HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
October 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

RUBRACA (rucaparib), PARP (poly-ADP ribose polymerase) inhibitor

Substantial clinical benefit and minor clinical added value in the maintenance treatment of patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Insufficient clinical benefit to justify reimbursement in the third or later-line treatment of patients with platinum-sensitive, relapsed or progressive, BRCA mutated, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are unable to tolerate further platinum-based chemotherapy.

Key points

- RUBRACA has an MA as monotherapy in high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer: for the maintenance treatment of patients with platinum-sensitive relapsed cancer who are in response (complete or partial) to platinum-based chemotherapy, and also for third or later-line treatment of patients with BRCA mutated cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.
- Its superiority over placebo has been established on survival-free progression in maintenance treatment from the second line of treatment, regardless of BRCA mutation status.
- RUBRACA has no role in the care pathway for third or later-line treatment in BRCA-mutated patients.

Care pathway

- Following initial diagnostic and excision surgery, the standard systemic chemotherapy for advanced stages is a combination of platinum and taxane, combined or otherwise with an anti-VEGF (bevacizumab). Maintenance treatment with an anti-VEGF agent alone is then administered, when this was introduced in first-line treatment, or simple monitoring in all other cases.
- The medical management of late (i.e. platinum-sensitive) relapses is determined mainly by the BRCA mutation status.
  • For patients with somatic or constitutional BRCA mutation, platinum-based multiple-agent chemotherapy is recommended, followed by olaparib or niraparib, if no prior olaparib or niraparib treatment has been administered. To date, there is no validated indication for initiating maintenance treatment with olaparib or niraparib following non-platinum-based chemotherapy.
  • In the absence of BRCA mutation, a platinum-based combination remains recommended, followed by niraparib. In the event of contraindication to platinum, the trabectidin-pegylated liposomal doxorubicin combination can be used.
- **Role of the medicinal product in the care pathway**
  RUBRACA is a maintenance therapy from the second line of treatment, regardless of BRCA status, in adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy and who have not received previous treatment with a PARP inhibitor. The patients most likely to benefit from treatment with RUBRACA may be those with a BRCA mutation.
  In the absence of any comparative data, its role compared to niraparib is not known. In the event of BRCA mutation, its role compared to olaparib is not known. In this context, the choice between the three PARP inhibitors will be determined, in particular, by the safety profile of each of these medicinal products.

RUBRACA has no role in the care pathway in the third or later-line treatment of patients with platinum-sensitive, relapsed or progressive, BRCA mutated, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are unable to tolerate further platinum-based chemotherapy.

Clinical data

- A phase 3 randomised, double-blind study assessed maintenance treatment using rucaparib monotherapy versus placebo in 564 patients with relapsed and mainly high-grade serous epithelial ovarian cancer, who were sensitive to the platinum-based treatment regimen and in complete or partial response to the last line of platinum-based chemotherapy. Treatment with rucaparib resulted in an improvement in progression-free survival (primary outcome measure):
  - In the BRCAm population, with BRCA mutation (N=196), the median progression-free survival was 16.6 months in the rucaparib group versus 5.4 months in the placebo group, i.e., an absolute increase of 11.2 months in favour of rucaparib (HR 0.231; $CI_{95\%}$ [0.156-0.342]);
  - In the HRD (N=354), which includes the BRCAm population and 158 patients without BRCA mutation with a loss of heterozygosity rate in the tumour genome (LOH) <16%, the median progression-free survival was 13.6 months in the rucaparib group versus 5.4 months in the placebo group, i.e., an absolute increase of 8.2 months in favour of rucaparib treatment (HR 0.317; $CI_{95\%}$ [0.239-0.420]);
  - In the ITT population (N=564), the median progression-free survival was 10.8 months in the rucaparib group versus 5.4 months in the placebo group, i.e., an absolute increase of 5.4 months in favour of rucaparib (HR 0.365; $CI_{95\%}$ [0.295-0.451]).
- In the BRCAm population (N=196), no difference was observed between the rucaparib group (1.9 months) and the placebo group (4.2 months) in time to worsening of symptoms according to the DRS-P subscale score (ranked secondary outcome measure), defined as the time between randomisation and a 4-point decrease in DRS-P scale score, NS.
- No conclusion could be reached concerning overall survival (ranked analysis discontinued).
- Adverse events resulted in treatment discontinuation in 14.2% of patients in the rucaparib group and in 2.6% in the placebo group. The incidence of adverse events of grades ≥ 3 was 56.2% in the rucaparib group and 14.8% in the placebo group. The main toxicities identified with a frequency > 10% were anaemia (18.8%) and elevated ALT/AST (10.5%).

Specific prescribing conditions

- Medicinal product subject to hospital prescription.
- Prescription reserved for oncology specialists or physicians with oncology expertise.

Benefit of the medicinal product

- The clinical benefit* of RUBRACA in monotherapy is:
  - substantial in second and later-line maintenance treatment, irrespective of BRCA mutation status;
  - insufficient for third or later-line treatment in BRCA-mutated patients.
- RUBRACA provides a minor clinical added value** (CAV IV) compared to placebo in the MA indication in second and later-line maintenance treatment, irrespective of BRCA mutation status.
- Favourable opinion for retail pharmacy and hospital reimbursement in second and later-line maintenance treatment, irrespective of BRCA mutation status.
  Unfavourable opinion for retail pharmacy and hospital reimbursement for third or later-line treatment in BRCA-mutated patients.

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This document was drafted on the basis of the Transparency Committee opinion dated 09 October 2019 (CT-17654) available at **www.has-sante.fr**

* The clinical benefit (CB) 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 CB, which may be substantial, 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".