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

HEALTH TECHNOLOGY ASSESSMENT

Amvuttra

25 mg (50 mg/ml - 0.5 ml) solution for injection x 1 pre-filled syringe (glass)

INN Vutrisiran

Therapeutic indication(s)	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients with stage 1 or stage 2 polyneuropathy.
Start/end date of procedure	04.08.2023 – 21.12.2023
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 Amvuttra

Health problem

Amyloidosis is a pathological process associated with the accumulation of protein aggregates (amyloids) in the interstitium of the tissues. The deposition of amyloid fibrils, which originate from improper dissociation of the protein transthyretin, leads to the development of transthyretin amyloidosis (ATTR). ATTR manifests clinically in various ways depending on the location of amyloid deposition. The two main phenotypes of ATTR are: Transthyretin amyloid polyneuropathy (ATTR-PN), where amyloid deposits primarily cause damage to peripheral nerves; and Transthyretin amyloid cardiomyopathy (ATTR-CM), where amyloid deposits in the heart primarily lead to cardiomyopathy. ATTR-PN typically begins with sensory disturbances in the toes, progressing rapidly to the more proximal parts of the lower limbs, and eventually involving the upper limbs. Sensations of pain and temperature are impaired, while touch and proprioception are relatively preserved. Early stages of the disease may also involve autonomic nervous system dysfunctions such as diarrhea alternating with constipation, postprandial vomiting, orthostatic hypotension, sweating, and urinary disturbances. Erectile dysfunction is an early sign in men. Gradually, larger sensory and motor nerves are affected, leading to progressive weakness and atrophy. Motor deficits also progress, resulting in difficulties with walking. In the absence of treatment for hATTR, patient survival is estimated at 7 to 12 years from the onset of symptoms. From the moment of diagnosis, the median survival can be estimated at approximately 4.7 years, decreasing to 3.4 years in patients with cardiomyopathy.

Amvuttra contains vutrisiran, a chemically stabilized double-stranded small interfering ribonucleic acid (siRNA) that, through a natural process called RNA interference (RNAi), causes the catalytic degradation of TTR mRNA in the liver, leading to a reduction in serum levels of both variant and wild-type TTR protein.

Epidemiological data

Transthyretin amyloid polyneuropathy is a rare disease with a global prevalence of 1.1 per 100,000. The highest prevalence is observed in Portugal, followed by Sweden and Japan.

To date, six different mutations have been identified in Bulgaria: p.Glu89Gln, p.Val30Met, p.Ser77Phe, p.Gly47Glu, p.Glu54Leu, and p.Ser52Pro. The p.Glu89Gln mutation is the most common in Bulgaria, identified in 102 unrelated families with 190 patients and 100 carriers of the pathogenic mutation. The average age of disease onset is around 52 years.

Efficacy data

The efficacy and safety of vutrisiran for the treatment of polyneuropathy in hATTR amyloidosis in adults is supported by two clinical trials.

HELIOS-A is a phase 3, randomized, open-label, multicenter, global trial designed to evaluate the efficacy and safety of vutrisiran over 18 months in adult patients with a broad range of polyneuropathy severity, genetic variants, and disease manifestations caused by hATTR amyloidosis. The primary endpoint is the change from baseline to month 9 in the modified Neuropathy Impairment Score +7 (mNIS +7), a multidimensional composite clinical measure of motor, sensory, and autonomic polyneuropathy. The 9-month primary endpoint is considered appropriate for assessing the efficacy of vutrisiran in the HELIOS-A trial based on the results of the APOLLO trial, which was designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of Onpattro in patients with hATTR amyloidosis with polyneuropathy. Treatment with vutrisiran significantly improves polyneuropathy, as measured by mNIS+7, compared to placebo. At month 9, the least squares (LS) mean change from baseline in mNIS+7 is significantly more favorable for the vutrisiran arm compared to the placebo arm of APOLLO, with a treatment difference of -17.00. The LS mean change from baseline for the vutrisiran arm is -2.24, where a negative value indicates an overall improvement compared to baseline, while the LS mean change from baseline for the placebo arm is 14.76, where a positive value indicates overall deterioration compared to baseline. The majority of patients (50.4%) in the vutrisiran arm showed improvement in neurological impairment from baseline, as evidenced by achieving a negative change in mNIS+7 from baseline, compared to 18.2% of patients in the placebo arm (odds ratio [OR] 4.8). The average improvement from baseline compared to the placebo arm of APOLLO is consistent across all subgroups regardless of age, gender, race, geographic region, baseline NIS, genotype, previous use of TTR stabilizers, FAP stage, and cardiac manifestations. Patients in the vutrisiran arm achieved rapid and sustained reductions in serum TTR levels similar to patients in the patisiran arm. The mean (SD) reduction at steady state from baseline, measured on samples collected at month 9 (week 39), is 83% (17%) for the vutrisiran arm and 73% (19%) for the patisiran arm.

