**Health Technology Assessment of Inotersen (Tegsedi®) for the Treatment of Stage 1 or Stage 2 Polyneuropathy in Adult Patients with Hereditary Transthyretin Amyloidosis.**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of inotersen for the treatment of stage 1 or stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis. Following assessment of the Applicant's submission, the NCPE recommends that inotersen be considered for reimbursement if 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 NCPE to carry out an evaluation of the Applicant's (Swedish Orphan Biovitrum AB) Health Technology Assessment dossier on inotersen. 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 2022**

**Summary**

On the 23rd of July 2021, Swedish Orphan Biovitrum AB submitted a health technology assessment dossier on inotersen (Tegsedi®) for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis. Transthyretin amyloidosis (ATTR) is a rare disease in which widespread deposition of amyloid protein leads to disruption of normal cellular function resulting in progressive peripheral neuropathy, cardiomyopathy, nephropathy and gastro-intestinal dysfunction. The average life expectancy, if untreated, from symptom onset is 3 to 15 years. The presence of cardiomyopathy is associated with a worse prognosis. When ATTR is caused by a genetic mutation it is referred to as hereditary ATTR (hATTR) and the most common variant in Ireland is T60A which is associated with cardiac and neurological manifestations and the median age at diagnosis is approximately 65 years.

Polyneuropathy is characterised by progressive sensory, motor and autonomic symptoms. Sensorimotor symptoms include pain, numbness and tingling, distal symmetrical weakness progressing from lower limbs to upper limbs and becoming more proximal in nature. The profound loss of motor function will eventually render patients wheelchair bound. Autonomic symptoms include dizziness or fainting, nausea, vomiting, severe diarrhoea and/or constipation, neurogenic bladder and cachexia. Erectile dysfunction may be an early feature in men. Focal lesions may occur at disease onset and carpal tunnel syndrome is a common, non-specific manifestation of hATTR. Treatment to date has largely focused on the symptomatic management of complications such as cardiomyopathy and peripheral neuropathy. The submitted dossier considered best supportive care as the relevant comparator. From the 1st October 2021 disease specific therapy is now available following the reimbursement (with a Patient Access Scheme) of patisiran an RNA interference (RNAi) therapeutic agent that reduces hepatic synthesis of serum transthyretin. A Managed Access Protocol in in place for patisiran therapy.

Inotersen is a 2'-O-methoxyethyl- modified antisense oligo-nucleotide inhibitor of the hepatic production of transthyretin protein. It binds to wild-type and mutant transthyretin RNA transcripts resulting in their degradation in the nucleus by ribonuclease H. It demonstrates a dose-dependent and sustained reduction in circulating transthyretin levels. The pharmaceutical formulation of inotersen is a 284mg solution for injection supplied in a

1.5ml pre-filled syringe. Inotersen 284mg is administered subcutaneously once every week. Treatment is long term and discontinuation is considered if patients progress to being wheelchair bound or bedridden.

1. **Comparative effectiveness**

The main clinical evidence comes from the NEURO-TTR study, a randomised, double-blind, placebo-controlled, phase 3 trial to determine the efficacy and safety of inotersen treatment in adult patients with hereditary transthyretin amyloidosis with polyneuropathy in the presence or absence of cardiomyopathy. The 15 month study was conducted at 24 centres in 10 countries and included 172 adult patients aged 18 to 82 years diagnosed with hATTR stage 1 or stage 2 polyneuropathy who had a Neuropathy Impairment Score (NIS) of 10 to 130, a TTR mutation determined by genotyping and documented amyloid deposits determined on biopsy. The use of tafamidis or diflunisal was not allowed during the study period. After a 6 week screening period eligible patients were randomly assigned, in a 2:1 ratio to receive 300mg inotersen (equivalent to 284mg of free acid) or placebo. Patients received three subcutaneous injections during the first week to achieve steady-state drug levels, followed by a once-weekly subcutaneous injection for the next 64 weeks. All patients received vitamin A supplementation at the recommended daily allowance (approximately 3,000 IU) to ensure adequate delivery of dietary vitamin A in the context of low transthyretin levels. The primary end-points were the change in the modified Neuropathy Impairment Score+7 (mNIS+7) and the change in the score on the patient-reported Norfolk Quality of Life – Diabetic Neuropathy (QOL–DN) questionnaire.

