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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

LYNPARZA (olaparib), PARP inhibitor

Minor improvement in the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA1- or BRCA2-mutated high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.

Main points

- LYNPARZA has been granted a Marketing Authorisation as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) to platinum-based chemotherapy.
- Its efficacy as a maintenance treatment of BRCA1- or BRCA2-mutated ovarian cancer has been demonstrated versus placebo in terms of progression-free survival, though with no demonstrated impact on overall survival.

Therapeutic use

- After initial diagnosis and resection surgery, standard systemic chemotherapy for advanced stages is a combination of platinum and taxane (usually carboplatin and paclitaxel), which may be combined or not with a VEGF inhibitor (bevacizumab). Maintenance treatment with a VEGF inhibitor is then administered when it has been introduced in the first-line treatment.
- In case of a platinum-sensitive relapse, the regimen is modified by combining the platinum salt drug product with another medicinal product, in particular gemcitabine or pegylated liposomal doxorubicin. At the end of this second line treatment, patients are actively monitored with no specific medicinal treatment. For patients who have not received bevacizumab in first line, it can be introduced in combination with carboplatin/gemcitabine. In spite of a high response rate, relapse remains common.
  Despite the opportunity to personalise their care, no dedicated and specific treatment is available for patients with a BRCA (1 or 2) mutation who have ovarian cancer and the provided care follows the therapeutic strategy described above.

- **Position of the medicinal product in the therapeutic strategy**

  LYNPARZA is a maintenance treatment indicated for adult patients with platinum-sensitive relapsed BRCA 1 or 2 mutated (germline or somatic) high-grade serous ovarian cancer, starting from the second or later line of platinum-based chemotherapy. Testing for BRCA mutations is carried out in healthcare establishments that perform oncogenetic consultations or in molecular genetic platforms of the French National Cancer Institute [INCa].

  Owing to a lack of available data in patients who have been given platinium based chemotherapy in combination with bevacizumab followed by bevacizumab monotherapy as maintenance treatment (in the first line or in second line for a platinum-sensitive tumour), its place in the therapeutic strategy is unknown. Bevacizumab, while also administered as a maintenance therapy, cannot be considered as a competitor due to its different administration regimen and because it is not restricted to a population with a BRCA mutation.
  There is no medicinal product with an identical indication to LYNPARZA.

Clinical data

- A phase II, randomised, double-blind study to assess the efficacy of olaparib as a monotherapy maintenance treatment versus placebo, in platinum-sensitive relapsed high-grade serous ovarian cancer following treatment with two or more lines of platinum based chemotherapy.

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Patients were not selected according to their BRCA mutation status. A subgroups analysis defined in the protocol (tumour response, platinum sensitivity, Jewish descent, BRCA status) was planned. This subpopulation analysis based on the existence of a BRCA mutation has been performed retrospectively.
In the overall population, (ITT analysis population, median follow-up 37.3 months) progression-free survival (the primary efficacy endpoint) was 8.4 months in the olaparib group versus 4.8 months in the placebo group, meaning an absolute gain of 3.6 months in favour of olaparib (HR = 0.35, 95% CI [0.25-0.49]; p < 0.00001).

- No difference has been observed between the two groups for overall survival: 29.8 months in the olaparib group versus 27.8 months in the placebo group, not significant.

- A retrospectively defined subgroups analysis, showed for BRCA mutated patients (n = 136), a median progression-free survival improvement of 6.9 months in the olaparib group compared to placebo group (11.2 months versus 4.3 months; HR = 0.18; 95% CI [0.10-0.31]; p < 0.00001). As this analysis was not planned, the evidence level of this result is low. Nevertheless, this population matches to the targeted population mentioned in the Marketing Authorisation for olaparib.
- Eighteen patients had a BRCA somatic mutation (without germline mutation). Due to the small size, no formal analysis of this population was performed. Nevertheless, disease progression has been reported in 38% of patients (3/8) in the olaparib group and 60% of patients (6/10) in the placebo group, supporting better results in the olaparib group.
  The interim analysis of the overall survival has been performed after 71 occurred deaths (about half of the expected events for the analysis of this criterion: 52% of the subgroup population). The results do not demonstrate any significant difference between the olaparib and placebo groups in the population with a BRCA gene mutation.
- There was no difference in quality of life between the two groups neither the global population nor the BRCA mutated population.

- The principal adverse events reported in the olaparib group, with a frequency ≥ 10%, were nausea, fatigue and vomiting.
- As this is a maintenance treatment which will be administered until disease progression, additional safety data are required in order to reach a decision on the longer-term safety.

Prescribing conditions

Medicine for hospital prescription. Prescription restricted to oncology specialists or physicians specialised in cancer.

Benefit of the medicinal product

- The actual benefit* of LYNPARZA is substantial.
- In patients with relapsed ovarian cancer with a BRCA mutation who respond to platinum-based chemotherapy, maintenance treatment with LYNPARZA provides minor clinical added value** (CAV IV) in terms of efficacy compared with placebo.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 03 June 2015 (CT-14098) and is 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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