**Cost-effectiveness of lanadelumab (Takhzyro®) for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of lanadelumab (Takhzyro®). Following assessment of the Applicant's submission, the NCPE recommends that lanadelumab (Takhzyro®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Takeda) economic dossier on the cost effectiveness of lanadelumab (Takhzyro®). 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.

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

**National Centre for Pharmacoeconomics** **June 2020**

**Summary**

In October 2019, Takeda (the Applicant) submitted a dossier of clinical effectiveness, safety and economic evidence on lanadelumab (Takhzyro®) which is licensed for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients (aged 12 years and older). HAE is a rare genetic condition arising from deficiency or dysfunction of the C1-esterase inhibitor protein which is involved in the regulation of the plasma contact system.

Lanadelumab is a fully human monoclonal antibody which inhibits active plasma kallikrein proteolytic activity, thereby limiting the generation of bradykinin which is the primary mediator of HAE attacks. Lanadelumab represents a novel mechanism of action for the long-term prophylaxis (LTP) of HAE attacks. The recommended dose is 300mg by subcutaneous injection once every two weeks. In patients who are stable and attack free on treatment, a dose reduction to 300mg once every four weeks may be considered particularly in low weight patients (<50kg). Treatment may be continued for life. The current standard of care for the LTP of HAE in Ireland are oral therapies: anti-fibrinolytics (e.g. tranexamic acid) and attenuated androgens (e.g. danazol). C1-esterase inhibitors (C1-INHs), Cinryze® and Berinert®, are considered for LTP in patients for whom oral therapy is not effective or not tolerated. C1-INHs are administered by slow intravenous injection every three to four days; doses and dosing frequency are adjusted in line with clinical response.

The Applicant proposes that lanadelumab will be used in patients aged 12 years and older who would otherwise be considered for LTP with C1-INHs. The NCPE considers C1-INHs to be the relevant comparators.

## 1. Comparative effectiveness of lanadelumab

The clinical efficacy of lanadelumab versus placebo was derived from one pivotal double-blind placebo controlled phase III study of 26 week's treatment duration (HELP-03). Patients had a confirmed HAE-attack rate of at least one attack per four weeks as confirmed during the run-in period before the trial. A total of 125 patients participated in the study. Patients

were randomised to receive placebo (n=41) or lanadelumab (n=84). Patients receiving lanadelumab were assigned to one of three treatment arms; 300mg every two weeks (n=27), 300mg every four weeks (n=29) or 150mg every four weeks (n=28). The number of investigator-confirmed HAE attacks during the treatment period was reduced in all lanadelumab treatment arms compared to placebo ($p<0.001$). The risk reduction in attacks compared to placebo was 87% in the 300mg every two weeks treatment arm, 73% in the 300mg every four weeks treatment arm and 76% in the 150mg every four weeks treatment arm. This corresponded to an average attack rate of approximately 0.26 attacks per four weeks, 0.53 attacks per four weeks and 0.48 attacks per four weeks, in the 300mg every two weeks, 300mg every four weeks and 150mg every four weeks treatment arms respectively, versus 1.97 attacks per four weeks for placebo. Supportive evidence has been provided from the phase III open-label single-arm extension study, HELP-04, in which all patients received lanadelumab 300mg every two weeks. Patients enrolled in the trial had either completed HELP-03 (rollover patients, n= 109) or were new patients (non-rollover n=103). The latest data from the trial (average follow-up period of 19 months) are consistent with the HELP-03 results and demonstrate that efficacy is maintained when administered at a dose of 300mg every two weeks.

An indirect treatment comparison (ITC) was used to derive estimates of comparative efficacy for the cost-effectiveness analysis. Data was derived from the HELP-03 trial (lanadelumab versus placebo) and from the CHANGE trial, which compared a C1-INH (Cinryze®) versus placebo. The results of the fixed-effects model showed a reduction in estimated HAE attack rates for the treatments versus placebo. Although, the results from the ITC suggest that reduction in attacks with lanadelumab is likely greater than that associated with C1-INH for LTP, a considerable degree of uncertainty remains (due to low patient numbers, difference in trial populations, treatment period differences).

