Cost-effectiveness of sebelipase alfa (Kanuma®) for the treatment of lysosomal acid lipase (LAL) deficiency

The NCPE has issued a recommendation regarding the cost-effectiveness of sebelipase alfa (Kanuma®).

Following assessment of the applicant's submission for the **infantile** presentation, the NCPE recommends that sebelipase alfa (Kanuma®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments.

Following assessment of the applicant's submission for the **paediatric adult** presentation, the NCPE recommends that sebelipase alfa (Kanuma®) not be considered for reimbursement.

This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

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 2018**

Summary

In November 2017, Alexion Pharmaceuticals submitted a dossier of clinical, safety and economic evidence in support of sebelipase alfa, for the treatment of lysosomal acid lipase (LAL) deficiency, a rare autosomal recessive inherited metabolic disorder. Deficiency of the enzyme leads to the accumulation of cholesteryl esters and triglycerides in various tissues; mainly the liver, gastrointestinal tract, and cardiovascular system (1). The disease presents across a clinical spectrum from infancy to adulthood. Sebelipase alfa is a recombinant form of the human LAL enzyme and therefore, is designed to address the underlying cause of LAL deficiency. The recommended starting dose of sebelipase alfa in infants (<6 months of age) presenting with rapidly progressive LAL deficiency is 1mg/kg administered as an IV infusion once weekly with dose escalation to 3mg/kg once weekly considered. The recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to 6 months of age is 1 mg/kg administered as an IV infusion once every other week.

1. Comparative effectiveness of sebelipase alfa

The applicant presented results for two different patient populations (i) infantile onset LAL deficiency, which is fatal and rapidly progressive and (ii) older patients (paediatric and adult) who present with a less rapid form of disease progression.

Two intervention studies and one historical control study were presented. One of the intervention studies (ARISE) was a placebo controlled randomised trial.

Infantile patients

Two studies were included for this population. LAL-CL03 was a phase 2/3 open label, multicentre, dose escalation study designed to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of sebelipase alfa in 9 infants with growth failure due to LAL deficiency. The study consisted of a screening period of up to 3 weeks, a treatment period of up to 4 years, and a follow-up visit at least 30 days after the last dose. The age range at study entry was 1-6 months. All subjects received sebelipase alfa, administered by IV infusion at a starting dose of 0.35 mg/kg (8 subjects) or 0.2 mg/kg (1 subject), and escalating to 1 mg/kg once weekly and 3 mg/kg once weekly, as applicable. The primary outcome was the proportion of infants surviving to 12 months of age. Study LAL-1-NH01 was a retrospective historical control study including 35 patients diagnosed between 1985 and 2012.

In LAL-CL03, six of nine sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, one additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival, 95% CI: 0% to 16%).

Paediatric Adult patients

Study LAL-CL02 (ARISE) was a 20-week placebo controlled randomized trial including 36 sebelipase alfa-treated patients (1 mg/kg every other week) and 30 placebo patients. This was followed by an open-label period of up to 130 weeks. Median age at symptom onset was 4 years; the median age at randomisation was 13 years. The primary outcome in LAL-CL02 was the proportion of patients who achieved normalisation of alanine aminotransferase (ALT) levels at week 20. Results showed that sebelipase alfa was statistically significantly more effective than placebo in improving a broad range of disease-related abnormalities, including normalisation of serum transaminases (ALT and AST), improvement in dyslipidemia (reductions in LDL-c, non-HDL-c, and TG, and increases in HDL-c), and reduction in liver fat content as assessed by MRI. Furthermore, sebelipase alfa treatment produced clear reductions in MRI-estimated liver volume during the 20-week double-blind treatment period.

