Medicines Management Programme

Managed Access Protocol – Medicines for routine prevention of recurrent attacks of hereditary angioedema

Medicine	Date of addition to Managed Access Protocol
Lanadelumab (TAKHZYRO®)	01/09/2021
Berotralstat (Orladeyo®)	01/10/2024

Approved by:	Professor Michael Barry, Clinical Lead, Medicines Management Programme	
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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. Medicines for routine prevention of recurrent attacks of hereditary angioedema

There are two medicines available under the High Tech Arrangement for routine prevention of recurrent attacks of hereditary angioedema (HAE), berotralstat (Orladeyo®) and lanadelumab (TAKHZYRO®).

Orladeyo® contains berotralstat. Berotralstat is an inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high-molecular-weight-kininogen, releasing bradykinin.

From October 2024, one presentation of berotralstat is available on the High Tech Arrangement:

- Orladeyo® 150 mg hard capsules

TAKHZYRO® contains 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).

1.1 Licensed indications

Lanadelumab is indicated for routine prevention of recurrent attacks of HAE in patients aged 2 years and older.

Berotralstat is indicated for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older.

1.2 Reimbursement

Reimbursement of berotralstat and lanadelumab on the High Tech Arrangement for routine prevention of recurrent attacks of HAE under this managed access protocol (MAP) is confined to the following subgroup of the licensed population:

- Patients aged 12 years and older with 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.*

All criteria must be satisfied in order for reimbursement to be supported.

An application for reimbursement approval is required to be submitted on an individual patient basis. The *Medicines for Routine Prevention of Recurrent Attacks of Hereditary Angioedema Application Form* should be completed and sent by secure email to the Health Service Executive (HSE)-Medicines Management Programme (MMP) at mmp@hse.ie.

Table 1 outlines the licensed therapeutic dosages of berotralstat (Orladeyo®) and lanadelumab (TAKHZYRO®) for the routine prevention of recurrent attacks of HAE, for patients aged 12 years and older weighing ≥ 40 kg. Please refer to the Summary of Product Characteristics (SmPC) for further prescribing information.

Table 1 Licensed dosing of berotralstat (Orladeyo®) and lanadelumab (TAKHZYRO®) for routine prevention of recurrent attacks of HAE for patients aged 12 years and older weighing ≥40 kg

Medicine	Route of administration	Dosage
Berotralstat	Oral	150 mg once daily
Lanadelumab	Subcutaneous	300 mg once every two weeks **or** 300 mg once every four weeks*

mg: milligram
*In patients who are stably attack free for more than six months a dose reduction to 300mg lanadelumab every four weeks may be considered, especially in patients with low weight.

If a patient is recommended for reimbursement of berotralstat or lanadelumab, reimbursement will be supported up to the maximum licensed dosage specified in Table 1. Reimbursement of dosages in excess of the licensed therapeutic dosages (as outlined in Table 1) is not supported. Reimbursement is not supported for concomitant use of berotralstat and lanadelumab.

For further details on lanadelumab dose reduction, see Section 3.3 *Reimbursement criteria – Dose reduction for lanadelumab.*

1.3 Reimbursement price

The reimbursement prices of the presentations of berotralstat and lanadelumab available on the High Tech Arrangement are outlined in Table 2. Commercial in confidence arrangements are in place with the marketing authorisation holders to reduce the net acquisition cost of Orladeyo® and TAKHZYRO® to the HSE.

Table 2 Reimbursement codes and prices of the presentations of berotralstat and lanadelumab available on the High Tech Arrangement

Strength (pack size)	Code	Reimbursement price*
Orladeyo® 150 mg (28 capsules)	89342	€12,811.77
TAKHZYRO® 300 mg PFS (1 x 2ml)	89097	€13,292.93

mg: milligram, ml: millilitre, PFS: Pre-filled syringe
*Correct as at 26/09/2024

Based on the published reimbursement prices (as set out in table 2 above) the annual treatment cost to maintain a patient on lanadelumab every two weeks is approximately €400,000. This is an approximate doubling of the annual treatment costs of dosing every four weeks with lanadelumab.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for patients to be recommended for reimbursement of berotralstat (Orladeyo®) or lanadelumab (TAKHZYRO®) for routine prevention of recurrent attacks of HAE under the High Tech Arrangement.

2.1 Prescribers

Applications for reimbursement approval for berotralstat or lanadelumab for routine prevention of recurrent attacks of HAE under the High Tech Arrangement will only be considered from consultant immunologists from five specialist centres in Ireland who have agreed to the terms of this MAP and have been approved by the HSE ('approved consultants'). The five specialist centres are:

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

Approved consultants are responsible for ensuring that the patient or their representative/guardian is aware that the application for reimbursement approval is being made on their behalf.

