Cost-effectiveness of tafamidis (Vyndaqel®) for the treatment transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tafamidis (Vyndaqel®) for the treatment of transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). The NCPE recommends that tafamidis 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 NCPE to carry out an assessment of the Applicant's (Pfizer Healthcare Ireland) economic dossier on the cost effectiveness of tafamidis for ATTR-CM. 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 **September 2020**

Summary

On the 1st July 2020 Pfizer Healthcare Ireland submitted an economic dossier on the cost-effectiveness of tafamidis (Vyndaqel®) for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). Reimbursement is sought under the High Tech Drug Arrangement. ATTR-CM is a life-threatening disease characterised by the accumulation of amyloid fibrils composed of misfolded transthyretin protein in the heart leading to cardiomyopathy and symptoms of heart failure.

ATTR-CM may be divided into two subtypes. It may be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene TTR (ATTRm) (which may affect men and women as early as 45 years) or may be as a result of the deposition of wild type transthyretin protein (ATTRwt) (previously known as senile amyloidosis as patients with ATTRwt are invariably over 60 years of age). Treatment of ATTR-CM has been limited to supportive care including the management of heart failure. Orthotopic liver transplantation and heart transplantation are potential interventions but would not be a routine approach in Ireland. Hereditary ATTR-CM is generally associated with a worse prognosis as compared with wild-type ATTR-CM with a median survival of 2.5 years as compared with 3.6 years. There is no disease modifying therapy available for the treatment of ATTR-CM in the Irish healthcare setting.

Tafamidis is a benzoxazole derivative lacking nonsteroidal anti-inflammatory activity that binds to the thyroxine binding sites of transthyretin with high affinity and selectivity and inhibits the dissociation of tetramers into monomers, the rate limiting step in the amyloidogenic process. The recommended dose is one capsule of tafamidis 61mg (Vyndaqel®) orally once daily which corresponds to 80mg tafamidis meglumine. Marketing authorisation was granted by the European Medicines Agency (EMA) in February 2020 for this indication; it is a license extension.

1. Comparative effectiveness

The submitted dossier outlines the clinical programme supporting the registration of tafamidis which consisted of a phase II trial and a pivotal phase III trial and their respective

extension studies. The multicentre, international, double-blind, placebo-controlled, phase III trial (ATTR-ACT) was the main source of clinical evidence supporting product registration. In this study 441 patients aged between 18 and 90 years with transthyretin amyloid cardiomyopathy were randomised in a 2:1:2 ratio to receive 80mg of tafamidis meglumine, 20mg tafamidis meglumine or placebo once daily for 30 months. The mean age of participants was 74.5 years and approximately 90% were male. Over 61% of patients treated with tafamidis meglumine had New York Heart Association (NYHA) class II heart failure, 29.5% were NYHA III with 9% classified as NYHA I. The majority of participants were ATTR-CM wild type (76%) with the remaining confirmed as hereditary ATTR-CM and all had a history of heart failure with at least one prior hospitalisation for heart failure or clinical evidence of failure (without hospitalisation) requiring treatment with a diuretic for improvement.

The primary endpoint included a hierarchical assessment of all-cause mortality followed by frequency of cardiovascular-related hospitalisations according to the Finkelstein-Schoenfeld method. Key secondary endpoints included the change from baseline to month 30 for the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS).

In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalisations were lower among the 264 patients who received tafamidis meglumine (pooled data) than among the 177 patients who received placebo (P<0.001). Tafamidis meglumine was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] versus 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalisations, with a relative risk ratio of 0.68 (0.48 per year versus 0.70 per year; 95% CI, 0.56 to 0.81). At month 30, tafamidis meglumine was also associated with a lower rate of decline in KCCQ-QS score (P<0.001). Patients treated with tafamidis meglumine experienced a smaller decline in EQ-5D-3L index scores over 30 months than patients treated with placebo. A statistically significant effect favouring tafamidis meglumine was first seen at month 18 and remained significant through month 30.

The ongoing ATTR-ACT extension study is designed to obtain additional safety data for tafamidis meglumine 20mg and 80mg or tafamidis 61mg (i.e. some participants were assigned to tafamidis free-acid 61 mg in the extension study).

2. Safety

In the pivotal ATTR-ACT trial the safety profiles of tafamidis meglumine and placebo were similar. A higher proportion of patients in the placebo arm (50.8%) reported treatment-emergent adverse events (TEAEs) as compared with the tafamidis meglumine 20mg (38.6%) and tafamidis meglumine 80mg (44.9%) treatment arms. The most commonly reported TEAEs included cardiac failure, dyspnoea, dizziness, falls, diarrhoea and nausea. There was no meaningful difference in the safety of the two doses of tafamidis meglumine. Dose reduction due to adverse events were uncommon i.e less than 1% in the tafamidis meglumine treatment arms. Both diarrhoea and urinary tract infections, adverse events previously reported in patients with familial amyloid polyneuropathy, were less common in patients who received tafamidis meglumine than in those who received placebo in the ATTR-ACT trial. The results of laboratory analysis related to safety did not differ between the treatment arms.

