained to the use of patiromer in a single scenario: patients with chronic kidney disease (CKD) stage 3-4 and receiving renin angiotensin aldosterone (RAAS) inhibitors who experience hyperkalaemia defined as a serum potassium (K+) level from 5.5 to <6.5mmol/L. The applicant positions patiromer treatment as an alternative to RAAS inhibitor dose reduction or discontinuation in these patients.

1. Comparative effectiveness of patiromer

OPAL-HK was an international, multicentre, single blind, phase III trial to evaluate the safety and efficacy of patiromer for the treatment of hyperkalaemia. The study was carried out in two sequential parts over 12 weeks.

The treatment phase (Part A), was a single blind, single arm trial of patiromer for four weeks. Patients were eligible for inclusion if they had stage 3 or 4 CKD, a serum K+ of 5.1 to <6.5mmol/L and were receiving a stable dose of RAAS inhibitors. At the time of screening, patients were assigned to receive a starting dose of 4.2g twice daily or 8.4g twice daily depending on the severity of hyperkalaemia. Patiromer could be titrated to reach and maintain a target potassium level according to a pre-specified algorithm. The maximum permitted patiromer dose in the trial was 50.4g/day - twice the current licensed maximum dose of 25.2g/day. In this phase, RAAS inhibitor doses were not adjusted; they were only discontinued if the potassium level was ≥ 6.5 mmol/L (≥ 5.1 mmol/L if on the maximum permitted patiromer dose).

A total of 243 patients were enrolled in the initial treatment phase. The primary efficacy endpoint was the mean change in potassium level from baseline to week four. Patiromer

significantly reduced potassium levels. The mean (\pm standard error) change observed was -1.01 ± 0.03 mmol/L (95% Confidence Interval [CI], -1.07 to -0.95 ; $p < 0.001$). The secondary efficacy endpoint was the proportion of patients with serum potassium levels in the target range. Seventy six percent of patients had a serum potassium level between 3.8 and 5.1 mmol/L at week 4 (95% CI, 70 to 81).

The withdrawal phase (Part B), was a placebo controlled, single blind, randomised withdrawal trial of patiromer for eight weeks. The objective of the withdrawal phase was to evaluate the effect of withdrawing patiromer on serum K⁺ control and to assess whether chronic treatment with patiromer prevents the recurrence of hyperkalaemia.

Completion of Part A was required to be eligible for enrolment for Part B but additional criteria were also required:

- A serum K⁺ of >5.5 mmol/L or higher at baseline of the initial treatment phase
- A potassium level at the end of the initial treatment phase that was within the target range while receiving patiromer and RAAS inhibitors

Consenting eligible patients were randomised in a 1:1 ratio to continue receiving patiromer (at the same daily dose they were receiving at week four of the initial treatment phase) or to receive placebo. During the randomised withdrawal phase, pre-specified treatment algorithms were developed to manage a recurrence of hyperkalaemia either by an increase in the dose of patiromer (patiromer group) or by modification of the RAAS inhibitor regimen (placebo group) at the time of first event of hyperkalaemia. From week four to eight of this phase, the algorithm mandated discontinuation of RAAS inhibitor medications after a second event >5.1 mmol/L.

Of the 219 patients who completed the initial treatment phase, 109 were not eligible to enter the randomised withdrawal phase and three declined further participation in the study. The remaining 107 patients were randomised. The estimated median change in the potassium level from the start of the randomised withdrawal phase to week four of this phase was 0.72 mmol/L in the placebo group and 0 mmol/L in the patiromer group resulting in a between group difference of 0.72 mmol/L (95% CI, 0.46 to 0.99 ; $p < 0.001$). However, the EMA advised that this should be interpreted with caution given that last observation carried forward was used to impute the week four data for patients who had serum potassium outside the target range.

An exploratory endpoint was the time to RAAS inhibitor discontinuation. Kaplan Meier analysis indicated that the time to discontinuation was slower in the patiromer group. However, interpretation of this endpoint is confounded by the large number of withdrawals

which was driven by the trial protocol. Furthermore, the proportion of patients on RAAS inhibitors was driven by the treatment algorithm mandated by the trial protocol which may not be generalisable to current clinical practice in Ireland. NICE guidelines recommend RAAS inhibitor dose reduction or discontinuation for serum potassium values above 6mmol/L. However, in the second half of the treatment phase, the trial protocol mandated RAAS inhibitor discontinuation for values >5mmol/L in the placebo arm. In addition, the population in this phase is only representative of those who have initially responded to therapy in the treatment phase.

Supportive clinical information from the additional trials AMETHYST-DN, PEARL-HF and TOURMALINE was provided by the applicant.

2. Safety of patiomer

The applicant presented detailed safety information from OPAL-HK (n=243) and pooled data from AMETYST DN and OPAL-HK studies (n=547). Adverse events were experienced by 62.2% of patients who received patiomer, with 8.6% reported as serious. Adverse events were balanced in the subgroup of patients who underwent the randomised withdrawal phase of OPAL-HK. Common adverse events as highlighted in the summary of product characteristics are constipation (6.2%), diarrhoea (3%), abdominal pain (2.9%), flatulence (1.8%) and hypomagnesaemia (5.3%).

