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National Health Care Institute
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Our reference
2024002818

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Date 13 February 2024
Re: Advice lock procedure medicinal product olaparib (Lynparza®) for the treatment of HER2-negative high-risk early-stage breast cancer with germline BRCA mutations

Dear Mrs Dijkstra,

We are hereby sending you the package advice for olaparib (Lynparza®) for the adjuvant treatment of adult patients with germline BRCA1/2 mutations who have early HER2-negative, high-risk breast cancer. The reason for this advice was the placement of olaparib in the lock procedure for expensive medicinal products.

Registered indication
Olaparib is indicated as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Claim by the marketing authorisation holder
1 In the adjuvant treatment of adult patients with germline BRCA1/2 mutations who have HER2-negative, high-risk early breast cancer and have previously been treated with neoadjuvant or adjuvant chemotherapy, olaparib treatment as monotherapy or in combination with endocrine therapy has a added value over active monitoring.
2 In the adjuvant treatment of adult patients with germline BRCA1/2 mutations that have triple negative (TNBC), high-risk early breast cancer and have residual disease (non-PCR) after neoadjuvant chemotherapy, olaparib monotherapy has added value over capecitabine as monotherapy.

Package advice
The National Health Care Institute recommends that olaparib be included in the basic health care package for the treatment of adult patients with germline BRCA1/2 mutations who have triple negative (TNBC), high-risk early breast cancer and who do not achieve a pathological complete response (pCR) after neoadjuvant chemotherapy and surgery (hereafter: *'TNBC patients'),* provided that the net price after successful price negotiations does not exceed the net price of the current standard treatment with capecitabine. The National Health Care Institute has established that, in the present indication for *'TNBC patients'*, olaparib has an equal value to capecitabine and thus meets the legal criterion of 'established medical science and medical practice'. There is no scientifically adequate evidence of added value.

The National Health Care Institute advises you to not include olaparib in the basic health care package for the treatment of adult patients with germline BRCA1/2 mutations who have hormone receptor positive (HR+), HER2- negative (HER2-) early breast cancer (hereinafter: *'HR+HER- patients'*). Olaparib does not comply with the established medical science and medical practice for the present indication for *'HR+HER2- patients'*.

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The development of this package advice is explained below.

General
At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums. The National Health Care Institute assesses on the basis of the four package criteria [1]: effectiveness[2], cost-effectiveness[3], necessity[4] and feasibility[5]. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment.

Comprehensive weighting of package criteria
Established medical science and medical practice
Olaparib was studied for the present indication in the randomized, double-blind, placebo-controlled, multicentre, Phase 3 OlympiA study. Included patients had high-risk HER2 negative breast cancer with a germline BRCA mutation and had undergone completed local therapy with adjuvant or neoadjuvant chemotherapy. The randomisation was stratified by hormone receptor status (HR+ or TNBC), time of chemotherapy (adjuvant or neoadjuvant) and the administration of platinum-containing chemotherapy in pre-treatment. The use of adjuvant capecitabine was not allowed. The majority of included patients (~80%) had TNBC. The comparative treatment in the control arm of the OlympiA study was not consistent with the treatment(s) used in the Netherlands. Based on the current treatment options in Dutch practice, the comparative treatment with (adjuvant) olaparib differs for *'HR+HER2- patients'* and *'TNBC patients'*. As usual, the National Health Care Institute has joined the status determination and treatments as indicated by the physicians' association in the CieBOM advice for adjuvant capecitabine (2018), the NABON/NIV 'Breast cancer' guideline (2019) and the CieBOM advice for olaparib (2023). For *'HR+HER2- patients'*, 'active monitoring' is the most relevant comparative treatment. For *'TNBC patients'*, capecitabine is the most relevant comparative treatment. The beneficial effects of olaparib have therefore been assessed separately in these subgroups.

Direct comparison of olaparib with 'active monitoring' in 'HR+HER2- patients'
In *'HR+HER2- patients'*, olaparib in the present indication did not result in statistically significant and clinically relevant improvement in overall survival (OS) compared to placebo [HR: 0.90 (95%CI: 0.449; 1.784)]. No difference in quality of life has been demonstrated. The use of olaparib resulted in a clinically relevant increase in both the incidence of intervention-related severe undesirable effects and the discontinuation rate due to undesirable effects. Based on these findings, the National Health Care Institute concludes that in *'HR+HER2- patients'*, there is no scientifically adequate evidence for a added value of olaparib compared to 'active monitoring'.

