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ENDOCRINOLOGY
New medicinal product
November 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

NATPAR (recombinant parathyroid hormone)

Low clinical benefit in chronic hypoparathyroidism, but not clinical added value demonstrated in the therapeutic strategy

Main points

- NATPAR has been granted a MA for adjuvant treatment in adults with chronic hypoparathyroidism (HPT) that cannot be adequately controlled by conventional treatment alone.
- It is administered subcutaneously once per day and requires dose titration according to calcaemia.
- Its superiority over the placebo, in combination with a conventional treatment (calcium and/or active vitamin D) to achieve normalized calcaemia, with decreased oral supplementation with calcium and active vitamin D has been demonstrated.
- The available clinical data are limited: lack of robust demonstration of quality of life and prevention of renal complications, uncertainties concerning the optimal dosage regimen and long-term tolerance. However, in the absence of any alternative validated by MA, NATPAR could represent an alternative treatment, for a very limited number of patients, should the conventional treatment fail.

Therapeutic strategy

The goal of chronic HPT treatment is to eliminate symptoms, particularly neuromuscular, and to prevent complications, particularly renal (nephrocalcinosis, renal lithiasis, kidney failure). Management relies on hydroxyl derivatives of vitamin D, combined with sufficient calcium intake, via the diet and, if necessary, medicinal. Thiazide diuretics are occasionally used to reduce hypercalciuria. Teriparatide, the active sequence [1-34] of PTH (FORSTEO) has been granted an MA for post-menopausal osteoporosis and is used off-label by specialist departments in cases of HPT (total treatment duration limited to 24 months, non-renewable).

Role of the medicinal product in the therapeutic strategy

NATPAR, combined with a conventional treatment (vitamin D analogue and calcium), could represent an alternative treatment for a relatively limited number of patients, in the event of failure of the conventional treatment, in order to reduce calcium and active vitamin D supplementation and to avoid the ensuing complications.

Prescription should be reserved for reference centres with expertise in this rare disease. Considering the risk of hypocalcaemia or hypercalcaemia, treatment initiation should be closely monitored during the titration period, strictly following the dosage recommendations. Moreover, it must be combined with a therapeutic education programme to ensure the best possible adherence (persistence and compliance).

Clinical data

- In a study conducted on 124 patients, the superiority of NATPAR over the placebo, in addition to optimised conventional treatment (calcium and active vitamin D supplementation) was demonstrated in terms of responder patients: 52.3% difference between groups; CI 95% [40.4; 64.0], $p < 0.001$. The efficacy of NATPAR for ranked secondary endpoints was also demonstrated: reduction of the daily dose of calcium (mean reduction of 51.8 ± 45.7% with NATPAR versus increase of 2.4 ± 38.4% with the placebo, $p < 0.001$) and independence of active vitamin D and calcium supplementation (43% with NATPAR versus 6.1% with the placebo, $p < 0.001$).
  No statistically significant difference was detected between the two groups in terms of frequency of clinical symptoms of hypocalcaemia between weeks 16 and 24. No other demonstration can be derived from the other

relevant endpoints such as phosphaturia, calciuria and quality of life, which were validated only as exploratory endpoints.
- The important risks identified with NATPAR were hypercalcaemia during initiation and titration, along with hypocalcaemia.

Special prescription requirements

- Prescription reserved for endocrinology, diabetes and nutrition, or nephrology specialists
- Medicinal product requiring special monitoring during treatment

Benefit of the medicinal product

- The actual clinical benefit* of NATPAR is low.
- NATPAR does not provide any improvement in actual clinical benefit** (IACB V) in the therapeutic strategy.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 07 November 2018 (CT-17108) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease 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 improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"