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

HEALTH TECHNOLOGY ASSESSMENT

Orladeyo

150 mg capsule, hard x 28 blister

INN Berotralstat

Therapeutic indication(s)	For the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Start/end date of procedure	27.04.2023 – 13.12.2023
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases reimbursed by the National Health Insurance Fund (NHIF).

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

Health problem

Hereditary angioedema (HAE) is an autosomal dominant genetic disorder that is characterized by recurrent attacks of angioedema, which are intense and often disfiguring and/or extremely painful swelling of the subcutaneous or submucosal tissue that can impair the patients' ability to carry out their daily activities or even make breathing difficult depending on its location. Angioedema usually lasts a few hours but can last from two to five days. The subcutaneous tissue of the face (especially the lips and eyelids), hands, arms, legs, buttocks and genitalia, including the scrotum and penis or labia, are most commonly affected. HAE can affect the abdominal organs, including the stomach and gastrointestinal tract, as well as the bladder, kidneys and urethra. Patients may have acute symptoms of diarrhea, nausea, vomiting or paroxysmal colic pain. Edema of the upper respiratory tract, larynx, pharynx and tongue can lead to life-threatening obstruction and risk of asphyxiation. In some cases, patients with HAE report visual disturbances, such as diplopia or blurred vision, ataxia and severe headache. The significant burden of HAE on patients, their caregivers, the healthcare system and society at large is due to the debilitating, chronic, unpredictable and potentially life-threatening course of this currently incurable disease.

Patients with HAE-1/2 may also have comorbidities, including autoimmune disease, allergy, asthma, hypertension, fibromyalgia, depression and anxiety. Patients with HAE have a significant risk of mortality, which can be reduced by appropriate treatment. Orladeyo is the first and only oral plasma kallikrein inhibitor with proven efficacy and proven safety for the routine prevention of recurrent attacks of NAE in adults and adolescents aged 12 years and older.

Epidemiological data

The prevalence of HAE in the general population is 1 in 50,000, with a reported range of 1:10,000 to 1:150,000 with no significant differences by gender or ethnicity. In 2018, the number of patients diagnosed with HAE was 82 (26 families with HAE): 43 women (54%) and 37 (46%) men, based on which the prevalence of the disease was determined to be 1: 93 105.

Efficacy data

The therapeutic efficacy and safety profile of berotralstat was analyzed in three clinical trials.

Clinical trial Angioedema Prophylaxis-2 (APeX-2) - Phase 3, randomized, placebo-controlled, 3-part trial to evaluate the efficacy of prophylactic berotralstat 110 mg and 150 mg administered once daily (QD) for 24 weeks compared to placebo in patients with hereditary

angioedema (HAE). In Part 1 of APeX-2, Orladeyo 150 mg once daily was shown to achieve the primary efficacy endpoint: a reduction in the incidence of investigator-confirmed HAE attacks in the general intention-to-treat (ITT) population (1.31 attacks per month) compared to placebo (2.35 attacks per month). In APeX-2 Part 1, a total of 57.5% of patients had a ≥50% reduction in seizure frequency from baseline at 24 weeks, and 50.0% of patients had a ≥70% reduction in seizure frequency of relapses from baseline after 24 weeks. In comparison, 25% and 15% of patients on placebo had a ≥50% and ≥70% relative reduction, respectively. In patients initially randomized to placebo in Part 1, after initiation of berotralstat treatment in Part 2, the mean (SEM) relapse rate in patients who completed 48 weeks of dosing decreased from 2.3 (±0.60) at week 24 to 1.2 (±0.40) after 1 month of treatment with berotralstat 150 mg and to 0.50 (±0.23) after 6 months. Patients initially randomized to berotralstat 150 mg in Part 1 who completed 96 weeks of treatment (n=21) experienced a mean 80% reduction from baseline in mean seizure frequency per month during Parts 2 and 3. At week 96, an 86% reduction from baseline was observed. The mean seizure frequency decreased over time from 2.7 seizures per month at baseline to 0.0 seizures per month. A median of 0 relapses was reported for 16 of the 17 months during parts 2 and 3. A post-hoc analysis examined the long-term efficacy of berotralstat 150 mg in patients who completed 96 weeks of treatment in the APeX-2 trial. It was found that regardless of baseline seizure frequency, there was a significant reduction in mean seizure frequency observed from baseline to Week 96. The reduced mean and median seizure frequencies observed at the end of Part 1 continued to decrease through Week 96. At week 96, the mean attack frequency was 0.0, regardless of baseline attack frequency. The percentage of attack-free days during the entire trial period was 88%, 96%, and 96% in groups A, B, and C, respectively, and 94% overall. Thus, patients who remained on berotralstat 150 mg demonstrated a sustained reduction in the frequency of HAE attacks and a consistently high rate of attack-free days through week 96, regardless of the initial reduction in HAE attacks.

