HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
November 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

FOTIVDA (tivozanib), protein kinase inhibitor

Insufficient clinical benefit to justify reimbursement for the treatment of metastatic renal cancer

Main points

- FOTIVDA has been granted a marketing authorisation for the first-line treatment of adults suffering from advanced stage renal cell carcinoma (RCC) and in patients who have never received VEGFR and mTOR pathway inhibitors, following disease progression after previous cytokine treatment for advanced stage RCC.
- The available data do not allow the impact in terms of morbidity and mortality to be quantified due to the profile of the patients included (70% in first-line) and of the comparator, unsuitable for first-line, selected in the study.

Therapeutic strategy

- The management of metastatic renal cancer relies primarily on the classification of disease prognostic factors into 3 groups: favourable, intermediate and poor. This classification takes into consideration the patient's general condition, time from initial diagnosis to first-line treatment, LDH and haemoglobin levels and corrected calcaemia.
  In patients with a good or intermediate prognosis, the first-line treatments are sunitinib, bevacizumab/interferon combination and pazopanib. Cytokine monotherapy remains a potential treatment option for the first-line treatment of metastatic clear cell renal adenocarcinoma.
- In patients with a poor prognosis, the recommended treatment is temsirolimus, an mTOR inhibitor.
- After tyrosine kinase inhibitor failure, nivolumab and cabozanitib are the preferred therapeutic options. Failing any comparative data however, the role of tivozanib relative to nivolumab remains unknown. Other second-line options may be recommended: everolimus and axitinib.
  Sorafenib has been granted a marketing authorisation solely for cases of cytokine (interferon or IL2) failure.
- **Role of the medicinal product in the therapeutic strategy**

  FOTIVDA has no role in the therapeutic strategy of advanced stage renal cell carcinoma.

Clinical data

- One open-label, randomised (1:1) study compared tivozanib (FOTIVDA 1, 34 mg, once per day for 3 weeks, followed by 1 week without treatment) to sofarenib (NEXAVAR, 400 mg, twice daily) in 517 patients suffering from recurrent or metastatic clear cell renal carcinoma, who were treatment-naive or who had received prior systemic cytokine treatment.
- The final analysis of progression-free survival (primary endpoint) was performed after 321 events were observed in the overall study population (naïve or pre-treated patients). According to the independent blind X-ray examination, the median progression-free survival was of 11.9 months in the tivozanib group, versus 9.1 months in the sorafenib group, i.e. an absolute gain of 2.8 months in favour of tivozanib (HR = 0.797, CI95% [0.639 to 0.993]; p=0.042).
- The progression-free survival curves crossed over at month 5.
- There was no difference in overall median survival time between the two groups: 28.2 months (CI95% 22.5, 33.0) in the tivozanib group and 30.8 months (CI95% 28.4, 33.3) in the sorafenib group (HR = 1.147, p = 0.276).
- The choice of sorafenib as a comparator in this study was not appropriate for the following reasons:

- the population included was heterogeneous, with a majority (70%) of patients receiving first-line treatment, whereas the MA indication for the comparator, sorafenib, is for second-line treatment,
- the guidelines, in particular European, recommend (with the highest degree of confidence) for first-line treatment three medicinal products that possess marketing authorisations for first-line treatment: sunitinib, bevacizumab combined with interferon and pazopanib,
- at the date when this study was conducted, two of the three aforementioned medicinal products had already been granted a marketing authorisation: sunitinib and bevacizumab.

- Moreover, in the sub-group of second-line patients, the superiority of tivozanib in terms of the primary endpoint, progression-free survival, was not demonstrated.
  There were 14.7% treatment discontinuations due to adverse events in the tivozanib group versus 13.2% in the sorafenib group. The most frequent adverse events with tivozanib, by comparison to sorafenib, were hypertension (44.8% versus 35.4%) and dysphonia (21.2% versus 4.7%). Conversely, the most frequently observed adverse event with sorafenib were hand-foot syndrome (54.1% versus 13.9%), diarrhoea (33.1% versus 24.3%) and alopecia (21% versus 2.3%).

Special prescription requirements

- Medicinal product subject to hospital prescription.
- Prescription reserved for oncology specialists or physicians with oncology expertise

Benefit of the medicinal product

- The actual clinical benefit* of FOTIVDA is insufficient.
- Not 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-16876)
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.