Cost-effectiveness of Migalastat (Galafold®) for the treatment of patients with Fabry disease who have an amenable mutation

The NCPE has issued a recommendation regarding the cost-effectiveness of Migalastat (Galafold®). Following NCPE assessment of the applicant's submission, Migalastat (Galafold®) is considered cost-effective for the treatment of patients with Fabry disease who have an amenable mutation. Migalastat is recommended for reimbursement subject to continuing availability of a patient access scheme (PAS).

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Amicus Therapeutics) economic dossier on the cost effectiveness of Migalastat (Galafold®). 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 **June 2017**

Summary

In December 2016 Amicus Therapeutics submitted an economic dossier on the cost-effectiveness of Migalastat (Galafold®) for the treatment of Fabry disease in patients with an amenable mutation. The product obtained European marketing approval on the 26th May 2016. The recommended dose is 150 mg orally once every other day. Migalastat acts as a pharmacological chaperone that is designed to selectively and reversibly bind with high affinity to the active sites of certain mutant forms of the lysosomal enzyme α – galactosidase A (α – Gal A), the genotypes which are referred to as amenable mutations. Migalastat binding stabilises these mutant forms of α – Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes where dissociation of migalastat restores α – Gal A activity, leading to breakdown of globotriaosylceramide (GL3) and related substrates thereby preventing accumulation of same in the tissues.

1. Comparative effectiveness

The clinical evidence presented consisted of six phase 3 studies, published and unpublished. The main evidence came from the ATTRACT and FACETS studies. The ATTRACT study was an active – controlled, randomised, open-label, multinational study that was designed in collaboration with the European Medicines Agency (EMA). Participants in the trial had Fabry disease and were being treated with agalsidase alpha or agalsidase beta. Following a two month screening period 60 patients were stratified by gender and degree of proteinuria (low < 0.1 g/24 hours & high ≥ 0.1 g/24 hours) and randomised to two groups in a 1.5:1 ratio. Therefore 36 patients were switched from enzyme replacement therapy (ERT) to migalastat HCl 150mg every other day and 24 patients continued on ERT for 18 months after which they were eligible for a 12 month open label extension in which all patients received migalastat.

The co-primary endpoints demonstrated that renal function expressed as GFR (ml/min/1.73m²) remained stable over 18 months with migalastat which had comparable efficacy to ERT. The eGFRckd-epi annualized rate of change was -0.4±0.93 (-2.27, 1.48) for migalastat versus -1.03±1.29 (-3.64, 1.58) for ERT [mean±SE (95% CI)]. The mGFRiohexol annualized rate of change was -4.35±1.64 (-7.65, -1.06) for migalastat versus -3.24±2.27 (7.81, 1.33) for ERT [mean±SE (95%CI)]. The prespecified criteria for comparability of

migalastat and ERT were met for both co-primary endpoints.

In terms of secondary endpoints the comparability of migalastat and ERT for renal function was also demonstrated for eGFRmdrd. Of note the left ventricular mass index (LVMi) decreased from baseline to 18 months in patients who switched from ERT to migalastat. This decrease was statistically significant i.e. -6.6g/m² whereas patients remaining on ERT did not show any significant decrease in LVMi. Reductions in LVMi have been shown to improve health outcomes in Fabry disease. There was no significant difference between the two treatment groups in terms of composite clinical outcomes or in patient reported outcomes which remained stable in patients who switched from ERT to migalastat.

Patients who switched from ERT to migalastat had a numerically smaller increase from baseline over 18 months in 24-hour urinary protein (49.2 mg/day; SD 199.53) as compared with patients remaining on ERT (194.5 mg/day; SD 690.77). In patients with an amenable mutation, globotriasosylsphingosine (lyso-Gb3) levels remained low and stable throughout the 18 month treatment period in both treatment groups. In patients with a non-amenable mutation, lyso-Gb3 levels increased in 2 patients switched from ERT to migalastat but remained low in two patients who remained on ERT. Evaluation of α – Gal A activity in white blood cells demonstrated results consistent with the mechanism of action of migalastat.

The FACETS study was a double-blind, placebo controlled study where 67 patients were randomised to six months of migalastat HCl 150 mg every other day or placebo followed by open label migalastat from 6 to 12 months (stage 2) plus an additional year. Before unblinding, a new, validated assay showed that 50 of the 67 participants had mutant α – galactosidase forms suitable for targeting by migalastat. The primary endpoint was the percentage of patients who had a ≥ 50% reduction in the number of globotriaosylceramide inclusions per kidney interstitial capillary at 6 months.

The primary endpoint involving patients with mutant α – galactosidase forms that were amenable or not amenable for migalastat therapy, did not show a significant treatment effect as 13 of 32 patients (41%) who received migalastat and 9 of 32 patients (28%) who received placebo had a response at 6 months (p = 0.30). Among patients with amenable

mutant α – galactosidase who received migalastat for up to 24 months, the annualized changes from baseline in the estimated GFR and measured GFR were – 0.30 ± 0.66 and – 1.51 ±1.33 ml/min/1.73 m² of body surface area, respectively. The left ventricular mass index decreased significantly from baseline (-7.7 g/m²) particularly in the presence of left ventricular hypertrophy. The severity of diarrhoea, reflux and indigestion decreased.

