Medicines Management Programme

Managed Access Protocol – Lanadelumab (TAKHZYRO®▼) for routine prevention of recurrent attacks of hereditary angioedema

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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EPAR	European Public Assessment Report
HAE	Hereditary angioedema
HSE	Health Service Executive
HTH	High Tech Hub
LTP	Long-term prophylaxis
MAP	Managed Access Protocol
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
PFS	Pre-filled syringe
PCRS	Primary Care Reimbursement Service
SC	Subcutaneous
SmPC	Summary of product characteristics

1. Lanadelumab

Lanadelumab is a fully human monoclonal antibody which inhibits active plasma kallikrein proteolytic activity. It is produced in Chinese hamster ovary cells by recombinant DNA technology.

From September 2021, one presentation of lanadelumab is available on the High Tech Arrangement:

- TAKHZYRO® 300mg solution for injection in a pre-filled syringe [PFS]▼[i]

1.1 Licensed indication

Lanadelumab is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.[i]

1.2 Reimbursement

Reimbursement of lanadelumab is confined to the following subgroups of the licensed population for the routine prevention of recurrent attacks of HAE:

- Patients aged 12 years and older with a C1-inhibitor deficiency (Type I) or C1-inhibitor dysfunction (Type II) HAE, who would otherwise be considered for long-term prophylaxis (LTP) with C1-esterase inhibitors. *See Section 2 for further details on Reimbursement criteria – Initiation*

Approved prescribers are required to apply for reimbursement approval on an individual patient basis. The *Lanadelumab Application Form* for the individual reimbursement of lanadelumab should be completed and sent by secure email to the Medicines Management Programme (MMP) at mmp@hse.ie.

If a patient is recommended for reimbursement by the MMP, the High Tech prescription for lanadelumab should be generated on the High Tech Hub (HTH). High Tech prescriptions which are not hub generated for lanadelumab will not be eligible for reimbursement by the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS).

[i] Please refer to the summary of product characteristics for TAKHZYRO® for full prescribing information.

Table 1: Licensed dosing of lanadelumab (TAKHZYRO®) for the prevention of recurrent attacks of hereditary angioedema

Patient population	Route of administration	Dose
Adults and adolescents aged 12 years and older	SC	300mg once every two weeks **or** 300mg once every four weeks*

**In patients who are stably attack free for more than 6 months [especially patients of low weight (<50kg)]*

SC: Subcutaneous, mg: Milligram

Considerations for prescribers:

- The average weight and BMI in the HELP-03 trial may not be representative of the population who might be eligible for lanadelumab in Ireland.
- The *Lanadelumab European Public Assessment Report* (EPAR) showed weight to be a significant covariate for lanadelumab, i.e. low-weight patients (<50kg) are predicted to have a higher exposure to lanadelumab than a 70 kg person.

If a patient is recommended for reimbursement of lanadelumab, reimbursement will be supported for a maximum of two packs of lanadelumab (a total of two TAKHZYRO® 300mg PFSs) every four weeks i.e. in line with the licensed dose as per Summary of Product Characteristics (SmPC). *See Section 3 for further details on Reimbursement criteria – Dose reduction.*

1.3 Reimbursement price

The reimbursement price of the presentation(s) of lanadelumab available on the High Tech Arrangement as of September 2021 are as follows:

Table 2: Reimbursement price of the presentation(s) of lanadelumab available on the High Tech Arrangement

Strength and (pack size)	Reimbursement	
	Code	Price
TAKHZYRO® 300mg PFS (1 x 2ml)	89097	€14,906.00

PFS: Pre-filled syringe, ml: Millilitre, mg: Milligram

Table 3: Annual treatment costs* with lanadelumab per patient according to dosing regimen

Dosing frequency	Cost to HSE per patient per year
300mg once every two weeks	€387,556.00
300mg once every four weeks	€193,778.00

*Prices are listed as reimbursement price, including VAT

A commercial in confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of TAKHZYRO® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of lanadelumab for routine prevention of recurrent attacks of HAE under the High Tech Arrangement.

2.1 Prescribers

The prescribing of lanadelumab under the High Tech Arrangement will be confined to consultant immunologists from five specialist centres in Ireland who have agreed to the terms of this MAP and have been approved by the HSE:

- St. James' Hospital
- Children's Health Ireland (Crumlin)
- University Hospital Galway
- Beaumont Hospital
- Cork University Hospital

Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient age

Applications for reimbursement approval will only be considered for individuals aged ≥ 12 years at time of application.

2.3 Diagnosis

For reimbursement approval, clinicians will be required to confirm a diagnosis of type I or II HAE at the time of application. Clinicians must provide evidence of a documented diagnosis of type I or type II HAE based upon all of the following:

1. Documented clinical history consistent with HAE i.e. subcutaneous or mucosal, non-pruritic swelling episodes without accompanying urticaria and,
2. Documented diagnostic testing results obtained during screening confirming type I or type II HAE:

Table 4: Diagnostic testing results for type I & type II hereditary angioedema [ii]

	Type I HAE	Type II HAE
C1-inhibitor level	Low	Normal-elevated
C1-inhibitor functional level	Low (<40% of the normal level)	Low (40%-50% of the normal level)
C4 level	Low	Below normal
C1q	Normal	Normal

HAE: Hereditary angioedema

A copy of the laboratory investigation should be included with the application for reimbursement approval.

