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

HEALTH TECHNOLOGY ASSESSMENT

Ruconest

2100 IU powder and solvent for solution for injection x 1 vial

2100 IU powder and solvent for solution for injection x 1 vial + 1 vial +2 vial adapters + 1 syringe + 1 infusion set + 2 alcohol swabs + 1 sterile swab + 1 plaster

Conestat alfa

Therapeutic indication(s)	Indicated for the treatment of acute angioedema attacks in children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency
Start/end date of procedure	27.11.2020 - 22.12.2020
Final decision	Addition of therapeutic indication in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid 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 Ruconest

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. The disease has autosomal dominant inheritance (50% inheritance of the defect). The disease develops with periodic attacks of subcutaneous and mucosal edema, including laryngeal edema, as well as abdominal crises (due to intestinal edema). Attacks in the peripheral areas and in the abdominal organs are frequent and sometimes disabling. With a favorable outcome, the swelling disappears in 3-4 days.

Diagnosis is difficult and patients are often left undiagnosed or misdiagnosed. Given the challenges of diagnosing HAE based only on signs and symptoms and a family history, the diagnosis can only be confirmed by laboratory tests. In Bulgaria, so far 64% of patients have been diagnosed.

HAE is a chronic, lifelong disease that often manifests at an early age and usually worsens during puberty. The average age of onset is between 8 and 12 years, and in 84% of cases it occurs before the age of 20. It is characterized by edema (swelling) in various parts of the body, including the skin, mucous membranes and abdominal organs. Other areas, such as the chest, muscles, joints, kidneys and esophagus, are less frequently affected. The frequency and location of attacks are unpredictable. The most frequently affected areas are peripheral areas such as the face, genitals and limbs (50-58% of all attacks). Abdominal attacks are also common, accounting for 38-48% of all attacks, and laryngeal attacks are less common (4% of all attacks). Despite their low incidence, laryngeal attacks can result in death by suffocation if not treated properly and promptly.

Patients suffer from significant deterioration of the quality of life, which is further worsened by the frequency of attacks and increasing severity, a large proportion of patients is at risk of depression and anxiety.

The therapeutic approach in HAE is classified into three categories: emergency therapy of acute attack (if needed), short-term (pre-procedural) prophylactic therapy and long-term prophylactic therapy.

Ruconest is indicated for the treatment of acute attacks of angioedema in adults, adolescents and children (2 years of age and older) with hereditary angioedema (HAE) due to deficiency of a C1 esterase inhibitor.

Epidemiological data

The frequency of HAE is 1:50 000, which is about 140 potential patients for Bulgaria. The data on the prevalence of HAE in Bulgaria are similar to those in other European countries. The estimated prevalence is 1 in 93,105.

The distribution of patients with HAE type 1 and 2, monitored for the period 2013 - 2018, corresponds to the literature data for other countries. 68 cases with type 1 (85% of all monitored HAE cases) and 12 with type 2 (15% of all monitored NAE cases) were reported. The mean age of patients with HAE is 43 years. The percentage of distribution by gender in HAE is 54% women and 46% men.

Efficacy data

The efficacy of Ruconest in children was studied in an open-label study (NCT01359969) in 20 children with HAE (aged 5 to 14 years). 96% of attacks treated with a single dose of 50 U/kg, achieve a time to onset of relief within 4 hours. The Intention to treat (ITT) population includes 20 patients aged 5-14 years. The population treated with Ruconest had a total of 73 HAE attacks, seven cases of which were treated for 4 or more HAE attacks. The most common sites of attacks are: abdominal, peripheral, facial, urogenital and oropharyngeal/laryngeal. In two of the attacks more than one site was affected. Fifteen children completed the study (75%). Seventy of the attacks were controlled with a single administration of Ruconest.

The median TORS (time in minutes to relief onset) - primary endpoint in 73 seizures was 60 minutes. For the first attack of HAE, the median TORS is 60 minutes and in the majority of children, TORS values are within 4 hours (240 minutes).

The median TTMS (time in minutes to minimal symptoms) - secondary endpoint for 73 seizures, is 122.5 minutes. At the first attack of HAE, the median TTMS is 125 minutes and the majority of children have minimal symptoms (i.e. clinical remission) within 8 hours (480 minutes).

Safety data

The most frequent adverse events are nasopharyngitis, vomiting, abnormal lymphocyte morphology and viral infection. All events were mild in severity and no additional interventions were applied.

Data on comparators

According to the recommendations in the Pharmacotherapeutic Guide for the Treatment of Allergic Diseases, the first line of treatment for patients with HAE are the human (Berinert) and recombinant (Ruconest) C1-esterase inhibitors and icatibant (Firazyr).

Pharmacoeconomic indicators

Applied analysis

A pharmacoeconomic analysis of the cost-minimization type was performed. The analysis is based on a direct comparison of the cost of therapy with the studied alternatives for 1 attack of HAE. The main outcome measure in the analysis is the cost to control 1 attack. The analysis was conducted from the perspective of the paying institution – the NHIF. The cost of treating 1 attack is considered, as the therapy does not change the frequency of seizures. Discounting, as well as cost-benefit modeling is not applied. Berinert and Firazyr were chosen as comparators. The results of the analysis show that the average cost per pediatric patient is the lowest with Ruconest, with no statistically significant differences in the efficacy and safety as regards the comparators.

Analysis of subgroups

No subgroups have been analyzed.

Costs for the assessed health technology

Ruconest and comparator medication costs have been included.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the payer - the National Health Insurance Fund. The time horizon covers a period of five years. The estimated number of patients eligible for treatment with the assessed technology is 3 in the first year, reaching 5 in the fifth year. The reimbursement of Ruconest for the treatment of children with HAE has a negative budget impact on the NHIF as payer, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The C1 inhibitor concentrate medicinal products are life-saving first-line agents for the treatment of bradykinin-mediated angioedema in hereditary angioedema due to C1 inhibitor deficiency, manifested by peripheral angioedema of the limbs and genitals, facial angioedema and oropharyngeal angioedema, as well as intestinal angioedema characterized by abdominal crises. Laryngeal angioedema carries a high risk of death from asphyxia. The inclusion of Ruconest in the Positive Drug List for the treatment of HAE in children will lead to a negative budget impact and respectively savings for the NHIF budget.