3. Cost effectiveness of patiomer

Methods

A cost-utility analysis comparing patiomer to “no patiomer” under the HSE perspective was presented by the applicant. The modelled population was representative of the treatment phase of OPAL-HK – patients with stage 3-4 CKD on RAAS inhibitors with hyperkalaemia defined as a serum potassium value between 5.5 and 6.5mmol/L. The applicant positions patiomer treatment as an alternative to RAAS inhibitor dose reduction or discontinuation in these patients. However, the applicant did not sufficiently define patiomer’s place in therapy with respect to diuretic therapy or adjustment of drugs known to promote hyperkalaemia.

A cohort state transition Markov model was developed in Microsoft Excel. The model employed a lifetime time horizon and a monthly cycle length. A half cycle correction was applied. The model was designed to capture the natural history and progression of the modelled population. Health states included baseline stage 3-4 CKD, post-cardiovascular event, end-stage renal disease (ESRD) and death. Acute events acute events experienced by

patients, such as cardiovascular events and hyperkalaemia, were also accounted for. Baseline transition probabilities were obtained from the literature. The REVIEW GROUP had a number of concerns regarding the appropriateness of the values applied.

The applicant proposed that the treatment benefit of patiromer is mediated through the increase use of RAAS inhibitors in hyperkalaemic patients with CKD. Therefore, application of the patiromer treatment effect is applied in two parts.

1. The ability of patiromer to enable patients to remain on RAAS inhibitors.

The applicant applied this treatment effect by dividing each arm into two subcohorts – on RAAS inhibitors at baseline and off RAAS inhibitors at baseline. The proportions in each arm were estimated by the applicant according to the proportion of patients on RAAS inhibitors in the patiromer and placebo arms at the end of the treatment phase of OPAL-HK. These were adjusted by the applicant to account for the responder population. Given the limitations in the clinical evidence identified including the large number of withdrawals, and the generalisability of the trial protocol to Irish clinical practice, the review group were concerned that the treatment effect applied by the applicant may be biased for patiromer. In addition, the review group felt the applicant adjustments for the responder population were not sufficient.

2. The ability of RAAS inhibitors to reduce the risk of CKD progression, cardiovascular events and death.

Following a targeted literature search, the applicant estimated RAAS inhibitor treatment effects from a network meta-analysis conducted by Xie et al. (2016). The review group were concerned that a systematic review was not conducted.

The model included patiromer and RAAS inhibitor drug costs, costs associated with adverse events as well as CKD and ESRD costs. The review group were concerned that ESRD and adverse event costs may be underestimated.

Health benefits were measured in quality adjusted life years (QALYs). Health-Related Quality of Life was not measured in OPAL-HK. Therefore, the applicant conducted a systematic review to obtain literature values to populate the model. It was unclear how the utility values were chosen from the systematic review for inclusion in the model. It is unclear whether the population from which the utility values were derived are fully representative of the population and health state that they are applied to in the model.

Both costs and QALYS were discounted at a rate of 5% in line with national guidelines.

Results

The applicant conducted an incremental analysis of the cost and benefits of patiromer versus no patiromer. In the final applicant base case, the ICER was €37,951/QALY (Incremental Costs: €3,608, Incremental QALYs: 0.10)

Given the concerns identified during the model appraisal process, the review group made a number of adjustments to the economic model including amending the patiromer treatment effect; the probability of CKD progression; maximum patiromer treatment duration, cost of patiromer and ESRD costs. Under the NCPE preferred base-case, the review group estimated the deterministic ICER of patiromer versus no treatment as €117,396/QALY (Incremental Costs, €11,149; Incremental QALYS, 0.09). However, given the limitations in the clinical and cost-effectiveness evidence presented, neither the applicant's nor NCPE preferred base-case ICER is sufficiently robust for decision making.

Sensitivity analysis

A one-way sensitivity analysis was conducted using the NCPE preferred base-case. This indicated that the RAAS inhibitor treatment effect for all-cause mortality is the most influential parameter in the model. When varied across the modelled lower and upper bound the ICER varied between €75,436 and €356,858/QALY.

Running the probabilistic sensitivity analysis shows simulations across all four quadrants of the cost-effectiveness plane. This means that the cost-effectiveness of patiromer is very uncertain - patiromer may be cost saving, may reduce health gain or produce a health gain at an additional cost. Under the NCPE preferred assumptions, the probability of patiromer being cost-effective versus no patiromer at thresholds of €20,000/QALY and €45,000/QALY was 23.3% and 35.8% respectively.

4. Budget impact of patiromer

The proposed price to wholesaler of patiromer is €332.99 per 30 x 8.4g sachet pack. The total annual cost per patient including 12% wholesale mark-up, 5.5% mandatory rebate and pharmacy fees is €4,774.56 under a 8.4g/day dosing schedule. While the recommended starting dose is 8.4g once daily, the daily dose may be increased or decreased by 8.4g as necessary to a maximum of 25.2 g daily. In the NCPE base case, a weighted average annual drug cost based on US dispensing data of €5,166.34 is applied.

The applicant presented budget impact estimates for a subgroup of the licensed population – patients in CKD stage 3-4 who develop hyperkalaemia while on RAAS inhibitor therapy.

Using the applicant estimate of the estimated projected population, the review group estimate the gross budget impact as €0.2 million in year 1 rising to €2.8 million in year 5. The cumulative five year gross drug budget impact is estimated to be €7 million. Accounting for the increased use of RAAS inhibitors, the five-year net drug budget impact was marginally higher at €7.2million. However, the review group are concerned that these figures may underestimate the true budget impact associated with patiromer if reimbursed.

5. Patient Submissions

No patient submissions were received.

6. Conclusion

Following assessment of the applicant's submission, the NCPE recommends that patiromer (Veltassa®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.