2. Safety of sebelipase alfa

One hundred and thirty one patients have received sebelipase alfa in clinical studies (including expanded access trials) up to August 2017. No deaths were reported due to sebelipase alfa and no discontinuations were reported due to safety events. The SmPC for sebelipase alfa describes adverse reactions (i) reported in infants who received sebelipase alfa in clinical studies at doses up to 3 mg/kg weekly and (ii) reported in children and adults who received sebelipase alfa in clinical studies at a dose of 1 mg/kg once every other week. The most serious adverse reactions experienced by 3% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

In summary, the safety exposure of sebelipase alfa remains limited due to the orphan nature of the disease (especially in Wolman infants), differences in disease progression according to age, the relatively short period of follow up (in relation to the expected duration of treatment and the design of studies, only one study being placebo-controlled) and also due to dosing

regimens used in real world practice. There is a need to further monitor the long term efficacy and safety in the post authorisation setting in particular assessment of liver function (efficacy), hypersensitivity reactions, anaphylaxis and antidrug antibodies (safety) in all patients.

3. Cost effectiveness of sebelipase alfa

A cost utility analysis was submitted by the applicant for both the infantile patients and paediatric adult patient groups. The model for the infantile presentation was structured around survival. In the model, the treatment effect (improved survival versus BSC) is modelled by replicating the proportion of VITAL study patients surviving over the first year, compared to the proportion from the historical comparison study (NH01). The model for the paediatric adult presentation was based on fibrosis progression rate with treatment effectiveness taken from the ARISE study. The NCPE had concerns with how the paediatric adult cohort was modelled as there is no data from the trials which supports a difference in liver disease progression between people treated with BSC and sebelipase alfa.

The primary health outcome for the model was the quality adjusted life year (QALY) as per national guidelines. Resources estimated to be consumed by the infantile cohort were neonatal intensive care stays, the costs of which were estimated using national DRGs. Health state costs for the paediatric adult presentation were taken from Kieran et al (2015). Utility values were derived from the UK EQ-5D population norms. No utility decrements were included for the infantile cohort, while decrements from Crossan et al (2015) were included for the paediatric adult cohort. The NCPE highlighted that the applicant had not incorporated disutilities occurring as a result of adverse events into the model, and in doing so, failed to take into account the impact of hypersensitivity reactions which are a very real issue in the clinical management of these patients.

Results

Analyses presented in this summary document are based on the list price of the intervention.

The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's base case was €2,284,000/QALY for the infantile cohort and €1,790,000/QALY for the paediatric adult cohort. The probability of cost-effectiveness at a willingness-to-pay threshold of €45,000/QALY was 0% in both models. The NCPE did not consider that the

applicant's submitted models and resulting ICERs were a complete reflection of the cost effectiveness of sebelipase alfa, and explored the impact of incorporating utility decrements, alternative transition probabilities and treatment effectiveness estimates on cost effectiveness. The NCPE implemented a number of changes to the model based on plausible alternative assumptions. These changes resulted in increases in the ICER up to €2,813,000/QALY (in the infantile cohort) and €2,701,000/QALY (in the paediatric adult cohort).

4. Budget impact of sebelipase alfa

Sebelipase alfa has been submitted for reimbursement as a hospital product. The proposed price to wholesaler is €5,926.80 for a 20mg vial. Since the dosing is weight based, the reimbursement cost is patient specific, for example the reimbursement cost per patient per year including mark-ups and rebates, for a 5 year old patient weighing 16.4kg, diagnosed in infancy, could be in the region of €1,460,066. Based on the applicant's estimate of the current eligible population, the projected cumulative gross drug budget impact over the first five years is approximately €23.35million. Inclusion of administration (infusion) costs results in a budget impact of €23.5 million over 5 years. As sebelipase alfa is not expected to displace any existing treatments, the net drug budget impact is assumed to be the same as the gross budget impact.

5. Patient submissions

No patient submissions were received from patient representative organisations during the course of this appraisal.

6. Conclusion

The NCPE assessment of sebelipase alfa has demonstrated additional benefit in survival in infantile patients and some evidence of improvement in paediatric adult patients, albeit through the use of surrogate markers of liver disease progression. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments.

The NCPE recommends for the **infantile presentation**, that sebelipase alfa (Kanuma®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. For the **paediatric adult presentation**, sebelipase alfa has not

demonstrated robust evidence of additional clinical benefit and recommends that sebelipase alfa not be considered for reimbursement. These recommendations should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.