REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Xofigo

Solution for injection 1100 kBq/mL – 6 ml x 1 vial

Radium (223Ra) dichloride

Therapeutic indication(s)	Xofigo as monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.
Start/end date of procedure	19.04.2019 – 15.07.2020
Final decision	Rejects inclusion: - in Annex 2 of the Positive Drug List (PDL) for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act. - In Annex 3 of the PDL for the treatment of diseases, paid from the budget of the Ministry of Health.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Xofigo

Health problem

Prostate cancer is the most common solid tumor in men in the EU and the United States and is the second leading cause of cancer death in men in both regions. Despite the relatively sluggish course of disease, if not detected or treated, it can spread beyond the prostate to the lymph nodes and possibly to the bones. Prostate cancer that has metastasized to the bone is considered to be untreatable and comprises a significant humanitarian and economic burden, having a negative effect on patients, due to pain, fractures and reduced survival, as well as on the health care systems because of the expensive late-stage therapies, the treatment of the symptomatic skeletal events and related palliative care.

In the 2017 recommendations of the European Society of Medical Oncology for good clinical practice in the treatment and follow-up of metastatic castration-resistant prostate cancer (mCRPC), Radium-223 is included as a first-line treatment after prior treatment with docetaxel. In patients after docetaxel therapy, enzalutamide, abiraterone, cabazitaxel and radium-223 (without visceral disease) are recommended as therapeutic options. Abiraterone, enzalutamide and radium-223 reduce the risk of symptomatic skeletal events (SSE). The palliative treatment section states that the radionuclide beta emitters St-89 and Sm-153-HEDP have proven benefits in the treatment of metastatic CRPC, but their use is limited because of their myelotoxicity and they are being replaced byradium- 223.

Epidemiological data

Prostate cancer is the second most common cancer in men globally. The reported rate is 15% of all cancers in men. According to GLOBOCAN, the expected incidence of prostate cancer in 2018 was 1.3 million new cases worldwide.

According to European cancer registries, prostate cancer ranks first among the most commonly diagnosed cancers in middle-aged men in the EU, with the number of new cases being approximately 24% of all newly diagnosed cancers.

According to data from the cancer registry in Bulgaria for 2015, prostate cancer is the second most common in men and accounts for 15.7% of all malignancies in them and 9.3% of deaths as a result of malignant diseases in men. The mortality rate is 13.5/100,000 population.

Efficacy data

An analysis of data on the therapeutic efficacy and safety of radium 223 health technology for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases was performed.

ALSYMPCA (NCT00699751) - A multinational, randomized, double-blind, placebo-controlled, phase 3 study to assess survival with radium-223 treatment in patients with metastatic prostate cancer. Number of patients in the study - 921. Following an interim analysis, an independent panel reported an advantage in overall radium-223 survival with an acceptable safety profile. Radium-223 therapy reduces the risk of death by 30%.

Metaanalysis

Data from a meta-analysis to assess the effect of radiopharmaceuticals (RP) in castration-resistant prostate cancer on pain control in symptomatic skeletal events, toxicity profile, quality of life, and overall patient survival were cited. The use of radiopharmaceuticals resulted in a significant reduction in pain intensity and symptomatic skeletal events (OR: 0.63), improved quality of life (OR: 0.71), and minimal improvement in overall survival (OR: 0.84). Subgroup analysis showed an improvement in overall survival in radium-223 (OR: 0.68) and strontium-89 (OR: 0.21). The use of strontium-89 has been associated with thrombocytopenia (grade 3 and 4) (OR: 4.26), leukopenia (OR: 7.98), exacerbation of pain (OR: 6.82) and vomiting (OR: 3.61).

Data reported by patients

The effect of radium-223 treatment on the pain score (PMS) of the Functional Assessment of Cancer Therapy - Prostate (FACT-P) was assessed by evaluating subgroups identified by previous docetaxel use and baseline bone metastases. Significantly more of the patients treated with radium-223 were responders, compared to placebo. Improvement, as regards pain control, occurs with each visit. Radium-223 significantly increased the likelihood of improvement of pain control, compared to placebo at week 16 and week 24.

