HERCEPTIN (trastuzumab), monoclonal antibody

**Moderate clinical added value in combination with a taxane and pertuzumab as a first-line treatment for HER2+ metastatic breast cancer that has not been previously treated.**

No demonstrated clinical benefit in combination with an aromatase inhibitor as a first-line treatment for HER2+ metastatic breast cancer that has not been previously treated.

**Main points**

- HERCEPTIN has marketing authorisation in the treatment of HER2+ metastatic breast cancer:
  - in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable;
  - in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease;
  - in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

- HERCEPTIN in combination with a taxane remains the standard treatment in HER2+ metastatic breast cancer that has not been previously treated, however, the addition of pertuzumab to this dual therapy is now recommended.

- No data are available to document the efficacy of HERCEPTIN in combination with an aromatase inhibitor in situations where it could be a first-line treatment for HER2+ metastatic breast cancer.

**Pre-existing indications**

- HERCEPTIN also has marketing authorisation in the treatment of early HER2+ breast cancer, in metastatic HER2+ breast cancer as a third-line monotherapy and in metastatic gastric cancer.

**Therapeutic use**

- At the metastatic stage, if the tumour over-expresses HER2, initiating first-line triple therapy with pertuzumab/trastuzumab/taxane (preferably docetaxel) is recommended. In the presence of hormonal receptors, hormone therapy (especially aromatase inhibitor) either alone or in combination with trastuzumab may be recommended in certain situations (bone metastatic disease only, strong expression of hormone receptors, eligibility for or refusal of chemotherapy, etc.).

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

In combination with a taxane and pertuzumab, HERCEPTIN is a first-line treatment in the management of HER2+ metastatic breast cancer. In combination with an aromatase inhibitor, in certain situations, it can be a first-line treatment.

**Clinical data**

**HERCEPTIN in combination with a taxane:**

- The initial assessment of trastuzumab in this indication relied on two randomised, open-label clinical studies that aimed to demonstrate the superiority of the trastuzumab/chemotherapy combination versus chemotherapy alone.
- In the first study, conducted in 469 patients with HER2+ metastatic breast cancer that had not been previously treated, the trastuzumab/chemotherapy combination (anthracycline + cyclophosphamide or paclitaxel) versus chemotherapy alone demonstrated its superiority in terms of:

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^1 This summary does not cover these indications.

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- median time to progression (primary endpoint): 7.4 months versus 4.6 months (HR=0.51, 95% CI [0.41; 0.63]);
- overall survival: 25.1 months versus 20.3 months (HR=0.8, 95% CI [0.64; 1.00]).

In the second study, conducted in 186 patients with HER2+ metastatic breast cancer that had not been previously treated, the trastuzumab/docetaxel combination demonstrated its superiority versus docetaxel alone in terms of:
- overall response rate (primary endpoint): 61% versus 34% (p=0.0002);
- median overall survival: 31.2 months versus 22.7 months (p=0.0325).

The results from a randomised, open-label study that compared the trastuzumab/paclitaxel combination with paclitaxel alone in 124 patients with HER2+ metastatic breast cancer that had not been previously treated are available. After a median follow-up of 16.6 months, the trastuzumab/paclitaxel combination demonstrated its superiority in the overall response rate (primary endpoint): 75% versus 56.9%, (p=0.04). Superiority in terms of progression-free survival was only found in the subgroup of HER2+IHC3+ patients (369 days versus 272 days), without benefit on overall survival.

HERCEPTIN in combination with an aromatase inhibitor:

The initial assessment of trastuzumab in this indication relied on a randomised, open-label clinical study that compared the trastuzumab/anastrozole combination to anastrozole alone in 208 postmenopausal patients with HER2+ and Rh+ metastatic breast cancer that had not been previously treated. In this study, the time until progression (primary endpoint) was 4.8 months in the trastuzumab/anastrozole group versus 2.4 months in the anastrozole alone group, or an absolute gain of 2.4 months, p = 0.0016. On the other hand, median survival did not differ between the groups.

For this new assessment, the manufacturer relied on the results from a randomised, open-label clinical study that compared the trastuzumab/letrozole combination to letrozole alone in 93 postmenopausal patients with HER2+ and Rh+ metastatic breast cancer that had not been previously treated. In this study, the median time to progression (primary endpoint) did not differ in the two treatment groups.

These studies were not done in the population likely to receive hormone therapy as a first-line treatment according to the guidelines (bone disease only, high expression of hormonal receptors, ineligibility for or refusal of chemotherapy, etc.).

Cardiac toxicity, hypersensitivity reactions, haematotoxicity (febrile neutropenia in particular), and pulmonary adverse events remain the main safety concerns.

Special prescribing conditions

- Medicine for hospital prescription.
- Prescription restricted to cancer treatment and oncology specialists and departments.

Benefit of the medicinal product

- The actual benefit* of HERCEPTIN is substantial these indications.
- HERCEPTIN, in combination with a taxane and pertuzumab, just like PERJETA, has moderate clinical added value** (CAV III) in the therapeutic strategy for HER2 positive metastatic breast cancer.
- HERCEPTIN, in combination with an aromatase inhibitor, does not have clinical added value** (CAV V) in the therapeutic strategy for HER2 positive metastatic breast cancer.
- Recommends inclusion on the list of reimbursable products for hospital use.

This document was created on the basis of the Transparency Committee Opinion of 02 March 2016 (CT-14877) available at www.has-sante.fr

* 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 clinical added value.”

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