HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

CABOMETYX (cabozantinib), tyrosine kinase inhibitor

Insufficient clinical benefit to justify its reimbursement in advanced renal carcinoma in adult patients with intermediate or high risk, not previously treated due to strong uncertainties concerning the demonstration of efficacy, in light of the methodological weaknesses identified in the pivotal study.

Main points

- CABOMETYX has been granted a marketing authorisation for the treatment of advanced renal cell carcinoma in intermediate or high-risk adults not previously treated.
- One study demonstrated its superiority over sunitib in terms of progression-free survival, with a modest absolute improvement (+2.6 months), whose clinical relevance was questionable failing any difference in overall survival.
- This demonstration of efficacy, however, is uncertain considering the numerous methodological limitations of the pivotal study.
- No quality of life data are available.

Pre-existing indications*

- CABOMETYX has also been granted a marketing authorisation for the treatment:
  - of advanced renal cell carcinoma in adult patients following targeted vascular endothelium growth factor receptor therapy.
  - of hepatocellular carcinoma in adult patients previously treated with sorafenib.

Therapeutic strategy

- The treatment of metastatic kidney cancer depends on disease prognostic factors. The IMDC classification groups treatment-naive patients into 3 categories: favourable prognosis, intermediate prognosis and poor prognosis (≥3 criteria). Before the CABOMETYX marketing authorisation and the nivolumab (OPDIVO) + ipilimumab (YERVOY) combination, the recommended first-line treatments were as follows:
  - Sunitinib (SUTENT), the bevacizumab (AVASTIN)/interferon or pazopanib (VOTRIENT) combination in patients with a favourable or intermediate prognosis.
  - Temsirolimus (TORISEL) in patients with a poor prognosis.
  - Cytokine monotherapy remains a potential treatment option for the first-line treatment of metastatic clear cell renal adenocarcinoma.

- The new guidelines now recommend the nivolumab + ipilimumab combination as first-line treatment in intermediate or high risk patients. Cabzantinib, sunitinib and pazopanib are therapeutic alternatives to this combination.

- **Role of the medicinal product in the therapeutic strategy**

Considering:

- the demonstrated superiority of cabzantinib versus sunitinib in terms of progression-free survival, with a modest absolute improvement (+2.6 months, HR = 0.66, CI95% [0.46; 0.95]; p = 0.0012) and questionable clinical relevance failing any difference in overall survival (secondary endpoint),

* This summary does not concern these indications.

- the great uncertainty around this demonstration, in light of the many methodological weaknesses of the pivotal study (phase II conducted in an open manner, unilateral consented error of 12%, nearly 5 times greater than the commonly accepted threshold, with a primary analysis conducted by the investigator, using censorship rules that failed to conform to guidelines),
- the lack of advantage over sunitinib in terms of safety or quality of life,

a loss of opportunity by the patient of receiving CABOMETYX cannot be excluded. The use of sunitinib or alternatives should thus be preferred over cabozantinib.
Consequently, CABOMETYX has no role in the therapeutic strategy for patients suffering from intermediate or high-risk advanced renal cell carcinoma not previously treated. It maintains a role in advanced clear cell carcinoma, or carcinoma with a contingent of clear cells after failure of previous anti-VEGF treatment.

Clinical data

- The assessment of cabozantinib in this indication relies primarily on a phase II randomised, open comparative study versus sunitinib, that included 157 patients suffering from clear cell carcinoma with a contingent of clear cells and with intermediate (81%) or high risk (19%). This study contained numerous methodological weaknesses (see above).
- During the primary analysis, the median progression-free survival assessed by the investigator (primary endpoint) was higher in the cabozantinib group than in the sunitinib group: 8.2 months versus 5.6 months: HR=0.66, CI95% = [0.46; 0.95], p=0.012. No difference in overall survival was detected between the two groups (secondary endpoint with no adjustment associated with multiple analyses) and the protocol failed to stipulate the collection of quality of life data.
- The safety data in this indication are consistent with the already known safety profile of cabozantinib. The significant risks identified by the RMP remain: gastrointestinal perforation, gastrointestinal and non-gastrointestinal fistula, thromboembolic events, grade 3 or higher haemorrhage, wound healing complications, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS) and osteonecrosis.

Special prescription requirements

- Medicinal product subject to hospital prescription
- Prescription by oncology and medical oncology specialists and departments

Benefit of the medicinal product

- The actual clinical benefit* of CABOMETYX is insufficient to justify public funding cover.
- 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 27 February 2019 (CT-17224) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".