PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Lanadelumab

This is a summary of the risk management plan (RMP) for TAKHZYRO. The RMP details important risks of TAKHZYRO, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) for TAKHZYRO.

The summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how TAKHZYRO should be used.This summary of the RMP for TAKHZYRO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in RMP updates.

I. The medicine and what it is used for

TAKHZYRO is a recombinant, targeted against active plasma kallikrein that has been developed for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. It contains lanadelumab drug substance as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of TAKHZYRO benefits can be found in TAKHZYRO EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/takhzyro

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TAKHZYRO, together with measures to minimise such risks and the proposed studies for learning more about TAKHZYRO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size - the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of lanadelumab is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of lanadelumab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of lanadelumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table VI-1. List of Important Risks and Missing Information

Important identified risks	Hypersensitivity
Important potential risks	• Immunogenicity • Liver Toxicity
Missing information	• Long-term safety in paediatric population • Long-term safety in adult population • Use in Pregnancy and Lactation

II.B Summary of important risks

Table VI-2. Important Identified Risk: Hypersensitivity

Evidence for linking the risk to the medicine	Evidence source from clinical findings
Risk factors and risk groups	Important risk groups and factors that increase the probability of experiencing hypersensitivity are (Chung, 2008; Vogel, 2010; Lenz,

	2007): • Repeated exposure to drug leading to sensitization • History of allergies (atopy, asthma, etc.) and drug hypersensitivity, particularly to any component of drugs or drugs of the same chemical class • Concomitant antihypertensive medication use including ACE-inhibitors or β-blockers • Concomitant opioid use • Comorbid autoimmune disease, cardiac or pulmonary dysfunction. • Presence of anti-drug antibody • Immune-compromised patients Genetic factors i.e., HLA haplotypes, may modulate the immune response
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.8 • SmPC sections 4.4 state management of hypersensitivity • Package Leaflet sections 2 and 4 explain how to detect early signs and symptoms of hypersensitivity and reporting Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: DX-2930-04 (HELP Study Extension™) See section II.C of this summary for an overview of the post-authorisation development plan.

Table VI-3. Important Potential Risk: Immunogenicity

Evidence for linking the risk to the medicine	Evidence from non-clinical and clinical data findings
Risk factors and risk groups	Therapeutic monoclonal antibodies (mAb) have evolved from mice, to chimeric and humanized derivatives, to fully human molecules (Wang et al., 2009). Early, non-human biotherapeutics were expected to provoke an immune response, as they would be recognised as foreign. Recombinant human biotherapeutics, however, are not expected to evoke an immune response in humans given their similarity to endogenous proteins. Indeed, recombinant human proteins do display reduced immunogenicity compared with non-human sequences (Wadhwa & Thorpe, 2007), yet formation of anti-drug antibodies (ADA) was noted after patient treatment with such therapeutics.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 describe immunogenicity Additional risk minimisation measures: • None
Additional	Additional pharmacovigilance activities:

pharmacovigilance activities	DX-2930-04 (HELP Study Extension™) See section II.C of this summary for an overview of the post-authorisation development plan.

Table VI-4. Important Potential Risk: Liver Toxicity

Evidence for linking the risk to the medicine	Evidence from clinical data findings
Risk factors and risk groups	There are no clearly identified risk factors or risk groups for potential TA elevations with lanadelumab treatment. Data from the phase 3 placebo-controlled study revealed that there were the same percent in TA elevations regardless of treatment with placebo or lanadelumab - each 4.8%. Based on data from the Phase 3 studies, TA elevations were not dose or exposure-related and were transient in nature. TA elevations were variable and unpredictable, occurring anywhere from 1 week to 9 months, making an at-risk period unable to be defined. It is important to note that studies have found that the prevalence of elevated ALT levels are approximately 6-12% in the general population (Fraser et al., 2007) especially in those with risk factors for metabolic diseases such as type 2 diabetes mellitus (T2DM) or insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD). Many subjects in the lanadelumab clinical studies were obese, had T2DM or IR and/or had proven or suspected NAFLD. In addition to the very high incidence and prevalence of obesity and IR worldwide, NAFLD is the most common liver disease worldwide, affecting ~25% of the population (Younossi et al., 2018). Thus, it is to be expected that patients with these metabolic conditions will be seeking treatment with lanadelumab in the real-world setting.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: DX-2930-04 (HELP Study Extension™) See section II.C of this summary for an overview of the post-authorisation development plan.

Table VI-5. Missing Information: Long-term safety in Paediatric Population

Evidence for linking the risk to the medicine	Clinical Data
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: • SmPC Label and Package Leaflet caution with use in children as there is limited information Additional risk minimisation measures:

	• None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: DX-2930-04 (HELP Study Extension™) See section II.C of this summary for an overview of the post-authorisation development plan.

Table VI-6. Missing Information: Long-term safety in Adult Population

Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: • No risk minimisation activities are proposed. Additional information will be available after completion of HELP Study Extension ™ (DX-2930-04). Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: DX-2930-04 (HELP Study Extension™). See section II.C of this summary for an overview of the post-authorisation development plan

Table VI-7. Missing Information: Use in Pregnancy and Lactation

Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.6 describe Pregnancy, Fertility and Lactation Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: DX-2930-04 (HELP Study Extension™). See section II.C of this summary for an overview of the post-authorisation development plan

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of lanadelumab.

II.C.2 Other studies in the post-authorisation development plan

Table VI-8. Other Studies in the Post-Authorisation Development Plan

Study name	Purpose of the study
DX-2930-04 (HELP Study Extension™): An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)	**Primary Objective:** • To evaluate the long-term safety of repeated SC administrations of DX-2930 **Secondary Objectives:** • To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks • To characterize the outer bounds of dosing frequency for DX-2930