2. Safety

The safety of migalastat is demonstrated in the ATTRACT and FACETS studies. In the ATTRACT study migalastat appeared well tolerated during the 18 month treatment period and there were no significant differences in safety parameters between patients who were switched from ERT to migalastat and those remaining on ERT. There were no treatment discontinuations due to treatment – emergent adverse events (TEAEs) and the proportion of patients with a TEAE was similar for both treatment groups. Similarly in the FACETS study migalastat was well tolerated without any significant safety concerns. Adverse events with a higher frequency among patients receiving migalastat as compared with placebo included headache and nasopharyngitis.

3. Cost effectiveness

The cost effectiveness of migalastat was assessed using a Markov model, with a one year cycle and constructed in Microsoft Excel. The model time horizon is a lifetime horizon achieved by simulating the patient population up to the age of 100 years from the baseline of 40 years (consistent with the Fabry Registry data). The population in the economic model reflects the therapeutic indication i.e. patients who have amenable mutations who are at least 16 years old and have a GFR ≥ 30 ml/min/1.73m².

The intervention under assessment is migalastat (Galafold®) which contains 150 mg of migalastat HCl, which is equivalent to 123 mg of migalastat. The recommended administration in adults and adolescents 16 years and older is one capsule every other day. The comparator used in the cost-effectiveness model is ERT which includes two products i.e. agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®). A weighted average of the cost for ERT treatment and administration was calculated.

The treatment effect of migalastat was considered to be equivalent to that of ERT in reducing disease progression therefore there was no difference in disease transition probabilities for migalastat and ERT. This assumption was taken from the ATTRACT study. The NCPE review group highlighted the uncertainty associated with the assumption that equal efficacy is maintained over the lifetime of the model in view of the relatively short term follow-up in the ATTRACT study.

Health outcomes were expressed as quality adjusted life years i.e. QALYs. The baseline utility values were taken from the published literature and pain value was calculated from EQ-5D questionnaires completed by the majority of the patients in the Dutch Fabry disease cohort. Adverse event disutilities were applied for a range of health outcomes including headache, influenza, dyspnoea, upper respiratory tract infection, urinary tract infection and gastritis. Disutilities were also considered for the mode of treatment administration in Fabry disease.

The model incorporates cost data on drug acquisition, health states, adverse events, physician visits and costs of clinical complications. The price to wholesaler for a 28 day supply of migalastat (14 tablets) is €19,729.87. The annual price was calculated at €265,010.11 per patient. The price of agalsidase alfa (Replagal®) in the model is €1,710.09 per 3.5 mg vial. The recommended dose is 0.2 mg/kg and the annual price (ex VAT) was calculated at €210,640.34. The cost per vial for agalsidase beta (Fabrazyme®) in the model was €507.42 for the 5mg vial and €3,372.40 for the 35mg vial. The calculated annual cost of ERT per patient with Fabrazyme® was €191,158.73 (ex VAT). The costings for the various health states appeared reasonable. A discount rate of 5% was applied in line with current guidelines.

An incremental analysis of costs and QALYs was conducted based on a deterministic and a probabilistic analysis. The basecase estimates an incremental QALY gain of 0.75 at an incremental cost of €810,396/QALY giving an ICER of €1,092,097/QALY. The applicant presented a probabilistic analysis, which resulted in an incremental cost of €889,192 and a QALY gain of 0.765 giving an ICER of €1,160,923/QALY. The parameters that impacted QALYs

the most were discount rates for outcomes and the disutility per infusion. The parameters that impacted the costs were discount rates, the percent of female patients with Fabry disease and the market share of agalsidase alfa and agalsidase beta. The manufacturer proposed a patient access scheme which satisfied the current HSE cost-effectiveness thresholds.

4. Budget impact

The estimated gross budget impact was €1,669,564 in year 1 increasing to €3,206,622 in year 5. The 5 year gross budget impact was approximately €13.5 million. The net budget impact considered the costs of ERT that are offset from the increased use of migalastat. This resulted in a 5 year net budget impact of €765,000 increasing from €85,622 in year 1 to €185,454 in year 5.

5. Patient submission

A patient group submission was received from The Society for Mucopolysaccharide and Related Diseases, and was included in full in the final report to the HSE.

6. Conclusion

Migalastat is licensed for the treatment of patients with a confirmed diagnosis of Fabry disease who have an amenable mutation. Approximately 30% of patients currently receiving enzyme replacement therapy (ERT) will be eligible for therapy and the clinical data suggests that migalastat has similar efficacy to ERT. The manufacturer has proposed a patient access scheme which satisfies the current cost-effectiveness thresholds for the HSE. In view of this the NCPE is in a position to recommend the reimbursement of migalastat for the treatment of patients with a confirmed diagnosis of Fabry disease who have an amenable mutation.