The prescribing of Orladeyo® or TAKHZYRO® for approved patients for the routine prevention of recurrent attacks of HAE under the High Tech Arrangement will be confined to approved consultants

and their teams. The governance of the team on the High Tech Hub, including access, rests with the approved consultant.

2.2 Patient age

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

2.3 Patient 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 as described in Table 3.

Table 3 Diagnostic testing results for type I & type II hereditary angioedema

	Type I HAE	Type II HAE
C1-inhibitor level	Low	Normal-elevated
C1-inhibitor functional level	Low (< 40% of the normal level)	Low (40% to 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 SmPCs for Orladeyo® and TAKHZYRO ®, applications for reimbursement approval will not be considered for individuals who meet any of the contraindications for treatment as outlined in the relevant SmPCs.

The concomitant use of LTP treatment for HAE (C1-esterase inhibitor, attenuated androgens, or anti-fibrinolytics) should be reviewed in all patients approved for reimbursement of berotralstat or lanadelumab. In line with the initial approval for lanadelumab, as per National Institute for Health and Care Excellence (NICE) technology appraisal guidance *Lanadelumab for preventing recurrent*

attacks of hereditary angioedema (TA606), reimbursement of berotralstat and 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,
- Are having attacks which would be considered suitable for acute treatment with a C1-esterase inhibitor or icatibant (not all clinically significant attacks may be treated).

2.4.1 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 HAE attack must have had symptoms or signs consistent with an attack in ≥ 1 of the following anatomical 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, dyspnoea, 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 eight weeks prior to application:

- Date and time[i] 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.

[i] 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.

2.5 Patient's medical treatment[ii]

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

2.5.1 Acute treatment

Clinicians will be required to confirm that patients 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 in section 2.4.

2.5.2 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 (defined as treatment of at least two consecutive months in duration), 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 to an oral LTP treatment, defined as a lack of reduction in clinically significant attack frequency despite optimised treatment, clinicians will be required to submit supporting evidence as outlined in section 2.4. 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 – Requirement for outcome data

Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement. It is the responsibility of the approved consultant to ensure that the patient or their representative/guardian is aware that the provision of follow-up data is a

[ii] Not all medicines used in routine prevention of recurrent attacks of hereditary angioedema are licensed in Ireland. Please refer to each individual product's summary of product characteristics for further details.

condition of reimbursement, and that audits may occur during which their personal data will be reviewed.

3.1 Follow-up data for berotralstat

The recommended time frame for assessing response to berotralstat is at 24 weeks, in line with the designated treatment period in the APeX2 clinical trial for berotralstat. Further follow-up data may be required at later intervals. 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)
- Criteria in Section 2.4 – number and frequency of clinically significant HAE attacks since commencing treatment
- Whether berotralstat is being continued or discontinued.

3.2 Follow-up data for lanadelumab

The recommended time frame for assessing a response to lanadelumab is at six months and 12 months. Patients who were not identified by six months as candidates for reducing the frequency of administration of lanadelumab may be required to submit further follow-up data at later intervals. 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)
- Criteria outlined in Section 2.4 - number and frequency of clinically significant HAE attacks since commencing treatment
- Current dosing frequency and proposed ongoing frequency of dosing
- Whether lanadelumab is being continued or discontinued.

3.3 Dose reduction for lanadelumab

This section applies to lanadelumab only.

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 six months, a reduction in frequency of administration to 300mg lanadelumab SC every four weeks should be implemented, especially in

patients with low weight. Approved consultants should therefore monitor patient response and reduce the frequency of lanadelumab administration at the earliest opportunity where indicated.

A condition of reimbursement of TAKHZYRO® is that:

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

4. Prescribing of berotralstat (Orladeyo®) and lanadelumab (TAKHZYRO®) for approved patients

Please refer to the relevant SmPCs for Orladeyo® and TAKHZYRO® for full prescribing information including monitoring and patient counselling requirements.

If a patient is recommended for reimbursement by the HSE-Medicines Management Programme (MMP), the High Tech prescription should be generated on the High Tech Hub (HTH). High Tech prescriptions which are not hub generated for Orladeyo® or TAKHZYRO® will not be eligible for reimbursement by the HSE Primary Care Reimbursement Service (PCRS). Only approved consultants and their teams will have access to generate prescriptions.