HAUTE AUTORITÉ DE SANTÉ

INTENSIVE CARE
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

VELTASSA (patiromer), cation exchange resin

High clinical benefit in the treatment of hyperkalaemia in adults, but no demonstrated clinical added value in the therapeutic strategy

Main points

- VELTASSA has an MA for the treatment of hyperkalaemia in adults.
- Its efficacy has been demonstrated on the reduction and normalisation of serum potassium levels and the prevention of hyperkalaemia recurrences compared to placebo.
- No data are available concerning clinically relevant morbidity and mortality endpoints.
- No direct comparisons have been performed with other cation exchange resins or thiazide and loop diuretics.
- Uncertainties remain concerning the safety beyond one year.

Therapeutic strategy

- The management of hyperkalaemia differs between patients with life-threatening hyperkalaemia and patients in whom serum potassium levels need to be gradually lowered. The nature and urgency of potassium-lowering therapy depends on the severity of the hyperkalaemia.
- For the chronic treatment of hyperkalaemia or in cases in which serum potassium levels may be lowered gradually, a low-potassium diet, thiazide diuretics or loop diuretics, oral potassium exchange resins and/or, if applicable, the reduction or discontinuation of potassium-increasing medicinal products (RAAS inhibitors) are recommended. Chronic treatment aims to prevent recurrences of hyperkalaemia by correcting modifiable underlying causes (such as potassium intake or metabolic acidosis) and monitoring serum potassium concentrations.
- Two cation exchange resins are currently available for the treatment of hyperkalaemia: sodium polystyrene sulfonate (KAYEXALATE) and calcium polystyrene sulfonate (RESILAKI). Their use must be stopped if serum potassium levels are < 5 mEq/L. However, according to the experts, this threshold value does not appear to be clinically appropriate insofar as it is the desired target value. According to expert opinions, these two resins are currently used as long-term treatment of hyperkalaemia.
- **Role of the medicinal product in the therapeutic strategy**
  VELTASSA is a first-line therapy for the treatment of hyperkalaemia, like the other cation exchange resins available. VELTASSA contains sorbitol as part of the counterion complex. KAYEXALATE and RESIKALI have been the subject of warnings and precautions for use when combined with sorbitol (to prevent constipation) due to the rare occurrence of gastrointestinal necrosis. No cases of colonic necrosis were reported in clinical trials with VELTASSA. However, the duration of the studies (a maximum of 52 weeks) and the number of patients included are insufficient to exclude this risk given the rarity of this complication.
  Cation exchange resins have no role in the emergency treatment of hyperkalaemia due to their time to action onset.

Clinical data

- The evaluation of VELTASSA in the treatment of hyperkalaemia is based on the results of 2 studies conducted in patients with moderate to severe chronic kidney disease treated with RAAS inhibitors (patients at risk of chronic hyperkalaemia) and presenting hyperkalaemia.

- A randomised, open-label, non-comparative, dose-finding phase II study assessed the potassium-lowering effect of patiromer over a period of 52 weeks in 306 hypertensive patients with diabetic nephropathy and treated with RAAS inhibitors (± spironolactone). Eligible hyperkalaemic patients were stratified on the basis of their baseline serum potassium levels (serum potassium > 5.0 to < 6.0 mEq/L) then randomised in each stratum to receive one of the three initial doses of patiromer as two daily doses. The patiromer doses were adjusted to achieve and maintain serum potassium levels between the target values. After 4 weeks of treatment, or up to the 1st dose titration if this occurred before week 4, a significant reduction in serum potassium levels (primary endpoint) was observed in each initial dose group, irrespective of stratum, ranging from -0.35 mEq/L for patients receiving the lowest dose to -0.92 mEq/L for patients receiving the highest dose (p<0.001). The reductions in serum potassium levels were maintained for one year of treatment (secondary endpoint analysed on an exploratory basis). At the 52nd week of treatment, the majority of patients achieved the target serum potassium level of 3.8 to 5.0 mEq/L.
- A randomised, single-blind, phase III trial assessed the efficacy and safety of patiromer in hyperkalaemic patients (serum potassium between 5.1 and 6.5 mEq/L) with chronic kidney disease and treated with stable doses of RAAS inhibitors. The study consisted of two successive parts: part A, as a single 4-week arm, the objective of which was to assess the effect of patiromer in hyperkalaemic patients (n=243); part B was a randomised, comparative placebo-controlled 8-week assessment of the effect of the withdrawal of patiromer on serum potassium control, the efficacy of chronic treatment with patiromer on the prevention of recurrences of hyperkalaemia and the safety versus placebo (n=107).
  In part A, the initial patiromer dose could be adjusted with the aim of maintaining serum potassium between 3.8 and < 5.1 mEq/L. After 4 weeks of treatment, the mean reduction in serum potassium was -1.01 mEq/L (95% CI [−1.07; −0.95]; p<0.001), with a variation of -0.65 mEq/L in stratum 1 (baseline serum potassium between 5.1 and < 5.5 mEq/L) and -1.23 mEq/L in stratum 2 (baseline serum potassium between 5.5 and < 6.5 mEq/L). For the exploratory secondary endpoint, 76% of patients presented a controlled serum potassium level (3.8 to < 5.1 mEq/L) after 4 weeks.
  In part B, a higher number of patients under placebo withdrew prematurely from the study compared to patients receiving patiromer (42% compared to 18%), in particular due to the occurrence of hyperkalaemia meeting the study's pre-defined withdrawal criteria. The median variation in serum potassium over the 4 weeks of part B (or up to the 1st visit of part B during which serum potassium was outside the target range) was significantly higher in the placebo-treated group than in the group having continued treatment with patiromer: +0.72 mEq/L versus 0.0 mEq/L, (95% CI [0.46; 0.99]; p<0.001). Since measurements are not available after serum potassium levels exceeded the target range of 3.8 to < 5.5 mEq/L, estimations of the effect need to be interpreted with caution. The percentages of patients having presented a recurrent serum potassium level ≥ 5.1 mEq/L and ≥ 5.5 mEq/L during part B were significantly higher under placebo (91% and 60%) than under patiromer (43% and 15%), with absolute respective differences of 48% and 45% (p<0.001). Among the exploratory criteria, 44% of patients under placebo and 94% of patients under patiromer continued to receive RAAS inhibitor treatment at the end of part B.
- The available data demonstrated the efficacy of VELTASSA on the reduction and control of serum potassium levels after normalisation, as well as on the prevention of recurrences in hyperkalaemic patients (5.1 to < 6.5 mEq/L) with chronic kidney disease, treated with RAAS inhibitors and presenting several comorbidities, such as type 2 diabetes (57% to 100%), heart failure (35% to 42%) and hypertension (97% to 100%).
- The safety profile appears to be characterised by a high frequency of adverse events (58%), particularly gastrointestinal events (constipation, nausea, diarrhoea), hypomagnesaemia and hypokalaemia.

Benefit of the medicinal product

- The actual clinical benefit* of VELTASSA is high.
- VELTASSA does not provide clinical added value** (CAV V) in the current therapeutic strategy for the treatment of hyperkalaemia in adults, which includes cation exchange resins and diuretics.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 20 February 2019 (CT-16890) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".