BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

AVASTIN (bevacizumab), monoclonal antibody

No clinical added value demonstrated in treatment of the first recurrence of platinum-sensitive ovarian cancer or the recurrence of platinum-resistant ovarian cancer.

Main points

- AVASTIN has Marketing Authorisation:
  - in combination with carboplatin and gemcitabine, in the treatment of the first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer;
  - in combination with paclitaxel, with topotecan or with pegylated liposomal doxorubicin, in the case of recurrence of platinum-resistant recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer.
- The addition of bevacizumab to the chemotherapy has been shown to have a moderate effect on progression-free survival, without a demonstrated increase in overall survival and quality of life but with an increase in toxicity, particularly vascular toxicity.

Pre-existing indication

AVASTIN already has Marketing Authorisation in the first-line treatment of ovarian cancer and in other malignant tumours (breast, kidney, colorectum, lung).

This summary does not cover these indications.

Therapeutic use

The choice of second-line treatment is defined as the time to recurrence after a treatment with platinum therapy, the agents previously used, the toxicity of the medicinal products used in first-line treatment, the patient's general condition, and preferences of patient and physician. The time to recurrence, defined as the period between the end of the primary treatment and the progression of the disease, establishes definition of sensitivity or resistance to platinum therapy:
- if recurrence occurs more than 6 months after the last dose of platinum therapy, the cancer is defined as platinum-sensitive;
- if recurrence occurs less than 6 months after the last dose of platinum therapy, the cancer is considered as platinum-resistant.

Recurrence is treated by:
- in case of platinum-sensitive ovarian cancer:
  Carboplatin + paclitaxel or carboplatin + liposomal doxorubicin in category 1. The combination carboplatin + gemcitabine and bevacizumab in grade 2B.
- in case of platinum-resistant ovarian cancer:
  Bevacizumab in combination with paclitaxel or liposomal doxorubicin as one option among others; the grade is not specified.

Role of the medicinal product in the therapeutic strategy

AVASTIN in combination with chemotherapy is one therapeutic option in patients with recurrent ovarian cancer platinum-sensitive or platinum-resistant, and if the patient has not previously been treated with this medicinal product.
Clinical data

- The efficacy data for bevacizumab in the indication first recurrence of platinum-sensitive ovarian cancer are from a randomised, double blind trial (OCEANS study) that evaluated the effect of the addition of bevacizumab to chemotherapy with carboplatin and gemcitabine, followed by monotherapy with bevacizumab as maintenance therapy until progression occurred, in comparison with the same chemotherapy administered on its own and without maintenance therapy.

  The response to platinum salts was evaluated according to whether recurrence occurred more than 6 month after the end of this treatment. A total of 484 patients with a performance status 0-1 were randomised between the two arms (242 patients into each arm).

  Median progression-free survival (primary efficacy endpoint) was 12.4 months in the bevacizumab arm versus 8.4 months in the comparator arm, showing an absolute gain of 4 months in favour of the bevacizumab arm (HR = 0.484, 95% CI [0.388; 0.605], p < 0.0001).

  No difference in median overall survival was observed between the two arms: 33.6 months in the bevacizumab arm versus 32.9 months in the comparator arm (HR = 0.952, 95% CI [0.771; 1.176], p = 0.6479). The quality of life was not evaluated in this study.

- The efficacy data for bevacizumab in the indication recurrence of platinum-resistant ovarian cancer are from an open-label, randomised study (AURELIA study) that evaluated the effect of combining bevacizumab to chemotherapy (pegylated liposomal doxorubicin or paclitaxel or topotecan). The response to platinum salts was evaluated according to whether recurrence occurred within 6 months of the last dose of platinum salts.

  A total of 361 patients were randomised into two arms (representing the ITT population: 179 patients in the bevacizumab arm and 182 patients in the comparator arm).

  Median progression-free survival (primary efficacy endpoint) was 6.7 months in the bevacizumab arm versus 3.4 months in the comparator arm, showing an absolute gain of 3.3 months in favour of the bevacizumab arm (HR = 0.379, 95% CI [0.296; 0.485], p < 0.0001).

  The median overall survival did not differ between arms: 16.6 months in the bevacizumab arm and 13.3 months in the comparator arm (HR = 0.870; 95% CI [0.678; 1.116]; p = 0.2711).

  Assessment of quality-of-life did not reveal any difference between the two arms.

- Main adverse effects associated with bevacizumab in the two studies were hypertension (grade ≥ 3: 17.4% to 19%) and proteinuria (grade ≥ 3: 8.5% to 12.3%). Treatment with bevacizumab was discontinued due to adverse events in 19.8% of the patients in the OCEANS study and 43.6% of the patients in the AURELIA study.

Special prescribing conditions

- Medicinal product reserved for hospital use
- Prescription restricted to certain specialists

Benefit of the medicinal product

- The actual benefit* of AVASTIN is substantial.
- AVASTIN does not provide clinical added value** (CAV V) in these two extensions of indication (platinum-sensitive recurrent ovarian cancer and platinum-resistant recurrent ovarian cancer).
- Recommends inclusion on the list of reimbursable products for hospital use.

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1* 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.

2** 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".