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National Health Care Institute
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Our reference
2024004443

Date 25 March 2024
Re: Advice keto- and hydroxyanalogues (Ketosteril®)

Dear Mrs Dijkstra,

In your letter of 25 September 2023 [CIBG-23-06082], you asked the National Health Care Institute, as part of a request for placement on List 1B of the Health Insurance Regulation, to carry out a substantive assessment of whether keto- and hydroxyanalogues (Ketosteril®) are interchangeable with a product included in the reimbursed package and, if not, to assess the value for the indication for which reimbursement has been requested, including whether the pharmaco-economic assessment complies with the guidelines drawn up for that purpose. The National Health Care Institute has completed these assessments, and is now sending you its advice based on them.

Background
Chronic kidney disease (CKD) is irreversible. It is divided into 5 stages, which are based on kidney function and the amount of protein in the urine. Kidney function is determined by the estimated amount of blood in millilitres filtered by the kidneys per minute: eGFR. At an eGFR <15 ml/min/1.73m^2, this is considered CKD stage 5: (end-stage) renal failure. In that case, kidney dialysis or transplant is necessary to survive. People with CKD stage 5 have a greatly increased risk of death. They are monitored and treated by an internist nephrologist in accordance with the *'Chronische nierschade'* (chronic kidney disease) guideline (2018) of the Federation of Medical Specialists (FMS). For pregnant women with CKD, the FMS guideline *'Kinderwens en zwangerschap bij nierschade'* (desire to have children and pregnancy with kidney disease') (2021) is leading.

Ketosteril® is the brand name of a mixture of keto- and hydroxyanalogues of essential amino acids (hereafter referred to as keto- and hydroxyanalogues). The physicians' association sees a place for this medicinal product in patients with very severe renal impairment (CKD stage 5 with eGFR < 5-10 ml/min/1.73m^2) who have not yet been (able to be) dialysed. It is also suitable for pregnant women with CKD stages 3b - 5 (eGFR < 30 ml/min/1.73m^2) who are on a protein-restricted diet (i.e. up to 0.8g/kg ideal body weight per day).

Registered indication
Ketosteril® is registered for the prevention and treatment of damage due to faulty or defective protein metabolism in adults with chronic renal disease, in

combination with a restricted protein intake of ≤40 g/day. This applies to patients with eGFR ≤ 25 ml/min/1.73m^2.

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Claim from the marketing authorisation holder
Ketosteril® in combination with a very low protein diet *(VLPD)* of 0.28 – 0.43 g protein/kg body weight/day in patients with CKD stage 4 or 5 (eGFR ≤ 25 ml/min/1.73m^2) has an added value compared to standard treatment (i.e. protein intake via nutrition limited to 0.8 g protein/kg ideal body weight per day).

Assessment of interchangeability
To determine the place of a medicinal product in the Medicine Reimbursement System (GVS), the interchangeability of Ketosteril® with medicinal products already included in the GVS must be assessed. No medicinal product is included in the GVS for the above indication. Ketosteril® is not interchangeable with other medicinal products in the GVS and cannot be placed on List 1A. That is why it was assessed whether the product is eligible for inclusion on List 1B.

Established medical science and medical practice (therapeutic value)
The effects of a combination of keto- and hydroxyanalogues and a very low protein diet *(VLPD)* of 0.3g/kg/day were compared with the effects of a low protein diet (LPD) of 0.60 - 0.65 g/kg/day in five randomised, open-label studies with a total of 553 non-dialysis subjects with CKD stage 4 or 5 and a follow-up duration of 3 - 36 months.
In three studies, patients were required to follow a low protein diet (*LPD*; 0.60 g/kg/day) for three months prior to randomisation. In the other two studies, a low protein diet (*LPD*) prior to randomisation was not mandatory.
In patients who adhered to a low protein diet (*LPD*) prior to randomisation, treatment with the combination of keto- and hydroxyanalogues & the very low protein diet (*VLPD*) resulted in a clinically relevant reduction in the risk of CKD stage 5 compared to patients on a low protein diet *(LPD*). In patients who did not adhere to a low protein diet (*LPD*) prior to randomisation, treatment with the combination of keto- and hydroxyanalogues and the very low protein diet (VLPD) did not result in a clinically relevant reduction in the risk of CKD stage 5 compared to patients on a protein-restricted diet (*LPD*).
Keto- and hydroxyanalogues are most effective in humans who are able (and especially motivated) to adhere to a low protein diet (LPD) prior to treatment with keto- and hydroxyanalogues. According to the National Health Care Institute, only then has the addition of keto- and hydroxyanalogues added value. The physicians' association expects that pregnant women with CKD stages 3b - 5 will be strongly motivated to adhere to a very low protein diet (VLPD), as this will enable a longer pregnancy with a higher birth weight of a healthier child. According to the FMS guideline *'Chronische nierschade'* (2018), dietary guidance by a dietician is indicated for adherence to a (very) low protein diet and prevention of poor nutritional status.

Keto- and hydroxyanalogues in combination with a very low protein diet (*VLPD*) do not appear to have a clinically relevant effect on the risk of severe intervention-related adverse effects and do not increase the risk of discontinuation of treatment. All in all, Ketosteril® is safe to use in the patient groups studied by the National Health Care Institute in combination with a very low protein diet (*VLPD*).

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Ketosteril®, for the prevention and treatment of damage due to a faulty or defective protein metabolism, in combination with a very low protein diet (*VLPD*; 0.30 g/kg/day), meets the established medical science and medical practice for adults with chronic kidney disease (GFR ≤ 25 ml/min/1.73 m2) who have already successfully followed a low protein diet (LPD) of 0.60 g/kg/day.

Budget impact analysis
Taking into account the various assumptions regarding patient numbers, , market penetration and the number of tablets to be taken, the inclusion on List 1B of the GVS of keto- and hydroxyanalogues at CKD stages 4 and 5 will incur additional costs of €2.1 million in Year 3 after inclusion in the insured package. The total annual costs per patient are €3,832.50. It is expected that 553 patients will use this product. The National Health Care Institute emphasizes that it is assumed that keto- and hydroxyanalogues will be used for a smaller group of patients [i.e. patients with an eGFR<5-10 ml/min/1.73m2 and pregnant women with (very) advanced CKD] than it is registered for.

Pharmaco-economic analysis
Based on the estimated budget impact, the product is exempt from a pharmaco-economic analysis.

Advice
Based on the above, the National Health Care Institute recommends including Kestosteril® in List 1B and List 2 of the Health Insurance Regulation, with the conditions stated below.

Conditions Ketosteril®
Only if prescribed by an internist nephrologist and under the guidance of a dietician, with a very low protein diet (maximum 0.30 g protein/kg/day) for an insured person:
(a) with very severe renal impairment (CKD stage 5 with eGFR <5-10 ml/min/1.73m^2) who is not yet being or cannot be dialysed, or
b) who is pregnant and has severely impaired renal function (CKD stages 4 - 5 with eGFR < 25 ml/min/1.73m^2).

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board