HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
June 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

NEXAVAR (sorafenib), protein kinase inhibitor

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

Main points

- NEXAVAR has Marketing Authorisation in the treatment of progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma refractory to radioactive iodine.
- Given the increase in progression-free survival but lack of demonstrated impact on overall survival, the safety profile and deterioration in quality of life, the selection of patients in whom systemic treatment with NEXAVAR is justified must be based on various criteria, including maximum size of metastases (1-2 cm), symptoms associated with the disease and rate of progression.

Pre-existing indications

NEXAVAR already has Marketing Authorisation in hepatocellular carcinoma and renal cell carcinoma.
This summary does not cover these indications.

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;
  - systematic internal radiotherapy with iodine-131 is indicated only in high-risk patients and in metastatic disease;
  - the role of external radiotherapy is limited and the indication for this, where it arises, needs to be discussed at an interdisciplinary consultation meeting (ICM).
  - chemotherapy is not indicated in initial treatment.

  After total thyroidectomy, hormone replacement to overcome hypothyroidism and suppress TSH is essential for all patients irrespective of whether they additionally 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 correspond to the indications for local treatment (surgery, radiotherapy, Ablatherm treatment, etc.), treatment with a multikinase inhibitor is suggested.
- **Role of the medical product in the therapeutic strategy**
- NEXAVAR 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 maximum size of metastases (1-2 cm), symptoms associated with the disease and rate of progression.
- 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 800 mg sorafenib, in two daily oral doses, with placebo in 417 patients with differentiated (papillary, follicular, Hürthle cell) or poorly differentiated, locally advanced or

metastatic thyroid carcinoma that was progressing in the 14 months prior to inclusion and refractory to radioactive iodine or progressing despite treatment with iodine-131.
Compared with placebo, NEXAVAR showed:
- a longer median progression-free survival (primary endpoint): 10.8 versus 5.8 months, i.e. an absolute increase of 5 months (HR = 0.59; $CI_{95\%}$ [0.45; 0.76]; p < 0.0001);
- no difference in overall survival (median overall survival not reached by the time of the interim analysis);
- a similar percentage with stable disease (74%). The overall response rate (complete + partial response) was 12.2% versus 0.5% (p < 0.0001), with no complete response.
Nearly one in five patients treated with NEXAVAR discontinued treatment on account of adverse events and one patient in two experienced adverse events of grade 3. The most frequent were hand-foot syndrome, arterial hypertension, weight loss and hypocalcaemia.

- The most important serious adverse effects were myocardial infarction/myocardial ischaemia, gastrointestinal perforation, drug-induced hepatitis, haemorrhage and arterial hypertension/hypertensive crisis.
The adverse effects seen most frequently were: diarrhoea, fatigue, alopecia, infection, hand-foot syndrome and rash and elevations in ALT/AST and hyperglycaemia.
- The quality of life data suggested a deterioration in quality of life with NEXAVAR compared with placebo.

Benefit of the medicinal product

- The actual benefit* of NEXAVAR is substantial.
- NEXAVAR 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.
- 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 03 June 2015 (CT-14166) 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".