

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TAKHZYRO

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One unit (vial or pre-filled syringe) contains 300 mg of lanadelumab* in 2 mL solution.

*Lanadelumab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Solution for injection in pre-filled syringe.

The solution is colourless to slightly yellow, appearing either clear or slightly opalescent.

The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

This medicinal product should be initiated under the supervision of a physician experienced in the management of patients with hereditary angioedema (HAE).

Posology

The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

TAKHZYRO is not intended for treatment of acute HAE attacks (see section 4.4)

Missed doses

If a dose of TAKHZYRO is missed, the patient should be instructed to administer the dose as soon as possible ensuring at least 10 days between doses.

Special populations

Elderly

Age is not expected to affect exposure to lanadelumab. No dose adjustment is required for patients above 65 years of age (see section 5.2).

Hepatic impairment

No studies have been conducted in patients with hepatic impairment. Hepatic impairment is not expected to affect exposure to lanadelumab. No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Renal impairment

No studies have been conducted in patients with severe renal impairment. Renal impairment is not expected to affect exposure to lanadelumab or the safety profile. No dose adjustment is required in patients with renal impairment. (see section 5.2).

Paediatric population

The safety and efficacy of TAKHZYRO in children aged less than 12 years have not been established. No data are available.

Method of administration

TAKHZYRO is intended for subcutaneous (SC) administration only.

Each TAKHZYRO unit (vial or pre-filled syringe) is intended for single use only (see section 6.6).

The injection should be restricted to the recommended injection sites: the abdomen, the thighs, and the upper outer arms (see section 5.2). Rotation of the injection site is recommended.

TAKHZYRO may be self-administered or administered by a caregiver only after training on SC injection technique by a healthcare professional.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Hypersensitivity reactions have been observed. In case of a severe hypersensitivity reaction, administration of TAKHZYRO must be stopped immediately and appropriate treatment must be initiated.

General

TAKHZYRO is not intended for treatment of acute HAE attacks. In case of a breakthrough HAE attack, individualized treatment should be initiated with an approved rescue medication.

There are no available clinical data on the use of lanadelumab in HAE patients with normal C1-INH activity.

Interference with coagulation test

Lanadelumab can increase activated partial thromboplastin time (aPTT) due to an interaction of lanadelumab with the aPTT assay. The reagents used in the aPTT laboratory test initiate intrinsic coagulation through the activation of plasma kallikrein in the contact system. Inhibition of plasma kallikrein by lanadelumab can increase aPTT in this assay. None of the increases in aPTT in patients treated with TAKHZYRO were associated with abnormal bleeding adverse events. There were no differences in international normalised ratio (INR) between treatment groups.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated drug-drug interaction studies have been conducted. Based on the characteristics of lanadelumab, no pharmacokinetic interactions with co-administered medicinal products is expected.

As expected, concomitant use of the rescue medication C1 esterase inhibitor results in an additive effect on lanadelumab-cHMWK response based on the mechanism of action (MOA) of lanadelumab and C1 esterase inhibitor (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of lanadelumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive or developmental toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of lanadelumab during pregnancy.

Breast-feeding

It is unknown whether lanadelumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards, lanadelumab could be used during breast-feeding if clinically needed.

Fertility

Lanadelumab's effect on fertility has not been evaluated in humans. Lanadelumab had no effect on male or female fertility in cynomolgus monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

TAKHZYRO has negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly (52.4%) observed adverse reaction associated with TAKHZYRO was injection site reactions (ISR) including injection site pain, injection site erythema and injection site bruising. Of

these ISRs, 97% were of mild intensity, 90% resolved within 1 day after onset with a median duration of 6 minutes.

Hypersensitivity reaction (mild and moderate pruritus, discomfort and tingling of tongue) was observed (1.2%), see section 4.4.

Tabulated list of adverse reactions

Table 1 summarises adverse reactions observed in the HELP study that included 84 subjects with HAE, who received at least one dose of TAKHZYRO.

The frequency of adverse reactions listed in Table 1 is defined using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 1: Adverse reactions reported with lanadelumab

System organ class	Adverse drug reaction	Frequency
Immune system disorders	Hypersensitivity*	Common
Nervous system disorders	Dizziness	Common
Skin and subcutaneous tissue disorders	Rash maculo-papular	Common
Musculoskeletal and connective tissue disorders	Myalgia	Common
General disorders and administration site conditions	Injection site reactions**	Very common
Investigations	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common

*Hypersensitivity includes: pruritus, discomfort and tingling of tongue.

**Injection site reactions include: pain, erythema, bruising, discomfort, haematoma, haemorrhage, pruritus, swelling, induration, paraesthesia, reaction, warmth, oedema and rash.

Paediatric population

The safety of TAKHZYRO was evaluated in a subgroup of 23 subjects aged 12 to <18 years old. Results of the subgroup analysis were consistent with overall study results for all subjects.

