HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Update
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TRANSPARENCY COMMITTEE OPINION SUMMARY

HALAVEN (eribulin), antineoplastic agent

High clinical benefit in advanced or metastatic breast cancer, but no demonstrated clinical added value with respect to the existing therapeutic strategy in second-line treatment and minor clinical added value for third or later-line treatment.

Main points

- HALAVEN has a marketing authorisation for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.
- As third or later-line treatment for metastatic breast cancer, HALAVEN demonstrated an improvement in overall survival compared to treatment of physician's choice in a phase III study (EMBRACE study). The transposability of the data is not guaranteed due to the profile of the patients in the study, which no longer corresponds to that observed in clinical practice, particularly in terms of previous treatments.
- As second-line treatment, the results of the superiority study versus capecitabine were not conclusive and no non-inferiority study is available.

Therapeutic strategy

- The objective of treatment of locally advanced or metastatic breast cancer is to achieve stabilisation with an improvement of quality, of life or even remission of variable duration for up to several years. The choice of systemic treatment is dependent on the histological characteristics of the tumour, predictive factors for response to treatments (hormone receptor and/or HER2 receptor expression), previously administered treatments and their tolerance, metastatic disease presentation and the time to onset of recurrence.
- **Role of the medicinal product in the therapeutic strategy**
  - HALAVEN monotherapy as second-line chemotherapy is an alternative to the other monotherapies recommended: capecitabine (XELODA) and vinorelbine (NAVELBINE) in the treatment of locally advanced or metastatic breast cancer in HER2- patients whose disease has progressed. In the event of HER2+ breast cancer, eribulin is used at a later stage due to the existence of other medicinal products recommended as second-line therapy.
  - HALAVEN monotherapy as third or later-line chemotherapy represents a treatment of choice at this stage of the disease in locally advanced or metastatic breast cancer.
- The positioning as a second and third-line chemotherapy is liable to evolve due to the incorporation of new medicinal products in the therapeutic strategy that may result in HALAVEN being used for later-line therapy.

Clinical data

- Reminder of studies previously assessed
  In second-line therapy, an open-label, randomised phase III study (study 301) included 1,102 patients with locally advanced or metastatic breast cancer, previously treated with anthracyclines and taxanes, irrespective of the HER2 status of their tumours. There was no difference in terms of overall survival (joint primary efficacy endpoint) between the IV eribulin 1.23 mg/m^2 group and the oral capecitabine 2,500 mg/m^2 group (15.9 months versus 14.5 months), nor in terms of progression-free survival between the eribulin group and the capecitabine group (4.1 months versus 4.2 months).

In third or later-line therapy, an open-label, randomised phase III study (EMBRACE) conducted in 762 patients with locally advanced or metastatic breast cancer who have had at least two failed chemotherapeutic regimens including anthracycline and taxane, the median overall survival was higher in the eribulin group than in the treatment of physician's choice group, with 13.2 months versus 10.6 months, i.e., an absolute improvement of 2.6 months (HR= 0.815; 95% CI [0.696; 0.955]; p=0.011).
In second and later-line therapy, a grouped analysis was performed for the patients from the 2 studies at the request of the EMA. In the total population (n=1,864 patients), the median overall survival was higher in the eribulin group (15.2 months in 1,062 patients) than in the control group (12.8 months in 802 patients), i.e., an absolute improvement of 2.4 months (HR= 0.85; p=0.003). Analyses were performed on various subgroups (HER+, HER-, triple negative, etc.); however, these remain exploratory and do not enable any reliable conclusions to be reached with respect to the effect of the treatment in these subgroups.

- New data

A retrospective, observational comparative study conducted using the ESME database grouped together 16,703 metastatic breast cancer patients treated between January 2008 and December 2014. The results suggested the following:

- In second-line therapy (n=5,800 patients): the median overall survival was 12.4 months in the eribulin group and 11.8 months in the “other chemotherapy” group.
- In third-line therapy (n=3,315 patients): the median overall survival was 10.5 months in the eribulin group and 7.8 months in the “other chemotherapy” group.

These results suggest a benefit in favour of the use of eribulin. However, given their methodology, they are unable to provide a demonstration with the same level of evidence as clinical trials.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for oncology or haematology specialists or physicians with oncology expertise.

Benefit of the medicinal product

- The actual clinical benefit* of HALAVEN is high.
- In second-line therapy: in the absence of demonstration of superior efficacy or safety compared to the existing therapeutic strategy in second-line chemotherapy for locally advanced or metastatic breast cancer in which there has been disease progression, HALAVEN does not provide any clinical added value** (CAV V).
- In third or later-line therapy: the new efficacy data concerning HALAVEN in third or later-line chemotherapy for locally advanced or metastatic breast cancer in which there has been disease progression are not of a nature to modify the clinical added value** rating previously allocated by the Committee, i.e. a minor CAV (IV) in the therapeutic strategy.
- Approved for retention of hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated **21 November 2018** (CT-16951) 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".