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

HEALTH TECHNOLOGY ASSESSMENT

Onpattro

2 mg/ml – 5 ml concentrate for solution for infusion x 1 vial

patisiran

Therapeutic indication(s)	Indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.
Start/end date of procedure	19.04.2019 – 25.06.2020
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).

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

Health problem

Amyloidoses comprise a wide spectrum of diseases resulting from changes in protein structure, due of which a normally soluble tetrameric protein after destabilization of the quaternary structure and subsequent decomposition to free monomers, forms insoluble extracellular fibril deposits, leading to multiorgan dysfunction. All types of amyloid contain one basic fibril protein, which determines the type of amyloid, as well as smaller components. More than 20 different amyloidosis-associated fibril proteins have been described in humans, each with a different clinical picture.

Hereditary TTP amyloidosis (TTPA) (ICD10 - E85.1) is a genetic disease with an autosomal dominant type of inheritance caused by mutations in the TTP gene, in which the protein accumulates in the form of amyloid fibrils in various tissues and organs and leads to multiorgan involvement. Mutations of different localization within the TTP gene lead to a varying in severity involvement of peripheral nerves (carpal tunnel syndrome, sensorimotor and autonomic neuropathy), heart, gastrointestinal tract, kidneys and eyes.

Peripheral nerve involvement is one of the main clinical manifestations of the disease.
• Progressive distal sensorymotor polyneuropathy syndrome.
• Carpal tunnel syndrome.
• Involvement of the autonomic nervous system.

Classical transthyretin neuropathy is axonal, depending on the length of the nerve, so called length dependent small fiber neuropathy, described in Val30Met with early onset. At disease debut, the unmyelinated and small myelinated nerve fibers are affected, which leads to disorders of temperature and pain sensation, starting from the lower extremities, while the sense of touch and joint-muscular sensation are preserved. Paresthesias, dysesthesia, allodynia, hyperalgesia, or spontaneous burning pain in the legs have been reported. This has been described as dissociated sensory loss.

The clinical phenotype in patients in Bulgaria does not strictly follow this type of dissociated sensory loss. It is mixed, regardless of which of the five mutations has been identified (Glu89Gln, Ser77Phe, Val30Met, Gly47Glu, Ser52Pro): there is involvement of the peripheral nervous system and the heart, the gastrointestinal tract is involved in the more advanced cases.

Patisiran (Onpattro) is an RNA therapy indicated for the treatment of hereditary transthyretin-associated amyloidosis (hATTR amyloidosis) in adult patients with stage I or stage II polyneuropathy. The recommended dose of patisiran is 300 μg/kg body weight, administered by intravenous (i.v.) infusion once every 3 weeks. Patisiran demonstrates good therapeutic efficacy by slowing or halting disease progression and affecting its major manifestations - sensory, motor and autonomic neuropathy, as well as cardiomyopathy.

Epidemiological data

As at 2019, a total of 100 families with five different mutations in the TTR gene were identified in Bulgaria: Glu89 (109) Gln in 75 families, Ser77 (97) Phe in 11 families, Val30 (50) Met in 11 families, Gly47 (67) Glu in 2 families, Ser52 (72) Pro in 1 family. There are also isolated cases of double mutations.

As for the country, the average incidence of new cases for all mutations and clinically diagnosed patients over a ten-year follow-up period averaged 1/54,500. The prevalence of the disease averaged 1/28,700.

The disease is highly disabling and fatal if left untreated due to sudden cardiac death or infections in severely disabled patients.

Efficacy data

To evaluate the therapeutic efficacy and safety profile of patisiran, indicated for the treatment of hereditary transthyretin-related (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, the results of four clinical trials and one indirect comparison were compared and analyzed.

- APOLLO clinical trial, evaluating the efficacy and safety of patisiran versus placebo in patients with hATTR amyloidosis with polyneuropathy.
- Clinical study Suhr et al., evaluating the safety and tolerability of patisiran in adult patients with hATTR.
- OLE clinical trial, evaluating the long-term safety, clinical effect and pharmacokinetics of patisiran in hATTR patients already treated with the drug.
- GLOBAL OLE, evaluating the long-term efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy, who participated in OLE or APOLLO.
- Indirect comparison of patisiran and tafamidis for the treatment of hereditary transthyretin amyloidosis with polyneuropathy

APOLLO clinical trial

The baseline change in mNIS + 7 was significantly smaller in the patisiran group compared to the placebo group. At month 18 LSM ± SE the change in mNIS + 7 from baseline was -6.0 ± 1.7 points in the patisiran group and 28.0 ± 2.6 points in the placebo group.