Clinical trial APeX-S (NCT03472040) open-label trial of berotralstat 110 mg or 150 mg in patients with HAE type 1 or 2, to evaluate the long-term safety and tolerability of daily dosing of oral berotralstat in patients with HAE. Overall, patients switched to berotralstat monotherapy were found to remain flare-free >80% of the time, indicating that berotralstat monotherapy provides control of HAE flares. After switching from Takhzyro® to berotralstat monotherapy, patients remained relapse-free 88.4% of the time and 72.7% of the time when switching from SC C1-INH.

Clinical trial Apex-J (NCT03873116) phase 3, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of berotralstat 110 mg and 150 mg for the prevention of HAE attacks compared with placebo. The estimated frequency of expert-confirmed angioedema attacks over 24 weeks was 1.64 attacks/month for the 110 mg group, 1.11 attacks/month for the 150 mg group, and 2.18 attacks/month for the placebo. The primary endpoint was met for the 150 mg group, with the rate of expert-confirmed HAE attacks reduced by 49% compared with placebo. The 110 mg dose reduced the frequency of expert-confirmed HAE attacks by 25% compared to placebo. The reduction in the incidence of expert-confirmed HAE attacks from baseline with treatment with berotralstat 150 mg was observed at month 1 and remained persistently lower than with placebo throughout the 24-week dosing period.

Safety data

The most common side effects were abdominal pain (of various locations) (reported by 21% of patients), diarrhea (reported by 15% of patients) and headache (reported by 13% of patients). Gastrointestinal events were mainly reported during the first 1 to 3 months of Orladeyo use (median day of first onset 66 days for abdominal pain and 45 days for diarrhea) and resolved without drug administration while treatment with Orladeyo has continued. Almost all cases (99%) of abdominal pain were mild or moderate in severity with a median duration of 3.5 days (95% CI 2-8 days). Almost all events (98%) of diarrhea were mild or moderate with a median duration of 3.2 days (95% CI 2–8 days).

Data on comparators

In observation of the clinical practice in Bulgaria and the available clinical data for the relevant indication, Takhzyro (lanadelumab) therapy was chosen as a comparative alternative in the present analysis. Berinert (C1 esterase inhibitor, human), Firazyr (icatibant) and Ruconest (conestat alfa) are included in the pharmacotherapeutic guide for the treatment of allergic diseases, for the treatment of hereditary angioedema. Based on a review of the Summary of Product Characteristics and the NHIF list, it is found that they are indicated and reimbursed for the treatment of attacks, not for prophylaxis. Therefore, they are not included as comparative alternatives.

Pharmacoeconomic indicators

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

Four evaluations from other countries have been published – NICE- UK, HAS- France, SMC- Scotland and TLV- Sweden, all of which are positive but place certain conditions on starting treatment with Orladeyo.

Applied analysis

A cost-minimum analysis was performed, as evidence of comparative efficacy and safety of the two alternatives lanadelumab and berotralstat, an indirect comparison was presented- a meta-analysis based on data from 2 clinical studies of the evaluated berotralstat technology (APeX-2 and APeX-J) and one clinical comparative alternative lanadelumab (HELP) trial. According to the WAO/EAACI international guideline and the available evidence to date, the two alternative therapies in the analysis – Orladeyo (berotralstat) and Takhzyro (lanadelumab) are comparable in efficacy. The perspective of the analysis is that of the NHIF, the time horizon is one year. As a comparative alternative, the therapy - Takhzyro (lanadelumab) was chosen as a therapy for prophylactic treatment. The results show that the application of the evaluation health technology

Orladeyo for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older will result in a lower annual treatment cost compared to the alternative Takhzyro. In addition, the oral form of administration will also be convenient for the patient, in contrast to the subcutaneous administration of lanadelumab.

Subgroup analyses
No subgroup analyzes were performed.

Costs for the assessed health technology
The analysis included direct costs of drug therapy with Orladeyo and the comparative alternative - Takhzyro (lanadelumab), administration costs, disease monitoring costs, adverse event control costs and relapse control costs.

Budget impact analysis
The analysis of the budget impact was conducted from the point of view of the paying institution - NHIF. The time horizon of the analysis is 5 years. The expected number of patients who will be eligible for treatment with Orladeyo is 5 in the first year to 23 in the fifth year.

The results of the budget impact analysis show that reimbursing the medicinal product Orladeyo for adult patients and adolescents ≥ 12 years of age with hereditary angioedema as routine prevention of recurrent attacks will lead to savings for the paying institution NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Orladeyo is the first and only oral plasma kallikrein inhibitor with proven efficacy and proven safety for the routine prevention of recurrent attacks of NAE in adults and adolescents aged 12 years and older.

The inclusion of Orladeyo in the Positive Drug List will add another option for long-term disease control in patients with HAE, which is accompanied by a convenient intake for patients. The evaluated health technology will lead to savings for the paying institution NHIF over the five-year period of the analysis, with comparable efficacy and safety of the comparative therapy.