2.4 Patient clinical history

In line with the exclusion criteria[iii] from the HELP-03 and HELP-04 trials, reimbursement of lanadelumab will not be considered with concomitant use of a LTP treatment for HAE (C1-esterase inhibitor, attenuated androgens, or anti-fibrinolytics) within 3 weeks of starting treatment.

In line with the National Institute for Health and Care Excellence (NICE) technology appraisal guidance *Lanadelumab for preventing recurrent attacks of hereditary angioedema* (TA606), reimbursement of lanadelumab will only be supported in patients who:

- Are having two or more clinically significant attacks per week over eight weeks despite oral LTP treatment (or oral LTP treatment is contraindicated or not tolerated) and,
- Require acute treatment with a c1-esterase inhibitor or icatibant.

[ii] In type I HAE, both the concentration and function of C1 inhibitor are low. In type II HAE, C1 inhibitor concentrations are either normal or elevated, whereas C1 inhibitor function is reduced. C4 levels are usually low in type I & II HAE patients, but its sensitivity and specificity are limited. C1q levels are normal in type I and type II HAE and is required as a differential diagnosis from acquired angioedema. Abnormal results should be confirmed.

[iii] This list is not exhaustive; please refer to the summary of product characteristics for TAKHZYRO® for full prescribing information.

2.5 Clinically significant hereditary angioedema attacks

Clinicians will be required to confirm the patient's rate (average number of attacks in previous eight weeks) and severity of clinically significant HAE attack(s) per week at the time of application. A clinically significant hereditary angioedema attack must have had symptoms or signs consistent with an attack in ≥1 of the following locations;

- **Peripheral angioedema:** cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region,
- **Abdominal angioedema:** abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhoea,
- **Laryngeal angioedema:** stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.

Clinicians will be required to submit the following information on clinically significant HAE attacks experienced in the 8 weeks prior to application:

- Date and time[iv] symptoms of an attack was first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalisations or emergency department visits
- Any acute medications used to treat the attacks (including dose, duration of treatment and start and stop dates)
- If the attack resolved, date and time the patient was no longer experiencing symptoms.

2.6 Patient's medical treatment[v]

Clinicians will be required to confirm the patient's HAE medical treatment (both acute treatments and oral LTP treatment) at the time of application.

[iv] To be counted as a unique attack distinct from the previous attack, the new symptoms must have occurred ≥24 hours after resolution of the symptoms from the prior attack.
[v] Not all medicines are licensed in Ireland. Please refer to each individual product's summary of product characteristics for further details.

2.6.1 Acute treatment

Clinicians will be required to confirm patients who are requiring repeated acute treatment [e.g. with icatibant (Firazyr®) or a C1-esterase inhibitor (Cinryze® or Berinert®)] and are inadequately managed. Inadequate management will be determined by the details provided for section 2.5.

2.6.2 Oral long-term prophylaxis treatments

Clinicians will be required to confirm patient's current or previous oral LTP treatments. [e.g. attenuated androgens (danazol and stanozolol) or an anti-fibrinolytic (tranexamic acid)].

In cases where a patient did not tolerate a medicine and experienced a clinically significant adverse reaction which led to discontinuation of treatment prior to completion of an adequate trial[vi], information in relation to the duration of treatment and the adverse reaction experienced should be provided.

In cases where a patient has experienced an inadequate response[vii] to an oral LTP treatment, clinicians will be required to submit supporting evidence as outlined in section 2.5. When reviewing applications, the MMP may request evidence to demonstrate that the patient has been adherent to the specified medicine for a period of at least two months.

For patients in whom treatment with oral LTP treatment is contraindicated, details of the contraindication, including supporting evidence, must be provided at time of application for reimbursement approval.

3. Reimbursement criteria – Dose reduction

The SmPC recommends a starting dose of lanadelumab 300mg subcutaneously (SC) every two weeks. In patients who are stably attack free on treatment for more than 6 months, a reduction in frequency of administration to 300mg lanadelumab SC every four weeks should be implemented, especially in patients with low weight (<50kg). Prescribers should therefore monitor patient response and reduce the frequency of lanadelumab administration at the earliest opportunity where indicated.[viii]

[vi] An adequate trial of a medicine is defined as treatment of at least two consecutive months in duration.
[vii] An inadequate response is defined as a lack of reduction in clinically significant attack frequency despite optimised treatment.
[viii] Please refer to the summary of product characteristics for TAKHZYRO® for full prescribing information.

A condition of reimbursement of TAKHZYRO® is that:

Patients are reviewed at appropriate intervals and maintained on the lowest effective dose.

Therefore, following approval of a patient for reimbursement of lanadelumab under the High Tech Arrangement, the prescribing clinician will be required to submit follow-up information to the MMP, as requested. Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

3.1 Follow-up data

The recommended time frame for assessing a response to lanadelumab is at 6 months and 12 months. Patients who were not identified by 6 months as candidates for reducing the frequency of administration may be required to submit further follow-up data at 12 months.

Follow-up information should be submitted and sent by secure email to the MMP (mmp@hse.ie) when requested outlining:

- Patient's current weight (kg)
- Patient's current BMI
- Criteria outlined in Section 2.5 - Clinically significant hereditary angioedema attacks
- Current dosing frequency and proposed ongoing frequency of dosing
- Whether lanadelumab is being continued or discontinued.