Cost-effectiveness of patisiran (Onpattro®) for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

The NCPE has issued a recommendation regarding the cost-effectiveness of patisiran (Onpattro®). Following assessment of the Applicant's submission, the NCPE recommends that patisiran (Onpattro®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Alnylam Pharmaceuticals) economic dossier on the cost effectiveness of patisiran (Onpattro®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **February 2020**

Summary

In June 2019, Alnylam Pharmaceuticals submitted a pharmacoeconomic evaluation to support the reimbursement application for patisiran for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Alnylam are seeking reimbursement in the hospital setting.

Patisiran is a double-stranded small interfering ribonucleic acid (siRNA) which targets all mutant and wild-type transthyretin (TTR) and causes the degradation of TTR mRNA in the liver, thereby reducing serum TTR protein and so reducing amyloid deposition. The therapeutic hypothesis is that reducing the deposition and promoting the stabilisation or clearance of TTR amyloid deposits, will thereby stabilise (or maybe even improve) the disease manifestations including polyneuropathy and cardiomyopathy. Patisiran is licensed for use in patients with hATTR amyloidosis, who have stage 1 or 2 polyneuropathy.

Patisiran is available as a single vial containing patisiran sodium equivalent to 10mg patisiran. The recommended dose of patisiran is 300 micrograms per kg body weight administered via intravenous (IV) infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing 100 kg or more, the maximum recommended dose is 30 mg.

The main comparator for this analysis is best supportive care (BSC) which consists of treatments for the symptoms of polyneuropathy and cardiomyopathy. The Review Group note that inotersen is also currently undergoing appraisal, and was therefore included in a scenario analysis.

1. Comparative effectiveness of patisiran

The pivotal trial evaluating the clinical effectiveness of patisiran for hATTR is a multi-centre, randomized, double-blind, placebo-controlled, phase 3 clinical trial (APOLLO; Study ALN-TTR02- 004; hereafter referred to as APOLLO) of 18 months duration in adult patients with

hATTR with polyneuropathy. A total of 225 patients with hATTR polyneuropathy were randomly assigned 2:1 to patisiran 300 micrograms per kg once every 3 weeks (n=148) or placebo (n=77) and were stratified by neuropathy impairment score (NIS), disease onset/genotype and previous stabiliser use. It should be noted that patients in the placebo arm in the APOLLO trial were not prescribed a BSC regimen that specifically aligns with clinical practice in Ireland. The primary outcome was the change from baseline to 18 months in the modified neuropathy impairment score +7 (mNIS+7). This is a composite score that measures a range of motor, sensory, and autonomic neurologic impairments experienced by patients with hATTR polyneuropathy. The mNIS+7 scale ranges from 0 to 304, with higher scores indicating more impairment. Secondary outcomes included the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire. The EQ-5D-5L was an exploratory outcome.

In patients receiving patisiran, a statistically significant improvement in mNIS+7 score was achieved at 18 months ($p < 0.001$) compared with placebo. A similar effect was observed for mNIS+7 score across all subgroups based on stratified groups. Significant improvement in neuropathy related quality of life, as indicated by the Norfolk QoL-DN was also observed at 18 months ($p<0.001$) with patisiran compared with placebo. Additionally, significant differences in EQ-5D-5L and EQ-VAS were observed with patisiran compared with placebo at 18 months.

The benefit of patisiran in treating patients with hATTR polyneuropathy is supported by the results of an ongoing open label extension (OLE) study (NCT 02510261). In APOLLO, 86% of patients completed the 18-month treatment period and over 95% of these patients were eligible for participation in the OLE study. Treatment with patisiran for up to 29 months in patients who continued to receive patisiran in the extension study demonstrated disease stabilisation (as evidenced by mNIS+7). Disease stabilisation was also observed with patisiran in patients who previously received placebo.

The Review Group had concerns relating to the reliability of the clinical effectiveness evidence in the APOLLO trial. First, the benefits of patisiran in patients with non-polyneuropathy related hATTR symptoms have not been established – data from APOLLO does not provide any cardiac efficacy data. Second, no conclusion can be made regarding a potential long-term survival effect of patisiran. Third, it is unclear how generalisable the results from APOLLO are to patients in Ireland being treated for hATTR amyloidosis, when

considering the genotypic profile of patients enrolled in the APOLLO trial compared to those who present in clinical practice in Ireland.

2. Safety of patisiran

The safety and tolerability of patisiran as reported in the APOLLO trial relates to patients who received at least one dose of the study drug; (n=225). Overall, the number of adverse drug reactions and patient deaths were similar in the patisiran and placebo groups. The most frequently occurring adverse reactions reported in patients treated with patisiran were peripheral oedema (29.7% vs 22.1% in placebo arm) and infusion-related reactions (18.9% vs 9.1% in placebo arm). All infusion-related reactions were mild to moderate and resolved. The only adverse reaction that resulted in the discontinuation of patisiran was an infusion-related reaction (0.7%). Data from APOLLO demonstrated that almost all patients who received patisiran and placebo experienced adverse reactions. Similar proportions of patients who received patisiran and placebo experienced severe and serious adverse reactions. Fewer patients who received patisiran discontinued or withdrew due to an adverse reaction compared with the placebo group. Diarrhoea was the only serious adverse reaction that was reported in ≥2% more patients in the patisiran group than the placebo group (5.4% vs. 1.3%). Thirteen deaths were reported in APOLLO (7 [4.7%] in the patisiran group and 6 [7.8%] in the placebo group), none of which were considered to be related to study treatment.

