To: Members of Bestilleforum

Re: Takhzyro (lanadelumab) for routine prevention of recurrent attacks of hereditary angioedema (HAE) (ID2018_093) – **confidential**.

Takeda AS is disappointed with the recent Beslutningsforum decision to reject reimbursement of Takhzyro (lanadeumab) for the third time, despite its benefit recognized by NoMA in 2019 and a price that is the lowest in Europe.

Together with Norwegian clinicians and Patient Representatives, we are very concerned that **the current reimbursement and tender results severely limit effective prophylaxis options available in Norway compared to the other Nordic countries and beyond.** Specifically, for patients who fail or are not suitable for the newly-approved Orladeyo (berotralstat, ID2021_048), the only prophylaxis treatment is Cinryze IV, with lower efficacy, higher treatment burden and higher cost than Takhzyro. For patients who cannot receive IV infusions, **there will be no prophylaxis alternative at all.** As the relative effectiveness of Oreladeyo has not been assessed, we cannot estimate how many Norwegian patients could be affected.

We urge and request the members of Bestilleforum to recommend that Beslutningsforum reconsiders a restricted approved of Takhzyro, as described below. Our proposal reflects the results of the HAE tender and reimbursement conditions applied to Orladeyo. It should be noted that **had Takhzyro been approved in June 2021, the health system would have saved over 6 million NOK in the last 6 months vs currently used prophylaxis treatments** (Ref: Reseptregisteret); our proposal offers an even higher price discount.

Proposal:

1. Restricted population:

Patients with HAE, aged 12 years or older, who have failed *at least* 1 prophylaxis treatment or are not eligible for currently approved alternatives. The proposed population is based on the evidence showing that **efficacy of Takhzyro (reduction of number of attacks and duration of attack-free period) is observed irrespective of prior LTP use or severity of disease** (https://pubmed.ncbi.nlm.nih.gov/34287942/).

2. Reimbursement conditions – same as recently recommended for Orladeyo :

- Patients should have at least 1 attack per week at onset
- Treatment should be evaluated after 3 months, and terminated if the number of attacks has not been reduced by 50%.

3. Proposed price:

Max AUP: kr177,375.30 (no change)
AIP: kr138,411.00 (no change)
[redacted]

Summary of evidence

Takhzyro is currently **the only long-term prophylaxis drug for HAE with long term** efficacy and safety data (average 30 months) based on the results of the OLE study, after nearly 3 years of treatment, Takhzyro remained highly effective in reducing HAE attacks, including attacks requiring acute treatment, moderate/severe attacks, and high-morbidity attacks and was generally well tolerated (https://pubmed.ncbi.nlm.nih.gov/34287942/).

Takeda has also conducted statistical analyses of efficacy and safety data of Takhzyro, Orladeyo, C1-INH 1000 IU and placebo, which shows that [redacted]

[redacted]

Expected budged consequences

According to its SPC, **Takhzyro's dosing can be reduced** from 300mg every 2 weeks to every 4 weeks in patients who are stably attack free on treatment, especially in patients with low weight. This has **direct impact on reducing treatment costs**. Today, there is increasing evidence of this practice from markets where Takhzyro has been available for the sufficient length of time and Takeda has shared the most complete dataset available with LIS in April 2021 – it has been included in the *Prisnotat* and summarized below (B Buttgereit T, Vera C, Weller K, Gutsche A, Grekowitz EM, Aykanat S, Wahn V, Krüger R, Maurer M, Magerl M, Lanadelumab efficacy, safety, and injection interval extension in HAE - a real life study, *The Journal of Allergy and Clinical Immunology: In Practice* (2021)).

In summary, the results of 34 patients treated with Takhzyro show that the dosing (injection) interval of Takhzyro can be extended in most patients: at the time of data analysis, only 18% of patients were receiving Takhzyro every 2nd week and 22/34 patients were still in the process of increasing their dosing intervals. Importantly, **79% of patients were treated every 4th week or less frequently.** This is **the first study to show that increase in dosing interval of Takhzyro can minimize the treatment burden without a negative impact on efficacy.**

Dosing interval (QxW)	% of patients with the dosing interval
2	18%
3	3%
4	35%
5	21%
6	18%
7	3%
13	3%

With our last offer of [redacted] flat discount (LIS-GIP [redacted] /unit) and using the results from Germany, a weighted-average cost of Takhzyro in Norway would be [redacted] **per patient per year, [redacted] lower than the cost of Cinryze 1000IU** (kr1,274,574 per patient per year). Whilst we appreciate this data should be interpreted with a degree of caution, the results are consistent with the HELP-03 study, were 77% of patients were stably attack-free at 6 months, thus qualifying for an increase in dosing interval from Q2w to Q4w. Real-life data from other markets, whilst less mature, show a very similar trend.

Compared to current yearly HAE drug spending (Reseptregisteret data from 2017-2020) for 15 patients with highest drug consumption, Takhzyro **will be [redacted] cheaper and result in budget savings of 22 million NOK per year** at dosing intervals of Q2W; with less frequent dosing, the potential savings will be even greater as shown in the figure below.

FIGURE DELETED AS CONTAINED CONFIDENTIAL DETAILS