Indirect comparison of olaparib with capecitabine in 'TNBC patients'
This indirect comparison uses the study results for 'TNBC Patients' in the OlympiA and CREATE-X studies, respectively. The CREATE-X study was a randomised, open

label, multicentre phase 3 study. The study included only Japanese and Korean patients without distinction between patients with or without germline BRCA mutation. It was unclear how many patients had also been treated with platinum-containing chemotherapy. When used in *'TNBC patients'*, both olaparib (HR: 0.64 [95%CI: 0.459, 0.884]) and capecitabine (HR: 0.52 [95%CI: 0.30, 0.90]) show a clinically relevant gain in overall survival (OS) compared to placebo/active monitoring. Based on the indirect comparison, there was no clinically relevant difference in OS for olaparib versus capecitabine (HR: 1.09 [95%CI: 0.82; 1.45]). This difference was also not statistically significant. No differences in quality of life could be identified because relevant data was missing from the CREATE-X study. Although olaparib compared to capecitabine may have resulted in more toxicity but also fewer discontinuations due to undesirable effects, the confidence in (the reliability of) this comparison is very low, due to, among others, the naive indirect comparison, the open label design of the CREATE-X study and the significant differences in patient characteristics.
Taking everything into account, the National Health Care Institute has assessed that olaparib has an equal value to capecitabine. For the National Health Care Institute, the above data and additional recent scientific publications on the potentially reduced action of capecitabine in TNBC patients with a germline BRCA mutation do not provide convincing scientific evidence of a added value for olaparib over capecitabine.

Following the discussion of these observations with its Scientific Advisory Board (WAR), the National Health Care Institute has established that olaparib does not meet the established medical science and medical practice for the present indication 1) for *'HR+HER2- patients'* and 2) for *'TNBC patients'* it has an equal value to capecitabine and thus does meet the established medical science and medical practice.

Cost-effectiveness
As no added value for olaparib has been demonstrated in the present indication, the National Health Care Institute has not assessed the cost-effectiveness.

Budget impact analysis
The National Health Care Institute expects that olaparib will substitute for half of the capecitabine after 3 years. In this calculation, the pharmacy purchase prices of olaparib and capecitabine (reference date: October 2023) were the starting point. Based on a market penetration of 20% in year 1, 40% in year 2 and 50% in year 3, 47 patients are expected to be eligible for olaparib (Lynparza®) treatment in the third year following introduction for the present indication. Taking into account the substitution of capecitabine, the additional costs will be approximately €2.3 million in the third year. Based on two additional scenarios with a minimum and maximum market penetration, the National Health Care Institute expects the additional costs to be between €1.1 million and €3.6 million.

The National Health Care Institute is well aware that the physicians' association's current guidelines for the treatment of TNBC patients, which were the basis for its assessment of olaparib, may have underemphasized the role and exact value of olaparib. In this context, however, the National Health Care Institute fully follows the principles and procedure described in its document 'Beoordeling Stand van de Wetenschap en Praktijk' (Assessment of the established medical science and medical practice) (2023). In its assessments, the current guideline(s) of the physicians' association are both normative and guiding. Therefore, if the physicians' association adapts the guidelines described earlier in this letter to the

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advancing medical-scientific insight regarding the therapeutic application and (added) value of olaparib for the present indication, the National Health Care Institute is willing to appropriately reconsider its advice.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report and budget impact analysis are attached to this letter.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Beoordeling Stand van de Wetenschap en Praktijk (2023) (Assessment of the established medical science and medical practice). National Health Care Institute. Via www.zorginstituutnederland.nl.

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

[4] Necessity deals with both the medical necessity and the result of the severity

[5] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic health care package. It is therefore mainly a test of a number of implementation aspects such as health care organisation, support, ethical and legal aspects, budget impact and so on. See the report on real-world package management 4 (2023).