Trial 001 is a randomized, single-blind, placebo-controlled trial with a single ascending dose in healthy adult subjects. It includes five dose cohorts, with subjects in each cohort receiving either vutrisiran or placebo. Each cohort consists of eight subjects, randomized 6:2 on Day 1 (prior to dosing) to receive either vutrisiran or placebo. Pharmacokinetic analysis shows that the time to maximum serum concentration (Tmax) of vutrisiran ranges from 3 to 5 hours post-dose, the mean half-life (t½) ranges from 4.2 to 7.5 hours, and the total plasma clearance ranges from 18 L/h to 31 L/h (mean 22 L/h). The analysis reveals that vutrisiran reduces serum TTR in a dose-dependent manner, with the mean maximum reduction in serum TTR from baseline ranging from 57% to 97% at doses of 5–300 mg. At all tested doses, vutrisiran achieves the lowest TTR levels between 50 and 90 days and maintains these low levels for approximately 90 days thereafter at doses of 25

mg and above. The average maximum reductions in TTR are similar between Japanese and non-Japanese subjects.

Safety data

In the HELIOS-A trial, most adverse events were mild or moderate in severity, and there were no drug-related discontinuations or deaths. Adverse events reported in ≥10% of patients in the vutrisiran arm included diarrhea, limb pain, falls, and urinary tract infections; each of these events occurred with similar or lower frequency compared to the external placebo group. Injection site reactions were reported in five patients (4.1%) receiving vutrisiran. In Trial 001, most adverse events were mild in severity. The most common adverse events occurring in ≥10% of patients receiving vutrisiran were nasopharyngitis and headache. The safety profile is similar between Japanese and non-Japanese subjects.

Data on comparators

Medicinal products reimbursed in Bulgaria for the treatment of hATTR-PN include Tafamidis (Vyndaqel), Patisiran (Onpattro), and Inotersen (Tegsedi). The primary comparative alternative in the analysis is patisiran, due to the availability of data from the HELIOS-A clinical trial demonstrating the non-inferiority of vutrisiran compared to patisiran.

Pharmacoeconomic indicators

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

A positive assessment has been published by another state institution, NICE (United Kingdom), for Amvuttra in adult patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy stage 1 or stage 2.

Applied analysis

The applied pharmacoeconomic analysis is of the cost-minimization type, for the purpose of evaluating the value-for-money of Amvuttra, with the measure of outcomes in the analysis being the costs of drug therapy and its administration. The perspective is from the viewpoint of the paying institution - NHIF. The time horizon is 1 year. Patisiran has been selected as the comparative alternative due to data from the HELIOS-A clinical trial demonstrating the non-inferiority of vutrisiran compared to patisiran. Discounting has been applied with an annual discount factor of 3.5%. The results of the CMA indicate that vutrisiran is associated with higher annual treatment costs compared to patisiran.

Subgroup analyses
No subgroup analyses have been conducted.

Costs for the assessed health technology
The analysis includes direct costs related to drug therapy.

Budget impact analysis
The budget impact analysis has been conducted from the perspective of the paying institution - NHIF. The time horizon of the analysis is 5 years. Two scenarios have been developed: 'World with Amvuttra' and 'World without Amvuttra'. The expected number of patients treated with Amvuttra is 32 in the first year and 108 in the fifth year. The payment for Amvuttra for the treatment of adult patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy stage 1 or 2 results in additional costs for the reimbursing institution over the five-year period of the analysis, without considering risk-sharing agreements and patient access schemes.

Conclusion

The treatment of hereditary transthyretin-mediated amyloidosis with Amvuttra (vutrisiran) is significantly more convenient for patients, being administered subcutaneously every three months compared to the intravenous administration of patisiran every three weeks, and with significantly fewer adverse effects compared to treatment with inotersen and patisiran. The results of the cost-minimization pharmacoeconomic analysis indicate that vutrisiran is associated with higher annual treatment costs compared to patisiran. The budget impact analysis shows that the reimbursement of Amvuttra generates additional costs for the reimbursing institution - NHIF over the five-year period of the analysis.