## 2. Safety of lanadelumab

Injection site reactions were the most commonly observed adverse reaction (52.4%) in the phase III clinical studies (i.e. HELP-03 and HELP-04). Hypersensitivity reactions were observed in 1.2% of patients. Discontinuations due to treatment emergent adverse events

(TEAEs) were infrequent. In HELP-03, one out of 84 patients treated with lanadelumab discontinued due to a TEAE. According to the most recent interim results from HELP-04, six out of 212 patients (2.8%) discontinued owing to TEAEs. The long term safety data in adult population remains limited but safety data will continue to be collected in the ongoing HELP-04 study.

## 3. Cost effectiveness of lanadelumab

*Methods*

The Applicant submitted a de-novo cost utility model comparing lanadelumab with a weighted C1-INH comparator, consisting of patients receiving Cinryze® (40%) and Berinert® (60%), over a time horizon of 60 years. The main clinical outcome in the model, HAE attack numbers in each cycle (28 days), was the same as the primary outcome of the pivotal clinical trials for both the intervention and the comparator (HELP-03 and CHANGE respectively). Attack numbers in each cycle were estimated using individual patient data from the HELP-03 trial. Attack numbers for patients receiving C1-INHs were estimated by applying the attack rate-ratio derived in the ITC, to the predicted attack numbers for the placebo arm of the HELP-03 trial. All patients in the lanadelumab arm were assumed to receive the 300 mg two weekly dose regimen initially, with proportions of the cohort switching to the 300mg four weekly dose regimen after six and 12 months. Patients were assumed to remain on treatment with lanadelumab or C1- INH until discontinuation or death, with all discontinuations taking place during the first six months.

Utility values in the model consisted of three main components: 'attack-free' utility values which represent the utility of a patient with HAE and not experiencing an attack; 'attack' utility values which represent the utility of a patient with HAE and experiencing an attack; and an 'administration' utility which is applied as an ongoing utility increment in the lanadelumab-treatment arm. This is to account for the claimed improvements in HRQOL associated with subcutaneous administration (of lanadelumab) compared with intravenous administration (of C1-INHs).

Utilities during each cycle are calculated as a weighted average of the 'attack-free' and

'attack' utilities, according to the length of time spent experiencing an attack in each cycle. In both the Applicant's base case and the NCPE adjusted base case the 'administration' utility accounts for approximately 68% of the gain in QALYs associated with lanadelumab versus C1-INHs. Healthcare resource use associated with the management of acute attacks and adverse events were included.

*Results*

The Review Group identified a number of limitations in the Applicant's base case. These limitations were addressed in the NCPE adjusted base case in which adjustments to the proportion of patients switching to the less frequent lanadelumab dose regimen at 12 months, utility values, comparator delivery and dispensing costs, acute attack treatments, attack duration, as well as treatment discontinuations in the comparator arm were made. The incremental cost-effectiveness ratio (ICER) for the NCPE adjusted base case was €2,887,679* per QALY (incremental costs €1,817,706; incremental QALYs 0.63). The ICER for the Applicant's base case was €1,481,257 per QALY. Using the NCPE adjusted base case, the probability of cost-effectiveness is 0% at €20,000 and €45,000 respectively. The main drivers of cost effectiveness in the model include the lanadelumab dose switching assumptions and the administration utility. The scenario analysis where all lanadelumab patients remain on the 300mg every two weeks dose regimen until death or discontinuation results in an ICER of €5,585,527 per QALY using the NCPE adjusted base case.

The NCPE consider that a 35% price reduction would bring the cost-effectiveness estimate towards the €45,000/QALY threshold however this is heavily contingent on the proportion of patients switching to four weekly dosing (50.9%).

**Figures may vary slightly due to rounding*

4. **Budget impact of lanadelumab**

The Applicant applied for reimbursement under the High Tech Drug Arrangement. The price to wholesaler per pack of one 300mg vial is €14,166. The drug acquisition cost for lanadelumab is estimated at €379,565 (€471,368 inclusive of VAT) or €190,154 (€236,056 inclusive of VAT) per patient per year depending on the dosing regimen i.e. every two weeks or every four weeks respectively.

The Applicant estimated that 14 patients in Ireland are eligible for treatment. These patients could be treated with lanadelumab or C1-INHs. Based on market share as predicted by the Applicant, the NCPE-adjusted projected cumulative net budget impact over the first five years is approximately €11.3 million for lanadelumab, increasing to €15.6 million assuming all patients receiving lanadelumab stay on the every two weeks regimen. These figures could be an underestimate as, in line with its licensed indication, lanadelumab may be used in all eligible patients.

## 5. Patient submissions.

Patient submissions were not received during the course of this assessment.

## 6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that lanadelumab 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.