The improvement in hospitalized patients with neuropathy in the group with patisiran was reported early, and at month 9 the difference in the change between the two groups was -15.98 points. Patisiran leads to improvement in mNIS + 7 and in the subgroups determined by age, race, mutational status, previous use of a stabilizer, stage of the disease, as well as in patients, meeting pre-defined criteria for cardiac involvement; the effect of treatment is significant in all subgroups and for all components of mNIS + 7. Patisiran demonstrated sustained benefit in patients with early and progressive neuropathy compared with placebo. An analysis of the mNIS + 7 threshold (baseline change < 0 points) found that most patients with patisiran (56%) showed improvement in neuropathy (baseline change in mNIS + 7 < 0 points) at month 18, compared with 4% of patients receiving placebo. Patients treated with patisiran preserved their motor power as measured by NIS-W, whereas a decrease was observed in the placebo group. Stabilization of the R-ODS score (daily activities and social activity) was observed in patients in the patisiran group, while in patients in the placebo group the deterioration increased. Patients treated with patisiran preserved their walking speed on the 10MWT test at month 18, and in patients in the placebo group this score deteriorated. At month 18, patients in the patisiran group preserved their nutritional status compared to baseline. At month 18, the patisiran group demonstrated significantly more beneficial changes in the autonomic symptoms of neuropathy.

Studies by Suhr et al. 2015, OLE and GLOBAL OLE

The chief outcomes of the non-randomized efficacy studies of patisiran were as follows:

- Significant decrease in serum TTR in patients treated with 0.3 mg/kg Q3W after the first and second doses of patisiran.
- Sustained mean reduction in serum TTR for 24 months.
- In 74.1% of patients treated with patisiran, mNIS + 7 remained lower or decreased from baseline at month 24.
- Subgroup of patients with cardiac involvement: sustained reduction (improvement) in mNIS + 7 at month 24 in patients with cardiac involvement.
- Patisiran has been shown to preserve its effect on mNIS + 7 for 36 months.
- Significant increase (indicative of improvement) in the density of the fibers, innervating the sweat glands (SGNGD) of the lower extremities and mean absolute change from baseline in the content of amyloid in the skin in the assessments in months 6, 12, 18 and 24, as well as in month 24 for SGNFD.

Data reported by patients

APOLLO clinical trial

At month 18, patients in the patisiran group showed improvement in baseline HRQoL, whereas HRQoL in the placebo group deteriorated and the difference between the groups was statistically significant.

Improvement in HRQoL with patisiran was observed in almost all subgroups and did not differ significantly by genotype; the improvement was sustained in the subgroup of patients with cardiac involvement and at all stages of amyloidosis. In patients treated with patisiran in the subpopulation with cardiac disorders, the change in Norfolk QoL-DN was more favorable than in the placebo arm from baseline through month 18. The change was significantly more favorable in patients treated with patisiran than with placebo as concerns all areas of Norfolk QoL-DN (except for patients with early-onset Val30Met), as well as physical function/large fiber-related symptoms and autonomic nerve function.

Indirect comparison of patisiran and tafamidis for the treatment of hereditary transthyretin amyloidosis with polyneuropathy

Norfolk QoL-DN

Base-case analysis show a significantly greater effect of patisiran treatment compared to tafamidis in terms of the difference in the mean change from baseline through month 18 (–13.10). In the sensitivity analysis, a significantly greater effect of patisiran versus tafamidis treatment was also observed in the mITT subgroup (–15.90) and in the staged disease subgroup and untreated patients (–19.00).

A tendency for a greater effect of treatment was found in the subgroup with stage 1 of the disease and V30M.

Safety data

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Bronchitis	Common
	Sinusitis	Common
	Rhinitis	Common
Immune system disorders	Infusion-related reaction	Very common
Ear and labyrinth disorders	Vertigo	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Dyspepsia	Common
Skin and subcutaneous tissue disorders	Erythema	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Muscle spasms	Common
General disorders and administration site conditions	Peripheral oedema	Very common
	Extravasation	Uncommon

Data on comparators

In the principal study, which included patients with early-stage V30M disease, tafamidis did not reach the additional primary endpoints for the proportion of patients with a response to NIS-LL (response was determined at NIS-LL < 2 points) and a change in Norfolk QoL-DN for 18 months in ITT population. Efficacy of tafamidis has not been established in patients with stage 2 or 3, nor in patients without the V30M mutation.

