M,HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
July 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

AFINITOR (everolimus), tyrosine kinase inhibitor

High clinical benefit but no proven clinical added value for the current treatment of progressive, non-functional, well-differentiated, non-resectable or metastatic gastrointestinal neuroendocrine tumours in adults

Main points

- AFINITOR has been granted a marketing authorisation for the treatment of progressive, non-functional, well-differentiated (Grade 1 or 2), non-resectable or metastatic gastrointestinal or pulmonary neuroendocrine tumours (NETs) in adults.
- A gain in progression-free survival versus placebo has been demonstrated, though there is no proven benefit in terms of overall survival or quality of life.
- Treatment discontinuation due to adverse events has been observed in almost one third of patients.
- No data versus recommended therapeutic alternatives are available for certain clinical gastrointestinal NET scenarios.

Pre-existing indications*

- AFINITOR has also been granted a marketing authorisation for the treatment of advanced hormone receptor-positive breast cancer, pancreatic neuroendocrine tumours and advanced kidney cancer.

Therapeutic strategy

- In the context of well-differentiated (Grade 1 or 2) non-resectable or metastatic pulmonary NETs, initiating anti-tumour therapy should only be discussed in cases of documented progressive disease.
  Everolimus treatment is recommended from the first-line stage for cases where these tumours are rapidly progressive. For cases where these tumours are slowly progressive, somatostatin analogue treatment is recommended and, upon progression, everolimus.
- The therapeutic guidelines from the first-line stage for non-functional, non-pancreatic gastrointestinal NETs are:
  - rapidly progressive, choice between:
    - o embolisation or chemoembolisation in a specialist centre, except in the presence of extrahepatic metastases where systemic treatment is preferable (off-label),
    - o everolimus therapy,
    - o vectorised internal radiation therapy. (LUTATHERA 370MBq/ml under temporary authorisation for use by a cohort).
  - slowly progressive:
    - o somatostatin analogues, in cases of liver invasion < 25-50% and where Ki67 < 2% and upon progression everolimus.
- **Role of the medicinal product in the therapeutic strategy**
  For pulmonary NETs, when these tumours are rapidly progressive, AFINITOR is recommended from the first-line stage and, in the case of slow progression after somatostatin analogue treatment.
  For gastrointestinal NETs, failing data versus chemoembolisation or vectorised radiation therapy, the role of AFINITOR has yet to be defined.

* This summary does not concern these indications.

Clinical data

- A double-blind randomised study compared the efficacy and safety of everolimus versus placebo in adults with progressive, non-functional, well-differentiated (Grade 1 or 2), non-resectable or metastatic, gastrointestinal or pulmonary NETs. In total, 302 patients were randomised: 205 to the everolimus group and 97 to the placebo group. Pancreatic NETs were not included in the study. Prior to the study, 59.0% of the patients of the everolimus group and 72.2% of the placebo group had received previous surgical treatment. Approximately half of the patients of each group had received prior somatostatin analogue treatment.
- The median progression-free survival (primary endpoint) was 11 months in the everolimus group versus 3.9 months in the placebo group, i.e. an absolute gain of 7.1 months in favour of everolimus (HR = 0.48 95% CI [0.35 - 0.67]; p<0.001).
- No difference was observed between the two groups in terms of overall survival or quality of life.
- Treatment discontinuations due to adverse events applied to 29.2% of the patients of the everolimus group and 7.1% of the patients of the placebo group. Grade 3 events applied to 56.9% of the patients of the everolimus group and 21.4% of the placebo group. The most frequently reported events in the everolimus group were diarrhoea (7.9%) and stomatitis (7.4%).

Special prescription requirements

- Hospital-prescribed medicinal product
- Prescription reserved for oncology, haematology and medical oncology specialists and departments
- Medicinal product requiring special monitoring during treatment

Benefit of the medicinal product

- AFINITOR has a high actual clinical benefit* for the treatment of progressive, non-functional, well-differentiated (Grade 1 or 2), non-resectable or metastatic gastrointestinal or pulmonary neuroendocrine tumours (NETs) in adults.
- AFINITOR does not provide any clinical added value** (CAV V) in this new indication.
- Approval for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 5 July 2017 (CT-15593) available at **www.has-sante.fr**

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