The Committee for Medicinal Products for Human Use (CHMP) recommended the extension of the marketing authorisation for Vyndaqel® on the 12/12/2019 with conditions. The Risk Management Plan outlined in the European public assessment report did not report any important identified risks, however a number of potential risks were identified including hepatotoxicity, reproductive and developmental toxicity and lactation and changes in thyroid function, particularly in pregnant women. The planned post-authorisation sub-study of the THAOS registry is a specific obligation under the European Medicines Agency conditional marketing authorisation and will provide further information on efficacy and safety in clinical practice.

3. Cost effectiveness

A discrete time cohort-level Markov state-transition model was used in this economic evaluation. There were five health states in the model including the death state. The remaining health states were based on NYHA functional class (class I to IV) for staging heart failure. All patients enter the model in NYHA I, II or III states, in keeping with the distribution outlined in the ATTR-ACT trial and may transition to alternative NYHA states or death. In each model cycle patients can accrue costs associated with drug acquisition, disease related resource usage and cardiovascular hospitalization. Health related quality of life was

determined via treatment specific NYHA class health state utilities with quality adjusted life years (QALYs) accrued on a cyclical basis. The occurrence of death events was determined using a relative survival approach incorporating the mortality risk of an age and sex matched general population and an additional disease specific hazard of mortality. An NYHA class IV treatment stopping rule was incorporated into the model as the ATTR-ACT study data demonstrated that patients discontinued treatment prior to progressing to NYHA class IV. Modelled events were evaluated at one of two time steps (a) major time-step of six months as NYHA class status and utility assessments were conducted at 6 monthly intervals in the ATTR-ACT trial and (b) minor time-step of one month which was employed for evaluating all other modelled events (cardiovascular related hospitalization, treatment related adverse events, discontinuation events and death) in addition to the evaluation of accrued costs and health benefits. A life time horizon (up to age 101 years) was chosen and the perspective was that of the Health Service Executive (HSE).

The ATTR-ACT phase III randomized controlled clinical trial provided direct evidence for tafamidis meglumine versus best supportive care and was selected to inform model inputs. For the within-trial phase (the first 30 months) of the modelled time horizon, individual transition matrices for each six-month period were derived from observed transitions in the clinical trial. A singular transition matrix was employed for the extrapolation phase with transition rates derived by fitting a smoothed multinomial distribution to all transitions observed during the within-trial phase of the ATTR-ACT study.

In relation to the extrapolation of overall survival beyond the clinical trial duration (30 months) the lognormal extrapolation was considered the most appropriate model to represent the tafamidis meglumine arm based on statistical goodness-of-fit and validation to the long term extension study data. The Weibull extrapolation was considered the most appropriate model to represent the best supportive care arm. Treatment discontinuation, informed by the pivotal trial was modelled in the tafamidis meglumine arm. Health outcomes were informed by the ATTR-ACT trial where EQ-5D-3L data was collected at six month intervals generating NYHA class specific values and expressed as QALYs. Resource usage and costs considered in the model included treatment related costs (diagnostic and drug costs), background (health state) resource use, cardiovascular related hospitalisation, treatment related adverse events and end of life care costs.

An incremental analysis of costs and QALYs was presented and the base case analysis indicated that tafamidis meglumine was associated with an incremental cost of €531,979 and a QALY gain of 2.2 versus best supportive care resulting in an incremental cost effectiveness ratio (ICER) of €241,754/QALY. The cost-effectiveness was also expressed using life years gained (LYG) and with the incremental LYGs of 2.865 the ICER was €185,685/LYG. A probabilistic sensitivity analysis (PSA) was conducted and the resultant ICER was €241,032/QALY. The probability of cost-effectiveness at the €45,000/QALY threshold was estimated at 0%.

4. Budget impact

The price to wholesaler cost for tafamidis is €11,191 per pack of 30 capsules. The total cost per patient per annum is €140,401 (including wholesale mark-up, rebates and pharmacy fees). The Applicant estimated that 51 patients would be treated with tafamidis in year one, rising to 170 in year five. It is estimated that the gross budget impact will increase from €8,133,956 in year 1 to €26,907,668 in year 5 resulting in a cumulative 5-year gross budget impact of €99,781,946. The net 5-year budget impact will approximate the gross budget impact. The NCPE Review Group considered the budget impact figures an underestimate due to the low patient numbers included in the calculations.

5. Conclusion

Tafamidis is not a cost-effective treatment for transthyretin amyloid cardiomyopathy and a substantial price reduction is required to satisfy the €45,000/QALY threshold. Therefore, the NCPE recommends that tafamidis 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.