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Contact
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2024035903

Date 10 October 2024
Re: Package advice olaparib (Lynparza®) for prostate cancer

Our reference
2024035903

Dear Ms Agema,

The National Health Care Institute advises you about olaparib (Lynparza®) in combination with abiraterone for the treatment of certain patients with metastatic castration-resistant prostate cancer (mCRPC). The reason for this advice was the placement of olaparib in the lock procedure for expensive medicinal products.

In the Netherlands, approximately 13,000 men are diagnosed with prostate cancer every year. Prostate cancer usually progresses slowly and does not show any obvious symptoms or problems at first. In case of metastatic prostate cancer, the chance of survival decreases significantly. The 10-year survival rate of Dutch patients with localised prostate cancer at diagnosis is more than 90%, but in metastatic prostate cancer, the 10-year survival rate drops to 31%. Hormone therapy is often given at the beginning of treatment when the prostate cancer is still hormone-sensitive. By decreasing testosterone levels, tumour growth decreases. If the tumour no longer responds adequately to hormone treatment and the prostate specific antigen (PSA) level increases, this is called castration-resistant prostate cancer (CRPC). Some patients with mCRPC have a mutation in the HRR genes. Patients with an HRR mutation generally face a worse prognosis.

Registered indication
Olaparib in combination with abiraterone and prednisone or prednisolone is indicated for the treatment of adult patients with mCRPC who do not have a clinical indication for chemotherapy.

Claim by the marketing authorisation holder
Olaparib in combination with abiraterone and prednisone or prednisolone, for the treatment of adult patients with mCRPC and a mutation in the *homologous recombination repair* (HRR) genes, has an added value compared to standard abiraterone treatment in combination with prednisone or prednisolone.

Package advice

The National Health Care Institute recommends that olaparib in combination with abiraterone and prednisone or prednisolone, for the treatment of adult patients with mCRPC and HRR mutations, not be included in the basic health care package. The National Health Care Institute has determined that olaparib does not meet the legal criterion of 'established medical science and medical practice' for the

indication mentioned. There is insufficient evidence that adding olaparib to the standard treatment in the said population has a clinically relevant effect on overall survival, while adverse effects are likely to increase. 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. Interested parties were also consulted in this context.

Since olaparib does not meet the legal criterion of 'the established medical science and medical practice' for the relevant indication, a comprehensive weighting of the four package criteria and advice from the Insured Package Advisory Committee (ACP) is not relevant in this case.

Comprehensive weighting of package criteria

Established medical science and medical practice

For the treatment of mCRPC, several treatment options are possible in the first line, namely hormonal therapy (abiraterone, enzalutamide), chemotherapy (docetaxel), and (internal) irradiation (radium-223). These treatments have shown a similar survival benefit and beneficial effects on quality of life in the first line. If patients are expected to be intolerant to chemotherapy, or when docetaxel has already been used in the hormone-sensitive stage, hormonal therapy is usually preferred as first-line therapy. Abiraterone and enzalutamide have a similar effectiveness. In the Netherlands, abiraterone is currently preferred because it has a lower price than enzalutamide due to it being out of patent. Abiraterone is given in combination with prednisone or prednisolone.

Olaparib is a so-called PARP inhibitor with a different mode of action from hormonal therapy. It is believed that olaparib and abiraterone may have a synergistic anti-tumour effect.

In April 2024, the CieBOM committee of the Dutch Association of Medical Oncology (NVMO) gave a positive advice for olaparib in combination with abiraterone and prednisone or prednisolone for mCRPC patients, regardless of an HRR mutation. This is a wider population than the population for which reimbursement is sought. The CieBOM advice is based on results of the primary

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

[2] Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Rapport kosteneffectiviteit (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[4] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

[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 the health care organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

outcome measure radiographic progression-free survival (rPFS) after a median follow-up of almost 2 years in the PROpel study. According to the CieBOM, the results obtained meet the PASKWIL2023 criteria for palliative treatment in studies in which the median survival in the control group is greater than 12 months.

The effectiveness and safety of olaparib in combination with abiraterone was investigated in a randomised, double-blind, phase III study (PROpel) in patients with mCRPC and directly compared to abiraterone in combination with prednisone or prednisolone. Because the results of the final analysis of overall survival (OS) are available, the National Health Care Institute bases its assessment primarily on OS data, not PFS data, as PFS is a surrogate outcome measure of survival. OS was a secondary outcome measure in the PROpel study. The final analysis of the entire study population (regardless of HRR mutation) showed that the median OS in the olaparib-abiraterone arm was 42.1 months, and 34.7 months in the abiraterone arm, resulting in a *hazard ratio* (HR) of 0.81 (95% CI: 0.67-1.00). This effect on the OS is not statistically significant and not clinically relevant according to the PASKWIL2023 criteria. Approximately one third of the patients in the study had an HRR mutation (i.e. the patient population for which reimbursement is sought). The final analysis of this subgroup of patients with an HRR mutation showed that the median OS was not yet achieved in the olaparib-abiraterone arm compared to 28.5 months in the abiraterone arm in the HRR mutation subgroup. This results in an HR of 0.66 (95% CI: 0.45 – 0.95). However, the National Health Care Institute takes the view that this subgroup analysis should be considered exploratory and that no hard conclusions can be drawn from this outcome. It would have been possible to carry out a better-designed study. Indeed, the European Medicines Agency (EMA) had recommended stratifying the study based on HRR mutation status and setting up the subgroup analysis with sufficient power. However, this advice was not followed by the marketing authorisation holder. Based on the current data, it has not been sufficiently proven that adding olaparib to abiraterone results in a clinically relevant improvement in overall survival. The addition of olaparib to abiraterone is unlikely to result in a clinically relevant effect on quality of life. However, it is evident that the safety profile of olaparib in combination with abiraterone is worse than that of abiraterone monotherapy. The addition of olaparib to the treatment with abiraterone will likely result in a clinically relevant increase in the serious adverse events and a clinically relevant increase in the number of discontinuations due to adverse events.

Combination treatment
When a new treatment is added to the standard treatment in the form of a combination treatment (new + standard treatment), there must be demonstrable added value compared to the standard treatment for health care to comply with the established medical science and medical practice. In this case, the conclusion of equal value is not possible.

Budget impact

Because olaparib does not meet the established medical science and medical practice for the indication mentioned, no budget impact analysis was performed.

Conclusion

Overall, there is insufficient evidence that adding olaparib to abiraterone in combination with prednisone or prednisolone has a clinically relevant effect on

overall survival in patients with mCRPC and HRR mutations, while the toxicity and the number of patients who discontinue treatment are likely to increase due to adverse reactions. Furthermore, the addition of olaparib is unlikely to have a clinically relevant effect on quality of life. In the absence of a clinically relevant improvement of the beneficial effects, a clinically relevant increase of adverse effects is unacceptable. The National Health Care Institute concludes that olaparib in combination with abiraterone has no demonstrated added value over abiraterone monotherapy, and therefore does not meet the established medical science and medical practice. The National Health Care Institute recommends that olaparib in combination with abiraterone and prednisone or prednisolone, for the treatment of adult patients with mCRPC and HRR mutations not be included in the basic health care package.

Yours sincerely,

Mark Janssen
Chairperson of the Executive Board