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National Health Care Institute
Care
Medicinal Products

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Our reference
2024021493

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Date 12 June 2024
Re: advice on lock procedure medicinal product niraparib-abiraterone (Akeega®)

Dear Ms Dijkstra,

The National Health Care Institute advises you about niraparib-abiraterone (Akeega®) for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations) in whom chemotherapy is not clinically indicated. The reason for this advice was the placement of niraparib-abiraterone in the lock procedure for expensive medicinal products.

Registered indication
Niraparib-abiraterone is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

Claim by the marketing authorisation holder
Niraparib-abiraterone, for the treatment of adult patients with mCRPC and BRCA1/2 mutations, has therapeutic added value over standard treatment with abiraterone or enzalutamide.

Package advice
The National Health Care Institute recommends that niraparib-abiraterone, for the treatment of adult patients with mCRPC and BRCA1/2 mutations, not be included in the basic health care package. The National Health Care Institute has determined that niraparib-abiraterone does not meet the legal criterion of 'established medical science and medical practice' for the indication mentioned. 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-

[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

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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 niraparib-abiraterone does not meet the legal criterion of 'the established medical science and medical practice' for the relevant indication, the full 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

Background

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 carcinoma 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 carcinoma (CRPC). Some patients with mCRPC have a mutation in the *BReast CAncer* genes (BRCA mutation). Patients with a BRCA1/2 mutation generally face a worse prognosis.

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 treatment. Abiraterone and enzalutamide have a similar effectiveness. In the Netherlands, abiraterone is currently preferred because of its lower price than enzalutamide since there is no longer a patent on it. Abiraterone is given in combination with prednisone or prednisolone.

Niraparib-abiraterone is a combination preparation of niraparib (as tosylate monohydrate) and abiraterone acetate. Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, which play a role in DNA repair. Abiraterone inhibits the CYP-17 enzyme that is involved in the production of androgens, such as testosterone.

In April 2024, the CieBOM committee of the Dutch Association of Medical Oncology (NVMO) gave a positive advice for niraparib-abiraterone for mCRPC

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[3] Cost-effectiveness report (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).

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patients with BRCA1/2 mutations. This advice is based on results of radiographic progression-free survival (rPFS) after a median follow-up of 18.6 months in the MAGNITUDE 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.

Effectiveness
The effectiveness and safety of niraparib-abiraterone in combination with prednisone or prednisolone was investigated in a randomised, double-blind, phase III study (MAGNITUDE) in patients with mCRPC and BRCA1/2 mutations, in which it was directly compared to abiraterone in combination with prednisone or prednisolone.

The National Health Care Institute concluded that patients with mCRPC and BRCA1/2 mutations treated with the niraparib-abiraterone combination treatment had a longer rPFS compared to patients treated with abiraterone monotherapy. The median rPFS in the niraparib-abiraterone arm was 16.6 months, compared to 10.9 months in the abiraterone arm, resulting in a hazard ratio (HR) of 0.53 (95% confidence interval (CI): 0.36 – 0.79). This effect on the surrogate outcome measure PFS was statistically significant and clinically relevant according to the PASKWIL2023 criteria. A *reasonable* correlation between rPFS and overall survival (OS) is described in the literature. It is therefore not possible to conclude with certainty that the benefit on rPFS will translate into a survival benefit. This is confirmed both by the interim analysis OS data (median follow-up duration: 18.6 months), and the final analysis OS data (median follow-up duration: 35.9 months). The interim analysis showed that OS was 29.3 months in the niraparib-abiraterone arm, compared to 28.6 months in the abiraterone arm, resulting in an HR of 0.88 (95% CI: 0.58 – 1.34). The final analysis showed that OS was 30.4 months in the niraparib-abiraterone arm, compared to 28.6 months in the abiraterone arm, resulting in an HR of 0.79 (95% CI: 0.55 – 1.12). Based on this data, the National Health Care Institute concluded that patients with mCRPC and BRCA1/2 mutations treated with the niraparib-abiraterone combination treatment did not show a clinically relevant longer survival rate compared to patients treated with abiraterone monotherapy.

Quality of life and adverse effects
The effect of niraparib-abiraterone on the quality of life is very uncertain. However, it is evident that the safety profile of niraparib-abiraterone is worse than that of abiraterone monotherapy. The addition of niraparib to the treatment with abiraterone resulted in a clinically relevant increase in the severe adverse events and a clinically relevant increase in the number of patients who discontinued treatment due to adverse effects.

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 in comparison with the standard treatment for health care to comply with the established medical science and medical practice. In that case, the conclusion of equal value is not sufficient.

Budget impact
Because niraparib-abiraterone does not meet the established medical science and

medical practice, no budget impact analysis was performed.

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Conclusion
All in all, niraparib-abiraterone does not result in clinically relevant longer survival or clinically relevant improvement in quality of life. However, the toxicity and the number of patients who discontinued treatment due to these adverse reactions showed a clinically relevant increase. 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 niraparib-abiraterone has no demonstrated added value over abiraterone and enzalutamide, and therefore does not meet the established medical science and medical practice. The National Health Care Institute recommends that niraparib-abiraterone, for the treatment of adult patients with mCRPC and BRCA1/2 mutations, not be included in the basic health care package.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board