Immunogenicity

Treatment with lanadelumab has been associated with development of treatment emergent anti-drug antibodies (ADA) in 11.9% (10/84) of subjects. All antibody titres were low. The ADA response was transient in 20% (2/10) of ADA positive subjects. 2.4% (2/84) of lanadelumab-treated subjects tested positive for neutralizing antibodies.

The development of ADA including neutralising antibodies against TAKHZYRO did not appear to adversely affect the pharmacokinetic (PK) and pharmacodynamics (PD) profiles or clinical response.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected

adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
<https://sideeffects.health.gov.il/>

4.9 Overdose

No case of overdose has been reported. There is no available information to identify potential signs and symptoms of overdose. If symptoms should occur, symptomatic treatment is recommended. There is no antidote available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema, ATC code: B06AC05

Mechanism of action

Lanadelumab is a fully human, monoclonal antibody (IgG1/ κ -light chain). Lanadelumab inhibits active plasma kallikrein proteolytic activity. Increased plasma kallikrein activity leads to angioedema attacks in patients with HAE through the proteolysis of high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in patients with HAE.

Pharmacodynamic effects

Concentration-dependent inhibition of plasma kallikrein, measured as reduction of cHMWK levels, was demonstrated after SC administration of TAKHZYRO 150 mg every 4 weeks, 300 mg every 4 weeks or 300 mg every 2 weeks in subjects with HAE.

The PK-PD relationship between TAKHZYRO and cHMWK is described by an indirect exposure-response pharmacological model. The cHMWK formation rate was maximally reduced by 53.7% with an IC_{50} of 5705 ng/ml.

Clinical efficacy and safety

HELP study

The HELP study was a multicenter, randomised, double-blind, placebo-controlled parallel-group study in 125 (115 adults and 10 adolescents) subjects with symptomatic type I or II HAE. Subjects were randomized into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, lanadelumab 150 mg every 4 weeks [q4wks], lanadelumab 300 mg every 4 weeks [q4wks], or lanadelumab 300 mg every 2 weeks [q2wks] by SC injection) for the 26-week treatment period.

The median (range) age of the study population was 42 (12 to 73) years with 88 female subjects (70%). A history of laryngeal angioedema attacks was reported in 65% (81/125) of subjects and 56% (70/125) were on prior long term prophylaxis (LTP). During the study run-in period, the mean attack rate was 3.7 attacks/month with 52% (65/125) of subjects experiencing ≥ 3 attacks/month.

All TAKHZYRO treatment arms produced statistically significant reductions in the mean HAE attack rate compared to placebo across all primary and secondary endpoints in the Intent-to-Treat population (ITT) (Table 2).

Table 2. Results of primary and secondary efficacy measures-ITT population

Endpoint statistics ^a	Placebo (N=41)	Lanadelumab		
		150mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)
Primary endpoint - Number of HAE attacks from Day 0 to 182				
LS Mean (95% CI) monthly attack rate ^b	1.97 (1.64, 2.36)	0.48 (0.31, 0.73)	0.53 (0.36, 0.77)	0.26 (0.14, 0.46)
% Reduction relative to placebo (95% CI) ^c		76 (61, 85)	73 (59, 82)	87 (76, 93)
Adjusted p-values ^d		<0.001	<0.001	<0.001
Secondary endpoint - Number of HAE attacks requiring acute treatment from Day 0 to 182				
LS Mean (95% CI) monthly attack rate ^b	1.64 (1.34, 2.00)	0.31 (0.18, 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
% Reduction relative to placebo (95% CI) ^c		81 (66, 89)	74 (59, 84)	87 (75, 93)
Adjusted p-values ^d		<0.001	<0.001	<0.001
Secondary endpoint - Number of moderate or severe HAE attacks from Day 0 to 182				
LS Mean (95% CI) monthly attack rate ^b	1.22 (0.97, 1.52)	0.36 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)
% Reduction relative to placebo (95% CI) ^c		70 (50, 83)	73 (54, 84)	83 (67, 92)
Adjusted p-values ^d		<0.001	<0.001	<0.001

Note: CI=confidence interval; LS=least squares.

^a Results are from a Poisson regression model accounting for over dispersion with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the treatment period as an offset variable in the model.

^b Model-based treatment period HAE attack rate (attacks/4 weeks).

^c % reduction relative to placebo corresponds to 100% * (1-rate ratio). The rate ratio is ratio of the model-based treatment period HAE attack rates.

^d Adjusted p-values for multiple testing.

The mean reduction in HAE attack rate was consistently higher across the TAKHZYRO treatment arms compared to placebo regardless of the baseline history of LTP, laryngeal attacks, or attack rate during the run-in period. The percentage of subjects who were attack free is provided in Table 3.