The mean age of the trial population was 59 years, 69% of patients were male and approximately half carried the Val30Met mutation. A total of 67% of patients had stage 1 polyneuropathy, 58% had previously been treated with diflunisal or tafamidis and 63% had cardiomyopathy. A total of 172 patients (112 in the inotersen group and 60 in the placebo group) received at least one dose of a trial regimen and 139 (81%) completed the intervention period. Both primary efficacy assessments favoured inotersen: the difference in the least-squares mean change from baseline to week 66 between the two groups (inotersen vs. placebo) was -19.7 points (95% confidence interval [CI], -26.4 to -13.0; $p<0.001$) for the mNIS+7 and -11.7 points (95% CI, -18.3 to -5.1; $p<0.001$) for the Norfolk

QOL-DN score. These improvements were independent of disease stage, mutation type or the presence of cardiomyopathy. Inotersen was associated with more favourable secondary outcomes including the Norfolk QOL-DN symptom domain score in stage 1 patients and Norfolk QOL-DN physical functioning/large fibre score in stage 2 patients. There was no evidence to suggest that inotersen impacted on hATTR cardiomyopathy in this study.

The NEURO-TTR OLE study is an ongoing open-label extension study of NEURO-TTR to evaluate the long-term efficacy and safety (up to 5 years) of inotersen, in patients with hATTR stage 1 and stage 2 polyneuropathy. Overall 97% (135/139) of patients who completed NEURO-TTR enrolled in OLE; 85 had received inotersen in NEURO-TTR (inotersen-inotersen group) and 50 had received placebo in NEURO-TTR (placebo- inotersen group). Patients in the inotersen - inotersen group (received inotersen for 39 cumulative months) continued to show benefit, patients in the placebo- inotersen group (n=50) demonstrated improvement or stabilization of neurological disease progression by mNIS+7, Norfolk QOL-DN and Short-form 36 Health Survey (SF36) Physical Component Summary (PCS) scores. However, the percentage of patients achieving an mNIS+7 score ≥ 2 points (the minimally clinically meaningful difference) has not been reported for NEURO-TTR OLE. In OLE the reduction in baseline serum transthyretin levels was maintained in the inotersen-inotersen group and levels in the placebo-inotersen group reduced substantially by week 7 in OLE and reached steady state by week 13, reaching a median nadir of 78% relative to OLE baseline. Limitations of OLE included the open-label design with no placebo group, the limited sample size and the fact that results were qualitative rather than quantitative.

## 2. Safety

There were five deaths in the NEURO-TTR trial, all in the inotersen group. Four of the five deaths were consistent with disease progression (two deaths due to cachexia, one related to intestinal perforation and one associated with congestive cardiac failure). One patient in the inotersen group had a fatal intracranial haemorrhage associated with a platelet count of less than 10,000 per cubic millimetre. Glomerulonephritis occurred in three patients (3%) in the inotersen group. Two patients had a decline in the eGFR and all three showed complex pathologic features consistent with crescentic glomerulonephritis superimposed on a

background of amyloidosis and interstitial fibrosis. A higher proportion of patients in the inotersen group (60 out of 112, 54%) had a confirmed decrease in the post-baseline platelet count to less than 140,000 per cubic millimetre than in the placebo group (8 out of 60, 13%). Thrombocytopaenia with platelet counts of less than 25,000 per cubic millimetre occurred in 3 patients (3%) who received inotersen. In the NEURO-TTR OLE study there was no evidence of increased risk of grade 4 thrombocytopaenia or severe renal events with increased duration of inotersen exposure. Platelet counts should be monitored every 2 weeks during inotersen therapy and for 8 weeks following treatment discontinuation.

## 3. Cost effectiveness

The cost-effectiveness model is a cohort-based Markov state-transition model developed in Microsoft Excel® to undertake a cost-utility analysis to estimate the costs and QALYs of a hypothetical cohort of 1,000 adult patients with hATTR polyneuropathy. The starting age in the model is 59 years, the cycle length is 1 month and it incorporates a lifetime horizon (41 years). The model included three health states based on Coutinho staging as follows, Stage 1: patient can walk without assistance. Stage 2: patient does require assistance with ambulation but does not require the assistance of a wheelchair. The stage 1 and 2 health states can be further defined as patients being 'on treatment', 'discontinued treatment' and best supportive care (BSC) to represent someone entering the state as part of the inotersen arm, previously part of the inotersen arm or part of the BSC arm respectively. BSC is assumed to be captured by the placebo arm in the NEURO-TTR trial. Stage 3 captures the proportion of patients at each point in time that need a wheelchair or are bedridden. Stage 3 can only be identified as being 'discontinued' or 'BSC' as no stage 3 patients receive inotersen. The fourth health state in the model was the death state. Patients enter the model in either stage 1 or stage 2. Assumptions in the model structure included (a) patients cannot move back from stage 3 to stage 2 or stage 1 (b) patients discontinued inotersen treatment on entering stage 3 and (c) all patients died on or before reaching the age of 100 years.

