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

HEALTH TECHNOLOGY ASSESSMENT

Erleada

60 mg film-coated tablet x 120

Apalutamide

Therapeutic indication(s)	Indicated in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.
Start/end date of procedure	27.04.2020 – 20.11.2020
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the cost of the rendered medical services.

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

Health problem

Prostate carcinoma occurs as a result of genetic mutations in prostate cells. Androgen-stimulated growth plays a key role in its development. The androgen receptor is activated by androgens (testosterone) binding to it, which are important growth factors for prostate cancer cells, as well as a number of other signaling pathways that can also alter its activity in prostate cancer cells. Unlike first-generation anti-androgens (bicalutamide), apalutamide binds selectively and irreversibly with high affinity to the androgen receptor, while binding minimally to other hormone and neurotransmitter receptors. Apalutamide - mediated suppression of androgen-regulated transcription suppresses the expression of genes that determine the viability and growth of a prostate tumor and inhibits its progression.

Most prostate cancers respond to androgen deprivation, which often stops the growth of prostate cancer and slows the progression, emphasizing the importance of this signaling pathway for the development of prostate cancer. Serum levels of prostate-specific antigen (PSA) are used to screen for prostate cancer and to assess disease progression.

Epidemiological data

In Bulgaria, prostate cancer is the second most common in men and represents 17.0% of all malignancies in males. The actual incidence is 82.9 per 100,000. The actual mortality is 26.3 per 100,000. The trends in prostate cancer incidence and mortality show an increase of 3.7% and 1.3% on average per year.

The incidence of prostate cancer increases with age after 45 years and reaches its peak in 75-79 year olds (543.9 per 100,000 men). Morphologically confirmed are 94% of cases and the majority of them are diagnosed with adenocarcinoma. More than half of the patients (64.3%) are diagnosed in the initial (first and second) stage of the disease. In 29.0% it is in the third and fourth stage while in the rest the stage is not specified.

According to the Bulgarian National Cancer Registry of the National Oncology Hospital (Volume XXV 2017), the five-year relative survival rate for prostate cancer in Bulgaria is 53.7%.

Efficacy data

The efficacy and safety of apalutamide in patients with non-metastatic, castration-resistant prostate cancer (nmCRPC) were ascertained in the phase 3 SPARTAN study.

Metastase-free survival (MFS) is the primary endpoint. Treatment with Erleada significantly improved MFS and reduced the relative risk of distant metastases or death by 70% compared with placebo, extending the median MFS by more than two years. An improvement in MFS in Erleada was observed in all predetermined subgroups, including age, race, region of the world, nodal status, previous number of hormone therapies, PSA at baseline, time to PSA doubling, ECOG status at baseline, and use of bone-sparing agents. Apalutamide significantly increased the median overall survival (OS) by 14 months. It prolonged the PFS2 median progression-free survival by 14.4 months. Apalutamide reduced the risk of symptomatic progression by 55%. Apalutamide reduced PSA by ≥ 50% compared to 89.7%, significantly reducing the risk of PSA progression by 94%. It significantly decreased the risk of initiating cytotoxic chemotherapy by 37% and accordingly delayed initiation of therapy. The addition of apalutamide to androgen deprivation therapy (ADT) is well tolerated and helps maintain a good health-related quality of life (HRQoL).

Analysis of patient-reported data

The overall score of FACT-P (Functional Assessment of Cancer Therapy - Prostate) in the apalutamide + ADT arm was comparable to that in the control group, with values maintained for the duration of treatment. The mean FACT-G (Functional Assessment of Cancer Therapy - General) apalutamide + ADT score is similar to the FACT-G score of the general population. In the subgroup of patients with symptomatic progression, the FACT-P score was higher in the apalutamide + ADT arm before and after progression. The results are similar for FACT-G.

Safety data

The most common side effects are fatigue (26%), skin rash (26% of any grade and 6% grade 3 or 4), hypertension (22%), hot flashes (18%), arthralgia (17%), diarrhea (16%), fall (13%) and weight loss (13%). Other important side effects include fractures (11%) and hypothyroidism (8%).

Data on comparators

The main comparator is the drug enzalutamide. An indirect comparison was made between the two alternatives in high-risk patients with nmCRPC. The results of SPARTAN (apalutamide) and PROSPER (enzalutamide) studies were used as a basis.

The results show that apalutamide + ADT is superior to enzalutamide + ADT in terms of MFS and OS. The results also show that apalutamide + ADT is highly likely to be superior to enzalutamide + ADT in terms of safety profile and patient-reported outcomes.

Pharmacoeconomic indicators

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

The medicinal product Erleada was evaluated by the governmental institutions of France (HAS) and Canada (CADTH), with both evaluations being positive and recommending reimbursement.

Applied analysis

Cost-benefit and cost-effectiveness methods with outcome measures quality-adjusted life years (QALYs) and years of life gained (LYG), respectively, were applied, as nmCRPC affects both patients' quality of life and life expectancy. The perspective is that of the paying institution – the NHIF. The time horizon of the analysis is 10 years. The target population of the analysis is high-risk patients with non-metastatic castration-resistant prostate cancer (nmCRPC). Therapeutic alternatives in the analysis are enzalutamide and apalutamide. A survival model was applied, including 3 mutually exclusive health conditions: patients with nmCRPC, patients with mCRPC, and death.

The results of the applied model show that Erleada prolongs life and improves the quality of life of patients. For additional acquired QALY and for an additional year of LYG life, a cost is added compared to ADT monotherapy and enzalutamide + ADT therapy. The values of the incremental cost-effectiveness ratio (ICER) compared to the alternative enzalutamide + ADT are on the threshold of cost effectiveness at the break-even point in Bulgaria.

Costs of the assessed health technology

The cost of drug therapy with alternatives is included. Costs of medicinal products administration, treatment of adverse reactions, subsequent therapy were not taken into account, as they are similar between the alternatives.

Budget impact analysis

The budget impact analysis is performed from the perspective of the public paying institution – the NHIF. The time horizon is 5 years. The estimated number of patients is 17 in the first year and reaches 107 in the fifth year. The reimbursement of the new health technology Erleada (apalutamide) generates additional costs, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Apalutamide significantly reduces the risk of distant metastases, reduces the risk of metastasis or death. Apalutamide significantly increases the median OS and the median PFS, in addition

to reducing the risk of symptomatic progression and the risk of initiating cytotoxic chemotherapy. The addition of Apalutamide to ADT is well tolerated and helps maintain a good HRQoL. Apalutamide has a safety profile that does not change with longer follow-up. Erleada prolongs patients' lives and improves quality of life, with additional cost of additional results defining Erleada as a cost-effective therapy. The inclusion of Erleada in the Positive Drug List leads to higher cost for the NHIF, without taking into account risk-sharing agreements and patient access schemes.