Table 3. Percentage of subjects who were attack free through treatment

Criteria	Placebo	Lanadelumab		
		150 mg q4wks	300 mg q4wks	300 mg q2wks
Treatment period (Day 0 to Day 182, 26 weeks)				
n	41	28	29	27
Attack free	2%	39%	31%	44%

The percentage of patients who were attack free for the last 16-weeks (Day 70 to Day 182) of the study was 77% in the 300 mg q2wks group, compared to 3% of patients in the placebo group.

100% of the subjects on 300 mg q2wks or q4wks and 89% on 150 mg q4wks achieved at least a 50% reduction in HAE attack rate compared to the run-in period.

Health related Quality of Life

All TAKHZYRO treatment groups observed an improvement in Angioedema Quality of Life Questionnaire (AE-QoL) total and domain (functioning, fatigue/mood, fear/shame, and nutrition) scores compared to the placebo group; the largest improvement was observed in the functioning score as shown in Table 4. A reduction of 6 points is considered a clinically meaningful improvement. The percentage of patients who achieved a clinically meaningful improvement in AE-QoL total score was 65% (Odds ratio vs placebo, [95% CI]= 3.2 [1.1, 9.2]), 63% (2.9 [1.1, 8.1]), and 81% (7.2 [2.2, 23.4]), in TAKHZYRO 150 mg q4 wks, 300 mg q4 wks, and 300 mg q2 wks groups, respectively, compared to 37% of patients in the placebo group.

Table 4 Change in AE-QoL score^a - placebo vs TAKHZYRO at week 26 in HELP study

LS mean change (SD) from baseline at week 26	Placebo	TAKHZYRO total
AE-QoL Total score	-4.7 (18.8)	-19.5 (18.6)
Functioning score	-5.4 (22.7)	-29.3 (22.9)
Fatigue/Mood score	-1.8 (23.3)	-13.0 (23.1)
Fear/Shame score	-9.0 (24.0)	-18.8 (23.7)
Nutrition score	0.5 (22.5)	-17.0 (22.3)

Note: AE-QoL= Angioedema Quality of Life; LS=least squares; SD=standard deviation.

^a Lower scores indicate lower impairment (or better health-related quality of life).

HELP study extension

Long-term safety and efficacy of TAKHZYRO for prophylaxis to prevent HAE attacks was evaluated in an open-label HELP study extension.

A total of 212 adult and adolescent subjects with symptomatic type I or II HAE received at least one dose of lanadelumab in this study, including 109 subjects who entered as rollover subjects from the HELP study and 103 new or non-rollover subjects (including 19 subjects from Phase 1b study) who had an historical baseline attack rate of ≥ 1 attack per 12 weeks. Subjects were allowed to initiate self-administration after receiving the first 2 doses from a health care professional in clinic and completing appropriate training. Interim analysis indicates that the effect was sustained up to one year of treatment.

5.2 Pharmacokinetic properties

The single and multiple dose pharmacokinetics of lanadelumab have been studied in patients with HAE. Pharmacokinetics of lanadelumab showed linear dose-exposure response with doses up to 400 mg and reproducible exposure following subcutaneous administration up to 12 months. The absolute bioavailability of lanadelumab after subcutaneous administration has not been determined. In the HELP study, patients treated with 300 mg q2 wks presented mean (SD) area under the curve over the dosing interval at steady-state (AUC_{tau,ss}), maximum concentration at steady-state (C_{max,ss}) and minimum concentration at steady-state (C_{min,ss}) of 408 $\mu\text{g}\cdot\text{day}/\text{ml}$ (138), 34.4 $\mu\text{g}/\text{mL}$ (11.2), and

25.4 µg/mL (9.18), respectively. The anticipated time to reach steady state concentration was approximately 70 days.

Absorption

Following SC administration, the time to maximum concentration is approximately 5 days. The site of SC injection (thigh, arm, or abdomen) and self-administration did not affect the absorption of lanadelumab.

Distribution

The mean (SD) volume of distribution of lanadelumab in patients with HAE is 14.5 litres (4.53). Lanadelumab is a therapeutic monoclonal antibody and is not expected to bind to plasma proteins.

Elimination

Lanadelumab has a mean (SD) total body clearance of 0.0297 L/h (0.0124) and a terminal elimination half-life of approximately 14 days.

Special populations

No dedicated studies have been conducted to evaluate the pharmacokinetics of lanadelumab in special patient populations including gender, age, pregnant women or the presence of renal or hepatic impairment.

In a population pharmacokinetic analysis, after correcting for body weight, no influence of gender or age (12 to 75 years) was apparent on the clearance or volume of distribution of lanadelumab.

Although body weight was identified as an important covariate describing the variability of clearance, a 300 mg q2wks dose regimen provided sufficient exposure for the indication (see section 5.1).