The pivotal study NEURO-TTR informed the model's baseline cohort demographics and transitions between the health states. The transition probabilities were calculated using

Norfolk total quality of life (TQOL) data. Based on the TQOL cut-off scores transition probabilities from the NEURO-TTR study were calculated by treatment arm. Inotersen transitions for 4-week probabilities post week 66, the extrapolation phase, were based on probabilities derived in weeks 35-66. It was assumed that on discontinuation of inotersen patients immediately reverted back to BSC transitions.

The NEURO-TTR and NEURO-TTR OLE studies collected quality of life data in terms of the patient-reported questionnaires Norfolk QOL-DN and the Short Form 36 Health Survey, version 2. However, these quality of life measures were considered unsuitable for use in the submitted economic model. Therefore, health outcomes, expressed as quality adjusted life-years (QALYs) were informed by an updated systematic literature review. Due to the paucity of available evidence Brazilian EQ-5D-3L utilities in patients with hATTR associated with Coutinho stage informed the utilities used in the economic evaluation. UK mapped utilities from the Brazilian data were applied in the model. Resource usage and costs considered in the model included treatment related costs, adverse event costs, health resource unit costs associated with hATTR polyneuropathy, monitoring costs of drugs and societal costs for scenario analysis.

In relation to the model inputs for treatment effectiveness the NCPE Review Group had a number of concerns including:

- The assumption that Coutinho stage has an impact on disease mortality in the economic model. There is no evidence that inotersen reduces mortality in patients with hATTR polyneuropathy, as mortality data from the pivotal clinical trial is immature.
- In the economic model familial amyloid polyneuropathy (FAP) stages are used to measure disease progression and determine mortality and utility. Treatment effectiveness is modelled via transitions between FAP stages. However, this outcome was not recorded in the NEURO-TTR study and the Norfolk TQOL score was mapped to FAP stages, using cut-offs obtained from the tafamidis NICE submission. As there was considerable variability in TQOL scores within the same FAP stage and a large number of misclassifications arising from the cut-off approach, treatment effectiveness in the model is highly uncertain

Results in the base case represent the perspective of the Health Service Executive (HSE). A discount rate of 4% was applied.

The incremental cost-effectiveness was estimated at €382,984/QALY. An analysis of costs and QALYs is shown in table 1.

Table 1. Cost-effectiveness of inotersen versus best supportive care.

| Treatment | Total QALYs | Total LYG | Total costs | Incremental costs | Incremental LYG | Incremental QALYs | ICER €/QALY |
|---|---|---|---|---|---|---|---|
| BSC | -0.07 | 10.71 | €1,250,139 | | | | |
| Inotersen | 1.77 | 11.96 | €1,955,450 | €705,310 | 1.25 | 1.84 | 382,984 |

BSC: Best Supportive Care ICER: Incremental cost-effectiveness ratio LYG: life years gained QALY: quality adjusted life years
Numbers are presented as rounded; calculations may not be directly replicable.

The ICER from the societal perspective was €363,086/QALY. A probabilistic sensitivity analysis (PSA) was conducted and the ICER for inotersen versus BSC was estimated at €383,057/QALY. The probability of inotersen being cost-effective at both the €45,000/QALY and €20,000/QALY thresholds was 0%. A deterministic sensitivity analysis was also presented. The parameters that impacted the cost-effectiveness to the greatest extent included: inotersen compliance rate, inotersen costs, discount rates and BSC health resource unit costs for stage 3 polyneuropathy. A number of scenario analyses were submitted but the ICERs remained above €340,000/QALY in each case.

## 4. Budget impact

A budget impact analysis was submitted based on the assumption that approximately 2 patients would be treated in year 1 increasing to 27 patients per annum by year 5. The price to wholesaler of inotersen is €30,106 per pack of 4 pre-filled syringes. The estimated 5 year net budget impact (inclusive of VAT) was €41.39 million.

## 5. Patient Organisation Submissions

A Patient Organisation Submission was received from ATTR Amyloidosis Ireland Support Group. It will be provided to the HSE and form part of the data that the HSE considers.

## 6. Conclusion

The NCPE recommends that inotersen be considered for reimbursement if 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.