HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
December 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

LENVIMA (lenvatinib), protein kinase inhibitor

Minor improvement in the treatment of locally advanced or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine

Main points

- LENVIMA has Marketing Authorisation in the treatment of progressive, locally advanced or metastatic, differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma refractory to radioactive iodine.
- Because of their concurrent development, no direct comparative study versus NEXAVAR (sorafenib) is available.
- Given the increase in progression-free survival but lack of demonstrated impact on overall survival and the safety profile, the selection of patients in whom systemic treatment with LENVIMA is justified must be based on various criteria, including the maximum size of metastases (1-2 cm), the symptoms associated with the disease and the rate of progression.

Therapeutic use

- The initial treatment of patients with differentiated follicular thyroid carcinoma is tailored to the level of risk defined by the TNM classification and by histological tumour type:
  - total thyroidectomy is the treatment of choice in the majority of cases;
  - internal vectorised radiation therapy with iodine-131 is indicated only in high-risk patients and in metastatic disease;
  - the role of external radiation therapy is limited and the indication for this, where it arises, needs to be discussed at an interdisciplinary consultation meeting;
  - chemotherapy is not indicated in initial treatment.

  After total thyroidectomy, hormone replacement to compensate for hypothyroidism and suppress the secretion of TSH is essential for all patients, irrespective of whether they also underwent radiotherapy. This may be for replacement or suppression.
- If the differentiated thyroid carcinoma is refractory to radioactive iodine, treatment is as follows:
  - metastases smaller than 1-2 cm that show little progression are treated by TSH suppression;
  - in the case of larger, progressing, refractory metastases that do not conform to the indications for local treatment (surgery, radiation therapy, Ablatherm treatment, etc.), treatment with a multikinase inhibitor is suggested.

  Among the available treatments, NEXAVAR (sorafenib) is a therapeutic option in the treatment of locally advanced, inoperable or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine, in patients selected on the basis of various criteria including the sizes of metastases (1-2 cm), the symptoms associated with the disease and the rate of progression.

- **Role of the medicinal product in the therapeutic strategy**
- In this indication, LENVIMA is an alternative to NEXAVAR.

  It is also a treatment option in patients who are refractory to radioactive iodine and in whom treatment with NEXAVAR has failed.
- Its prescription must be approved by a reference or specialist centre or during an interdisciplinary consultation meeting that includes an oncologist or clinician experienced in the treatment of differentiated thyroid carcinoma (endocrinologist).

Clinical data

- A randomised double-blind study compared lenvatinib (24 mg/day orally) with placebo in 392 patients with differentiated thyroid cancer, mainly metastatic, that was progressing in the 12 months before inclusion and refractory to radioactive iodine or progressing despite treatment with iodine-131. Almost a quarter had previously been given a treatment targeting the VEGF/VEGFR, mainly NEXAVAR.
- Compared with placebo, LENVIMA showed:
  - a longer median progression-free survival (primary efficacy endpoint): 18.3 *versus* 3.6 months, i.e. an absolute increase of 14.7 months (HR = 0.21; 95% CI [0.14-0.31]; p < 0.0001). The analysis of the subgroup of patients who had been given anti-VEGF therapy suggested that LENVIMA had a comparable efficacy in patients in whom this treatment had failed;
  - an overall response rate (complete + partial response) of 64.8% (with 1.5% complete response) *versus* 1.5% (with no complete response), p < 0.0001 ;
  - no difference in overall survival in the main analysis (median overall survival not reached in the two groups);
- The collection of data on the presence of symptoms due to the differentiated thyroid carcinoma and on the quality of life was not envisaged in the protocol.
- Almost 17% of patients treated with LENVIMA discontinued treatment due to adverse events; the most frequent were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea and pulmonary embolism. About 72% of patients treated with LENVIMA had a grade 3 adverse event; the most frequent were arterial hypertension, weight loss, proteinuria and diarrhoea. Adverse events with a fatal outcome were reported in 20 patients in the LENVIMA group (8%); 6 of them were considered to be treatment-related.
- The most common adverse events (≥ 5%) that led to a dose reduction were arterial hypertension, proteinuria, diarrhoea, fatigue, palmoplantar erythrodysesthesia, weight loss and decreased appetite.
- The dose was reduced in the course of the study in 78.5% of the patient population. Pending the results of the study comparing 24 mg with 14 or 20 mg, the optimal dose of LENVIMA remains to be determined.
- Given the methodological shortcomings, the results obtained from the indirect comparisons that were submitted are of a purely exploratory nature and do not allow any conclusions to be drawn about the benefit LENVIMA by comparison with NEXAVAR.

Special prescribing conditions

- Medicine for hospital prescription
- Prescription restricted to oncology specialists or doctors with cancer training.

Benefit of the medicinal product

- The actual benefit* of LENVIMA is substantial.
- LENVIMA provides minor clinical added value** (CAV IV), in terms of efficacy, in the treatment of progressive, locally advanced or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine in the same way as NEXAVAR (sorafenib).
- 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 02 December 2015 (CT-14510) and is available at **www.has-sante.fr**

[i] * 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".