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2021019941

National Health Care Institute
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Our reference
2021019941

Date 24 June 2021
Subject Package advice niraparib (Zejula®)

Dear Ms van Ark,

The National Health Care Institute advises you on niraparib (Zejula®) for the maintenance treatment of adult patients with advanced, epithelial, high-grade ovary, Fallopian tube or primary peritoneal cancer, who respond fully or partially to platinum-based chemotherapy. The reason for this advice was the placing of the above-mentioned medicinal product in the so-called 'sluice' for expensive medications.

The National Health Care Institute has concluded that, in the above indication, niraparib only meets the legal criterion 'established medical science and medical practice' for a sub-group of the said indication, for patients without proven BRCA1/2 mutation. This is an effective medicinal product with a favourable cost-effectiveness, but there is uncertainty about the effect on the overall survival rate.

I would like to explain our findings and final conclusion below.

General
At your request, the National Health Care Institute, from the point of view of the health care package paid from joint premiums, determines whether new health care should be part of the health insurance package. We take into consideration the degree of certainty that this will be achieved, both in the scientific sense, as well as in terms of public support, and we consider the efficiency and transparency aspects. The National Health Care Institute is advised by two independent committees: the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness, and the Insured Package Advisory Committee (ACP) for the appraisal. We also consulted stakeholders during the assessment process.

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The National Health Care Institute has assessed niraparib on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility.

Integral weighting of package criteria

Established medical science and medical practice
Patients without proven BRCA1/2 mutation
Adults patients with advanced, epithelial, high-grade ovary, Fallopian tube or primary peritoneal cancer without proven BRCA1/2 mutation received no active anti-cancer treatment after completion of a primary care treatment with platinum-based chemotherapy. The policy consists of after-care and follow-up (an active follow-up policy).

In one randomised phase III study (PRIMA study), niraparib demonstrated a clinically relevant prolongation of progression-free survival (PFS) compared to placebo. Niraparib results in an extension of the progression-free survival rate in ovarian carcinoma patients, regardless of biomarker status. The hazard ratio (HR) was 0.62 (95% BI: 0.50– 0.76). The Oncological Medicines Assessment Committee considers an HR less than 0.7 clinically relevant. Due to the immaturity of the data, it is not yet known whether the improvement in PFS leads to an improvement in overall survival (OS). The immaturity of the data is sufficient reason for the Oncological Medicines Assessment Committee to deem its positive recommendation about niraparib to be provisional at this stage.

Quality of life with niraparib did not seem to be much different from active monitoring. In addition, more grade 3-4 undesirable effects occurred in niraparib than in active monitoring. The relative risk (RR) was 9.96 (95% BI: 6.17– 16.06). Given the default limit of 1.25, this effect is clinically relevant. However, most of the side effects were reversible or treatable.

In relation to the desirable effects of niraparib, the National Health Care Institute considers the undesirable effects as acceptable. This medicine provides this group of patients with a longer disease-free period or longer period of control compared to the current active monitoring policy. Niraparib also delays follow-up treatments that may also be harmful.

Patients with a proven BRCA1/2 mutation
Adults patients with advanced, epithelial, high-grade ovary, Fallopian tube or primary peritoneal cancer with a proven BRCA1/2 mutation receive olaparib after completion of a primary care treatment with platinum-based chemotherapy. At the time of the PRIMA study, olaparib was not yet available as a primary care maintenance treatment. For the purpose of the assessment, the National Health Care Institute carried out an indirect comparison in order to rule on niraparib for patients with a proven BRCA1/2 mutation.

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[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Established medical science and medical practice assessment: updated version (2015). National Health Care Institute,
Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

In this sub-population, niraparib showed a less significant effect on the PFS than olaparib. Based on the indirect comparison, it remains unclear whether there is less effectiveness or whether there may be an equal value. The absolute and relative data on the PFS do not rule out less effectiveness of the maintenance treatment with niraparib compared to olaparib. Differences in prognostic factors only partly explain this worse outcome.
It can also not be ruled out that the maintenance treatment with niraparib is accompanied by more intervention-related grade 3-4 undesirable effects compared to olaparib.

The physicians association indicates that the maintenance treatment with olaparib is preferred. Patients with proven BRCA1/2 mutation already have a claim to olaparib.

The National Health Care Institute has concluded that for the maintenance treatment of adult patients with advanced, epithelial, high-grade ovary, Fallopian tube or primary peritoneal cancer, who respond fully or partially to platinum-based chemotherapy:

- and who have no proven BRCA1/2 mutation, niraparib has added value compared to active monitoring, and thus niraparib meets the established medical science and medical practice for patients without proven BRCA1/2 mutation;
- and who have a proven BRCA1/2 mutation, it cannot be determined whether niraparib has at least an equal value compared to olaparib. Thus, for patients with proven BRCA1/2 mutation, niraparib does not meet the established medical science and medical practice.

Budget impact analysis
Applying niraparib for the indication mentioned above, for patients without proven BRCA1/2 mutation, will mean additional costs estimated at €15.4 million in the third year after inclusion in the package.

Cost-effectiveness
The National Health Care Institute considers the cost-effectiveness analysis of niraparib compared to 'active monitoring' of sufficient quality. The incremental cost-effectiveness ratio (ICER) has been determined as €18,927 per QALY. With a reference value of €80,000/QALY, niraparib is cost-effective compared to 'active monitoring'. Niraparib remains cost-effective in all scenarios, even when the chance of overall survival is estimated as very low.

Package advice
After weighing up the four package criteria, the National Health Care Institute has decided on the following advice:
The National Health Care Institute advises you to include niraparib for a subgroup of the mentioned indication in the package: for patients without proven BRCA1/2 mutation.
This is an effective medicinal product with a favourable cost-effectiveness to which patients require rapid access. The National Health Care Institute will review its advice when the data on overall survival become available if the provisional positive advice of the BOM committee becomes a negative advice.

Appropriateness
For the selection of treatment, patients are examined for the BRCA1/2 mutation through genetic diagnostics of tumour material. These tests are already being done; the organisation of such testing can however vary from one medical centre to the next.

Evaluation
If niraparib is admitted into the health insurance package, the National Health Care Institute will actively monitor the use of niraparib. We will inform you about our findings no later than 2025. In the context of the treatment landscape, the National Health Care Institute takes the following points into consideration:
- The initial estimate of the number of patients compared to the actual number treated;
- The cost development compared to the original estimate.

If this monitoring yields signs that deviate a great deal from the current estimates, this may give the National Health Care Institute cause to reassess the position of niraparib.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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