Renal and hepatic impairment

As IgG monoclonal antibodies are mainly eliminated via intracellular catabolism, renal impairment or hepatic impairment is not expected to influence clearance of lanadelumab.

Accordingly, in a population pharmacokinetic analysis, renal impairment (estimated GFR: 60 to 89 ml/min/1.73 m² [mild, N=98] and 30 to 59 ml/min/1.73m² [moderate, N=9]) had no effect on the clearance or volume of distribution of lanadelumab.

5.3 Preclinical safety data

In repeat-dose studies evaluating once weekly SC injection in both rats (up to 28 days) and cynomolgus monkeys (up to 6 months) lanadelumab was well-tolerated at doses of up to and including 50 mg/kg (highest dose tested) with no organs of toxicity identified. Exposures in cynomolgus monkeys following 6 months of administration were approximately 23-fold greater than that noted at 300 mg q2 wks based on AUC.

Lanadelumab is not expected to interact directly with DNA or other chromosomal material, as it is made up entirely of naturally occurring amino acids and contains no inorganic or synthetic linkers or other nonprotein portions; therefore no genotoxicity evaluation has been conducted. Carcinogenicity has not been evaluated in animals as based on the weight of evidence approach, lanadelumab is considered to have a low risk for carcinogenicity.

The effects of lanadelumab on fertility were evaluated in sexually mature cynomolgus monkeys. In a 13-week study, once weekly SC administration of lanadelumab had no effects on male or female fertility at doses of 10 or 50 mg/kg (highest dose tested). Exposures in sexually mature cynomolgus monkeys in the fertility study were approximately 20- and 22-fold greater than that noted at 300 mg q2 wks based on C_{max} and AUC, respectively.

In the ePPND study in pregnant cynomolgus monkeys administered once weekly doses of 10 or 50 mg/kg (highest dose tested), there were no lanadelumab-related effects on pregnancy and parturition, embryo-foetal development, survival, growth, and/or postnatal development of offspring. Exposures in the ePPND study were approximately 32-fold greater than that noted at 300 mg q2 wks based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
L- Histidine
Sodium phosphate dibasic, dihydrate
Sodium chloride
Citric acid monohydrate
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Vial only:

Chemical and physical in-use stability has been demonstrated for 2 hours at 25°C and for 8 hours at 2°C to 8°C. From a microbiological point of view, unless the method of preparation precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. TAKHZYRO should be administered within 2 hours of preparing the dosing syringe. If not administered immediately after preparation, the syringe may be stored in the refrigerator (2°C to 8°C), protected from light and administered within 8 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the solution (vial or pre-filled syringe) in the outer carton in order to protect from light.

The solution (vial or pre-filled syringe) may be stored below 25°C for a single period of 14 days, but not beyond the expiry date. Do not return TAKHZYRO to refrigerated storage after storage at room temperature.

For storage conditions after first opening of the product in vial, see section 6.3.

6.5 Nature and contents of container

Vial:

2 ml of solution in a vial (type I glass) with a coated butyl rubber stopper and an aluminium seal with violet flip-off cap.

TAKHZYRO is available as a single pack containing one 2 ml vial.

Each pack also contains the following items:

- Empty 3 ml syringe
- 18G vial access needle
- 27G x ½ inch (0.4 x 13 mm) injection needle

Pre-filled syringe:

2 ml of solution in pre-filled syringe with a bromobutyl stopper, 27G x 13 mm staked needle and rigid needle cap.

TAKHZYRO is available as unit packs containing 1 or 2 pre-filled syringes and in multipacks containing 6 (3 packs of 2) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Lanadelumab is provided in single use vials and pre-filled syringes.

Before use, TAKHZYRO solution should be visually inspected for appearance. The solution should be clear or slightly yellow. Solutions that are discoloured or contain particles should not be used.

Avoid vigorous agitation.

Administration steps

Vial:

Using aseptic technique, withdraw the prescribed dose of TAKHZYRO from the vial into the syringe using an 18 gauge needle.

Change the needle on the syringe to a 27 gauge needle or other needle suitable for SC injection. Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm (see section 4.2).

Discard the vial with any unused contents.

Pre-filled syringe

After removing the pre-filled syringe from the refrigerator, wait 15-30 minutes before injecting to allow the solution to reach room temperature. Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm (see section 4.2).

Each pre-filled syringe is for single use only. Discard the pre-filled syringe after injection is completed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

All needles and syringes should be disposed of in a sharps container.

7. MANUFACTURER

Shire Pharmaceuticals Ireland Limited
Blocks 2 & 3 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
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8. LICENSE HOLDER

Takeda Israel Ltd.,
25 Eyal st., Petach-Tikva, 4951125

9. REGISTRATION NUMBER

163-47-35885-00

This leaflet format has been revised according to the Ministry of Health guidelines in October 2021.