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NEPHROLOGY
New medicinal product
April 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KETOSTERIL (ketoanalogues), combination of amino acids

No clinical benefit demonstrated in combination with a very low protein diet in chronic renal failure

Main points

- KETOSTERIL has Marketing Authorisation, in combination with a very low protein diet (0.4 g/kg/day) in chronic renal failure, to reduce the uraemic syndrome and better control the phosphorous-calcium metabolism.
- The data from clinical studies having evaluated its efficacy and safety are fragmentary.
- Its actual benefit is low and does not provide any improvement in the management of patients with chronic renal failure in combination with a very low protein diet.

Therapeutic use

- In chronic kidney disease (CKD) one of the main therapeutic objectives is to delay the initiation of dialysis by correcting the uraemic signs and symptoms and possibly by slowing the kidney disease progression. Management is also aimed at maintaining a satisfactory nutritional status while preventing the onset of complications associated with CKD, in particular of cardiovascular and metabolic origin.
- Nutritional treatment is based on the control of protein intake. Protein restriction, the main aim of which is to limit the uraemic toxicity and therefore preserve renal function, requires strict dietary monitoring, paying particular attention to calorie intake, due to its possible impact on the nutritional status.
- The benefit of protein restriction is also the correction of certain metabolic abnormalities: acidosis by reducing the load of sulfur-containing amino acids, secondary hyperparathyroidism by reducing the phosphorous intake, resistance to insulin and a reduction of sodium pump activity resulting from the slightest accumulation of inhibitory peptides, which leads to dietary protein degradation.
- Protein restriction is undertaken gradually depending on the degree of kidney disease, up to 0.6 g/kg/day, while ensuring the nitrogen balance remains balanced and the nutritional status is stable.
- **Role of the medicinal product in the therapeutic strategy**

  Reduction of protein intake below 0.6 g/kg/day requires the addition of essential amino acids. We can therefore reduce the protein intake to 0.3 g/kg/day by using ketoanalogues of essential amino acids such as KETOSTERIL. Such protein restriction, supplemented with essential amino acids and ketoanalogues, enables a balanced or positive nitrogen balance to be maintained during prolonged periods and does not compromise the nutritional outcome after the initiation of dialysis.

  The use of KETOSTERIL is advised:
  - optionally at stage 3B depending on the biological value of the dietary proteins,
  - at stages 4 and 5 (in patients not undergoing dialysis), when protein restriction is 0.3 to 0.4 g/kg/day or optionally when the protein restriction is 0.6 g/kg/day depending on the biological value of dietary proteins.

Clinical data

- A study evaluated the effect of a ketoanalogue-supplemented very low protein diet (SVLPD) compared with a low protein diet (LPD) in patients with chronic renal failure. Only the results of multiple intragroup comparisons are available between the final state and the initial state. No intergroup comparison is available. This does not enable the possible effect size of SVLPD treatment to be assessed.
- A second study also evaluated the effect of these two treatments. The results showed less CKD progression in the SVLPD group (9%) compared with the LPD group (32%), evaluated on the requirement to resort to replacement therapy and to reduce the glomerular filtration rate (GFR) by more than 50%. However it lacks data on whether or not a primary endpoint test was performed, its possible value and the number of patients per group which enabled these percentages to be calculated.

- A third study compared the mortality rate between two groups of patients aged over 70 years, not diabetic, with stage 5 CKD, the first group on SVLPD (with a product whose composition is close to that of KETOSTERIL) and the second group on dialysis. A total of 56 patients were randomised into each group. The median follow-up time was 26.5 months: 31 deaths (55%) were observed in the dialysis group and 28 deaths (50%) in the SVLPD group (insignificant difference).
- In conclusion, the clinical data evaluating the efficacy of KETOSTERIL have significant methodological flaws; they do not enable clear and precise evaluation of the benefit of this product in combination with a very low protein diet (0.4 g/kg/day) in patients with chronic renal failure.

- Concerning safety, there is a lack of data collected on the adverse events in one study. No adverse event was observed in the two other studies. These results could reveal a poor study quality: it is surprising that no adverse event was observed during the two studies in subjects with CKD, one of which included subjects aged 70 years and over.
- Data from marketing of the product do not report any particular safety signal.

Benefit of the medicinal product

- The actual benefit* of KETOSTERIL is low.
- KETOSTERIL does not provide clinical added value** (CAV V) in the treatment of patients with chronic renal failure in combination with a very low protein diet.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 29 April 2015 (CT-14013) and is available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary 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 AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".