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

HEALTH TECHNOLOGY ASSESSMENT

Takhzyro

300 mg solution for injection x 1 vial

lanadelumab

Therapeutic indication(s)	Indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.
Start/end date of procedure	03.04.2020 – 27.11.2020
Final decision	Inclusion in: - Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF); - Annex 2 of the PDL for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act.

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

Health problem

Hereditary angioedema is a clinical manifestation of a quantitative or qualitative deficiency of the C1 esterase inhibitor of the complement system due to a defect in its gene. There is a marked familiality - autosomal dominant inheritance (50% inheritance of the defect). Unbalanced activation of target proteases leads to accumulation of bradykinin, which increases vascular permeability. The disease progresses with periodic episodes of subcutaneous and mucosal edema, including laryngeal edema as well as abdominal attacks (due to intestinal edema). Episodes in the peripheral areas and in the abdominal organs are frequent and sometimes disabling. In the event of a favorable outcome, the swelling subsides in 3-4 days. Undiagnosed and untreated, some patients will die from laryngeal edema with asphyxia.

Takhzyro, containing the active substance lanadelumab, is administered as a subcutaneous injection. The health technology is used for the long-term prophylactic treatment of hereditary angioedema (HAE) in patients 12 years of age and older. HAE is a rare disease and Takhzyro is designated an orphan drug.

Epidemiological data

The frequency of HAE is 1:50 000, or about 140 people for Bulgaria. Data on the incidence of HAE in Bulgaria are similar to those in other European countries. The estimated prevalence is 1 in 93,105.

Efficacy data

The main studies included in the analysis of the efficacy, therapeutic effectiveness and safety are the Phase III clinical trial (HELP) and its open extension for long-term evaluation of the efficacy, therapeutic effectiveness and safety. Almost all patients, treated in the first study continued therapy with Takhzyro within the second. The median age of the study population was 42 years, with 65% of participants having a history of laryngeal angioedema attacks and 56% having been on previous long-term prophylaxis.

The HELP study is the largest and longest-running clinical trial in the field of HAE. The results showed that within 26 weeks of treatment, lanadelumab had a statistically significant reduction in the number of HAE attacks - an 86.9% reduction compared to placebo at a dose of 300 mg every 2 weeks (primary efficacy endpoint). Lanadelumab significantly reduced the number of HAE attacks requiring urgent treatment (secondary endpoint for efficacy assessment) compared to placebo for all doses. The reduction in these attacks at a dose of 300

mg every 2 weeks was 87.3%. Lanadelumab significantly reduced the proportion of moderate to severe HAE attacks compared to placebo for all doses. The reduction in these attacks at a dose of 300 mg every 2 weeks was 83.4%.

Patient-reported data

The quality of life assessment was performed using the AE-QoL questionnaire, which is a validated 17-element tool for assessing the health-related quality of life in patients with HAE.

In all lanadelumab treatment groups, there was an improvement in the overall score and in the individual areas compared to the placebo group. The greatest improvement is observed in the functional score. A significantly higher proportion of patients treated with lanadelumab than with placebo had a clinically significant improvement in the quality of life overall and in individual areas.

Safety data

Lanadelumab is well tolerated, with the majority of adverse events being mild to moderate in intensity. The proportion of patients reporting such events was 90.5% and 75.6%, respectively, for lanadelumab and placebo-treated controls. The proportion of severe adverse events was identical in patients treated with lanadelumab and placebo (9.5% vs. 9.8%, respectively). No deaths due to adverse events were reported in the HELP study.

The most common (52.4%) lanadelumab-related adverse reactions observed were injection site reactions, including injection site pain, erythema and bruising. Of these, 97% were mild in intensity, 90% resolved within 1 day of onset. Hypersensitivity reactions (mild and moderate pruritus, discomfort and tingling of the tongue) were observed (1.2%). As regards immunogenicity, lanadelumab treatment was associated with the development of anti-drug antibodies (ADA) appearing during treatment in 11.9% of participants. The ADA response was transient in 20% of participants with a positive ADA score. A positive result for neutralizing antibodies was observed in 2.4% of participants treated with lanadelumab.

The formation of ADA, including neutralizing antibodies to lanadelumab, has no adverse effect on the pharmacokinetic and pharmacodynamic profile or clinical response.

Data on comparators

Takhzyro, containing the active substance lanadelumab, is used for the long-term prevention of HAE attacks in patients 12 years of age and older. Three comparators were used - recombinant C1-INH concentrate - conestat alfa (Ruconest); C1-INH concentrate from human donor blood - C1-INH (Berinert); bradykinin receptor blocker - icatibant (Firazyr), the limitation of the comparison is that none of the alternatives is indicated for long-term

prevention of HAE attacks. Ruconest and Firazyr are indicated for the emergency treatment of acute attacks (if needed), Berinert is indicated for the emergency treatment of acute attacks (if needed) and for short-term (pre-procedure) prevention.

Pharmacoeconomic indicators

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

Health technology assessments have been provided, intended for the purposes of health systems in Germany and the United Kingdom, both of which are positive.

Applied analysis

A cost-effectiveness analysis was employed to evaluate the cost effectiveness of Takhzyro against the comparators Conestat alfa (Ruconest), C1-INH concentrate from human donor blood (Berinert), icatibant (Firazyr) from the perspective of the National Health Insurance Fund. No modeling has been performed. One-way sensitivity analysis was used as uncertainty assessment method.

Costs of the assessed health technology

The presented model includes:

• The cost of treatment with Takhzyro
• The cost of treatment with alternatives
• Costs related to the administration of the product, monitoring and evaluation of the effect of the treatment

The results show that the incremental ratio is lowest when comparing Takhzyro with Ruconest. The therapy is not cost-effective compared to the Berinert and Firazyr alternatives. The cost of Ruconest is expected to decrease after the introduction of Takhzyro health technology. Takhzyro is the most effective alternative and achieves the lowest cost per day without acute attack.

Budget impact analysis

The budget impact analysis shows that the reimbursement of the new technology by the NHIF will lead to an increase in the costs in the first year, while with long-term prevention in the coming years realization of savings for the payer are expected, not taking into account risk sharing agreements and patient access schemes.

Conclusion

The evaluation of the efficacy, therapeutic effectiveness, and safety of Takhzyro in the routine prevention of recurrent HAE attacks in patients 12 years of age and older supports the clinical

superiority of the evaluated health technology over available comparators. The additional costs in the budget impact analysis result from transition to long-term prophylactic therapy with Takhzyro. In the long term, Takhzyro leads to savings for the NHIF.