BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

STIVARGA (regorafenib), tyrosine kinase inhibitor

No clinical benefit demonstrated in the management of metastatic colorectal cancer
Actual benefit low in patients with an ECOG performance score equal to 0 or 1

Main points

- STIVARGA has Marketing Authorisation in the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies; these include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.
- Compared with placebo, it slightly improves overall survival and is associated with substantial toxicity.

Therapeutic use

- In the treatment of metastatic colorectal cancer, the anti-EGFR cetuximab can be combined with FOLFIRI or with FOLFOX, whereas panitumumab can be combined only with FOLFOX. These treatments can be administered only to patients with nonmutated KRAS and NRAS genes.
- In patients with progression on fluoropyrimidines, irinotecan, oxaliplatin and cetuximab or panitumumab and/or bevacizumab, there are two possible options:
  - regorafenib as monotherapy (orally administered at 160 mg/day for 3 weeks/4) (grade B recommendation).
  - palliative care or therapeutic trial (expert agreement).
- **Role of the medicinal product in the therapeutic strategy**
  STIVARGA is a treatment for patients who have previously been treated with or who are not eligible for the available treatments.

Clinical data

- A randomised (2:1) double-blind study compared regorafenib with placebo, both combined with the best supportive care for patients with metastatic colorectal cancer who have had disease progression after receiving all lines of standard recommended treatments.
  The 760 randomised patients (505 patients in the regorafenib group and 255 patients in the placebo group) had a median age of 61 years. At the start of the study, all patients had an ECOG performance status of 0 or 1. There are no data in patients in a worse condition (ECOG > 1).
  More than half the patients (52%) had already been treated with two or three lines of treatment for their metastatic disease, and approximately one quarter with at least five lines of treatment. Treatments included fluoropyrimidine-based chemotherapy, treatment with anti-VEGF agents and, in cases of wild-type KRAS gene, anti-EGFR therapies.
  Efficacy was demonstrated during a second predefined interim analysis, which led to the study being stopped due to positive results being achieved for the primary efficacy endpoint.
  In the regorafenib group, compared with the placebo group:
  - median overall survival (the primary endpoint) was 6.4 months (95% CI [5.9-7.3] versus 5 months (95% CI [4.4-5.8]), i.e. an increase of 1.4 months (HR = 0.774; 95% CI [0.636; 0.942], p = 0.005).
  - median progression-free survival was 1.9 months versus 1.7 months, i.e. an increase of 6 days in favour of regorafenib (HR = 0.494; 95% CI [0.419; 0.582], p < 0.000001).
  - stabilisation of the disease was observed in 42.8% versus 14.5%.

  The quality-of-life analysis did not show any difference between the two groups.

- The overall incidence of serious adverse events considered as being treatment-related was higher in the regorafenib group (11.8%) than in the placebo group (3.6%).
  The adverse events of any grade that were most commonly observed (≥ 10% difference between the two groups) with regorafenib compared with placebo were: fatigue (63% vs. 46%), hand-foot skin reaction (47.0% vs. 7.5%),

diarrhoea (43% vs. 17%), weight loss (32% vs. 11%), dysphonia (32% vs. 6%), hypertension (30% vs. 8%), skin rash or desquamation (29% vs. 5%), mucositis or stomatitis (29% vs. 5%), fever (28% vs. 15%), hyperbilirubinaemia (20% vs. 9%), haemorrhage (20% vs. 7%) and infections (25% vs. 14%).

Special prescribing conditions

Medicine for hospital prescription

Prescription medicine restricted to certain healthcare professionals: cancer treatment and clinical oncology specialists and departments.

Benefit of the medicinal product

- The actual benefit* of STIVARGA
  - is low for patients whose performance score is 0-1
  - is insufficient for patients whose performance score is > 1
- STIVARGA does not provide any clinical added value** (CAV V, non-existent) in the management of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for available therapies (fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy) and whose performance score is 0 or 1.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

HAUTE AUTORITÉ DE SANTÉ

This document was created on the basis of the Transparency Committee Opinion of 14 May 2014 (CT-13240) 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 added clinical value".