Safety data

The number of patients with adverse reactions (ADR) was lower in the radium-223 group than in the placebo group: 93% versus 96% for all adverse events, 56% versus 62% for grade 3 or 4 ADR, 47% compared to 60% for serious ADR. The rate of patients discontinuing therapy due to ADR were 16% in the radium-223 group versus 21% in the placebo group.

ADR occurring in at least 5% of patients were: haematological (anemia, thrombocytopenia, neutropenia) and non-hematological (constipation, diarrhea, nausea, vomiting, asthenia,

fatigue, deterioration of general health, peripheral edema, pyrexia, pneumonia, urinary tract infection, weight loss, anorexia, decreased appetite, bone pain, muscle weakness, pathological fracture, progression of malignant neoplasm, dizziness, spinal cord compression, insomnia, hematuria, urinary retention, dyspnoea).

The rate of serious ADR that occured in at least 5% of patients was as follows: disease progression (11% and 12%), bone pain (10% and 16%), anemia (8% and 9%), and spinal cord compression (4% and 5%).

Data on comparators

The available therapeutic alternatives for treating patients with CRPC in Bulgaria are Jevtana (cabazitaxel), Xtandi (enzalutamide), and Zytiga (abiraterone acetate).

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions, intended for the health care systems of other countries

Three assessments of the health technology performed by state institutions for the purposes of the national health care systems of the United Kingdom, Germany and France were presented, all of which are positive and recommend the reimbursement of the new technology.

Applied analysis

The selected methods for comparative evaluation of the health technology Radium (223Ra) dichloride are cost-utility and cost-effectiveness economic analyses. The results were measured and presented as long-term measures - years of life gained (LYs) and quality adjusted years of life (QALYs).

The main alternatives are abiraterone, cabazitaxel, enzalutamide and BSoC (best supportive care). The utility data calculated from the ALSYMPCA clinical trial were obtained using FACT-P, EQ-5D and EQ-VAS, primarily being based on EQ-5D. The analysis is from the point of view of the payer for a time horizon of 5 years with a discount of 3.5% and with sensitivity analysis included.

A Markov model with five mutually exclusive health conditions was applied: progression-free survival (PFS), no symptomatic skeletal events (SSE); PFS with SSE; progression without SSE; progression with SSE and absorbing state (death). The model simulates the treatment of a cohort of patients with mCRPC, taking into account the costs and health benefits for health conditions at each new cycle.

Radium-223 demonstrated more LYG than abiraterone and cabazitaxel, and data from the modeled time horizon showed that Radium-223 therapy was associated with higher quality of life compared to therapeutic alternatives abiraterone and cabazitaxel. The results of pharmacoeconomic analyses show that the additional benefits are associated with additional costs, with the incremental ratio being above the break-even point.

Costs for the assessed health technology

The model presents costs for BSoC (best supportive treatment - androgen blockade therapy, bisphosphonates, denosumab and analgesics, loccal radiation therapy), costs for methylprednisolone as addition to abiraterone and cabazitaxel therapy, costs of disease follow-up, costs of palliative care and costs of adverse reactions management.

Budget impact analysis

The number of patients included in the budget impact analysis was 8 in the first year, increasing to 22 in the fifth year.

The reimbursement of the new technology will lead to an increase in the costs in all of the cases considered, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Xofigo is the first in the class of alpha-emitting medicinal products ("alpha pharmaceuticals") and has a potent targeted antitumor effect on bone metastases with the potential to provide both a survival benefit and a very well tolerable safety profile, including a reduction of the chronic radiation exposure of the patient. The performed pharmacoeconomic analysis shows that the therapy leads to additional benefits, compared to the alternatives, at higher costs for therapy. The analysis of the budget impact shows an increase in the costs of the paying institution.