Patisiran reduces vitamin A levels in the body. Vitamin A supplementation at approximately 2500 IU vitamin A per day is advised for patients treated with patisiran. The important identified risks of infusion-related reactions can be reduced with pre-medications and a controlled rate of infusion and appears to diminish over time.

3. Cost effectiveness of patisiran

The cost-effectiveness of patisiran was evaluated using a de novo Markov model. The states in the model are based on a combination of the six stage Polyneuropathy Disability (PND) Score, and a binary measure of cardiomyopathy (NT-proBNP levels), which was less than (<), equal to or greater than (≥) 3,000pg per mL as an indicator of cardiac involvement. Patients

entered the model distributed across the NT-proBNP levels and PND health states according to the baseline distribution in the APOLLO trial. Transition probabilities for patisiran and BSC were estimated directly from the APOLLO trial. Treatment efficacy was separated into the efficacy period (initial 18 months, corresponding to the duration of the APOLLO trial) and the extrapolation period. Utility values were estimated using a regression model, which was derived from EQ-5D-5L data recorded in the APOLLO trial at baseline, 9 months and 18 months. These were mapped to EQ-5D-3L and then converted to utility values using UK tariffs. The Applicant fitted a regression model to this data, with time, treatment arm, the interaction of time and treatment arm, PND stage, and NT-proBNP level (equal to or greater than (≥) 3,000pg per mL (i.e. high) vs less than 3,000pg per mL (i.e. low)) as covariates. Drug acquisition costs, administration, monitoring, adverse reaction costs were included in the model. Resources for the management of polyneuropathy and cardiomyopathy were also included. End of life care for patients who are near death were also included. Within the patisiran group, the model assumes that patisiran will lead to reductions in resource use; the estimates for these reductions were elicited as part of the Delphi panel study of clinicians (n=7) in the UK. Constant reductions in resource use were applied to the polyneuropathy-related costs (per-cycle and one-off) and the cardiomyopathy-related costs, respectively.

The Review Group had concerns with the approaches and assumptions used by the Applicant in their economic model, including claims relating to the treatment effect of patisiran on cardiac-related outcomes. The Applicant used data from Ruberg et al (2012) to support an assumption of 'accelerating' cardiomyopathy for patients on BSC, which improves the life expectancy and quality of life of patients on patisiran compared with patients on BSC.

The Review Group also had a number of serious concerns with the Applicant's assumptions around the level of health related quality of life experienced by patients who receive patisiran or BSC over time. The approach used by the Applicant resulted in patients on patisiran improving over time and patients on BSC worsening over time, even within the same health state. The key drivers of the model were (i) the monthly increase in utilities for patients being treated with patisiran, (ii) the drug acquisition cost for patisiran and (iii) the discount rate.

Results

The Review Group applied changes to the model to derive their adjusted base case, choosing no treatment discontinuation among patirisan patients (in the model, the Applicant has modelled a reduction in drug costs with no corresponding reduction in efficacy), a relative dose intensity of 100% and capping the utility change after three years within each health state. The NCPE adjusted ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1: NCPE Review Group adjusted base case analysis*

Treatment	***Incremental Costs (€)***	***Incremental QALYs***	***ICER (€ per QALY)***
BSC			
Patisiran	3,453,205	5.71	604,696

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio
*A discount rate of 5% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2: Applicant base case analysis*

Treatment	***Incremental Costs (€)***	***Incremental QALYs***	***ICER (€ per QALY)***
BSC			
Patisiran	3,147,336	9.3	338,439

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio
*A discount rate of 5% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

A probabilistic analysis of the NCPE adjusted base case, resulted in an ICER of €669,392/QALY. The probability of cost effectiveness at €45,000/QALY and €20,000/QALY using the NCPE adjusted base case was 0% and 0% respectively.

4. Budget impact of patisiran

The price to wholesaler for patisiran is €8,520.84 per vial, and the dose is 300 micrograms per kg every three weeks. The number of vials required per dose varies between one and three, dependent on the patient's bodyweight. Assuming a weighted average of 2.38 vials required per administration, the annual per-patient cost of patisiran including VAT is €414,419.20 (€333,298.85 excluding VAT).

The Applicant assumed that a proportion of patients in the budget impact model receive inotersen. The Review Group removed this assumption and instead assumed that these patients would be treated with patisiran. With this amendment included, it is estimated that on average nine patients will receive treatment with patisiran in year one, rising to 45 patients in year five. Using an estimated annual per-patient cost for patisiran of €414,419.20 per year, the Review Group estimates the gross drug budget impact to be €3.8 million in year one, rising to €18.4 million in year five, giving a five-year cumulative total of €59.2 million (inclusive of VAT). The Applicant estimates a (cumulative) gross budget impact of €40.6m over 5 years.

Drug costs associated with BSC are included in disease management costs in the Applicant's model, therefore it is not possible to give a precise estimate of cost-offsets. However, these costs are negligible when compared with the drug costs for patisiran. For this reason, the Review Group estimates that the net drug budget impact of patisiran would be approximately the same as the gross budget impact.

The estimated budget impact is very sensitive to the numbers of patients receiving treatment, for example, a realistic increase in eligible patient numbers would see an cumulative five year budget impact of €72.4m.

5. State if any patient submissions were received, and name submitting organisations.

A patient submission was received during the course of this HTA, and is included in the full report to the HSE.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that patisiran (Onpattro®) is not considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.