Pharmacoeconomic indicators

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

Seven assessments of patisiran health technology, carried out by government institutions for the national health systems of the United Kingdom, Sweden, Germany, France, Canada, Scotland and Wales have been presented, all of which are positive and recommend the reimbursement of the new technology.

Applied analysis

The selected method for comparative evaluation of patisiran health technology is economic cost-utility analysis (CUA). The results were measured and presented as long-term measures - years of life gained (LYs) and quality-adjusted life-years (QALYs). The health benefit values used in the model were obtained directly from the EQ-5D data from the APOLLO study.

The main alternative to patisiran is the best supportive care (BSC), reflecting the therapeutic practice in all countries, including Bulgaria. According to the adopted pharmacotherapeutic

guide for the treatment of neurological diseases in Bulgaria, the main therapy includes symptomatic treatment for neuropathic pain and autonomic neuropathy.

The presented assessment considers two scenarios:
the main scenario is a cost-benefit analysis against best maintenance therapy (BSC), as currently in Bulgaria this is the only alternative in the event of disease progression (tafamidis is used in part of the population of patients with hATTR amyloidosis - only in adult patients with symptomatic stage 1 polyneuropathy for delaying peripheral neurological damage), i.e. patisiran therapy has no alternative in the event of progression (stage 2).

the additional scenario compared patisiran to tafamidis in patients with hATTR amyloidosis, stage 1 polyneuropathy.

The presented analysis uses the health perspective and the point of view of the paying institution – the National Health Insurance Fund. The time horizon is lifelong (40 years).
Health benefits and costs have been discounted at an annual discount rate of 3.5%.

The health benefits and costs of patisiran in the target group of patients were modeled. The input data to the model are the results recorded in the APOLLO study. A standard Markov model was used. The cohort of patients with hATTR amyloidosis went through six medical conditions defined by the polyneuropathy disability score (PND score) from 0 to IV. In general, the model consists of 13 health conditions, including death, transitioning to which is possible from any other condition. The analysis demonstrates that patisiran treatment resulted in a significant increase in QALYs in all health conditions compared to BSC and tafamidis therapy.

The evaluation of the pharmacoeconomic parameters of patisiran found that patisiran therapy demonstrated more health benefits compared to BSC and compared to tafamidis at a higher cost per patient. The higher cost of patisiran therapy can be interpreted as justified, as it is the only therapeutic alternative for patients with disease progression (stage 2 of hATTR amyloidosis). Patisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy and has significant clinical benefits.

To analyze the cost and benefit sensitivity to stochastic changes in the values of the therapeutic line patisiran, a probabilistic sensitivity analysis (PSA) and a one-way sensitivity analysis (DSA) were applied. The sensitivity analysis confirms the results of the main analysis.
Subgroup analysis has not been attached.

Costs for the assessed health technology

The presented model includes:

• Medication costs (patisiran and tafamidis);
• Drug administration costs;
• Premedication costs;
• Disease monitoring and follow-up costs;
• Adverse drug reactions management costs.

The cost of administering best supportive care (BSC) includes the cost of medical services and the cost of ADR management.

Budget impact analysis

The budget impact analysis was conducted from the point of view of the paying public institution, the time horizon is 5 years.

The target population is adult patients diagnosed with hereditary transthyretin-associated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy. TTR amyloidosis is the most common form of hereditary amyloidosis that results from mutations in the TTR protein. The disease genarally affects men over the age of 60. The estimated number of patients in the first year is 20, rising to 62 in the fifth year.

The reimbursement of the new technology by the NHIF will lead to an increase in the costs in all cases considered, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Hereditary transthyretin amyloidosis is a severe, multisystem and fatal disease with no currently available treatment, resulting from various mutations. Treatment with patisiran results in delayed nerve damage in patients with stage 1 or stage 2 hATTR amyloidosis, improvement in daily activities, and maintenance of nutritional status, which is a key factor in mortality in patients with hATTR amyloidosis. Patisiran is an innovative product that significantly expands the therapeutic possibilities for the treatment of hATTR amyloidosis, demonstrates efficacy in all major aspects of hereditary amyloidosis in patients, affected by the disease in varying degrees. Treatment with patisiran leads to a rapid and lasting improvement in the symptoms of neuropathy and cardiomyopathy, reduces disability, has a beneficial effect on nutritional status and overall quality of life. Compared to BSC and tafamidis, patisiran therapy demonstrated more health benefits at a higher cost per patient. The positioning of the health technology with respect to the analyzed disease as a therapy with no alternative for hATTR amyloidosis with rapid progression at stage 1 (assessed on the NIS scale) due to the Gly47Gln mutation is that of the only therapeutic option in stage 2 of the disease.