▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - TAKHZYRO™ (Lanadelumab) subcutaneous injection

1 NAME OF THE MEDICINE

Lanadelumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ready-to-use solution, for subcutaneous injection only.

TAKHZYRO is a sterile, preservative-free solution in a single-use glass vial. One vial contains 300 mg of lanadelumab in 2 mL solution.

Excipient with known effect:
Each mL of solution contains 3.45 mg (0.150 mmol) of sodium.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) in patients aged 12 years and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

TAKHZYRO therapy should be initiated under supervision of a physician experienced in the care of patients with hereditary angioedema (HAE).

Dosage

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.

Elderly:
Limited information is available on patients above 65 years of age. Available data indicates that no dose adjustment is required for patients above 65 years of age.

Hepatic impairment:
No studies have been conducted in patients with hepatic impairment.

Renal impairment:
No studies have been conducted in patients with renal impairment.

Paediatric population:
The safety and efficacy of TAKHZYRO in children aged <12 years has not been established and therefore treatment in children aged <12 years is not recommended.

Method of administration

TAKHZYRO is administered subcutaneously only.

TAKHZYRO is provided as a ready-to-use solution that does not require additional reconstitution or dilution for administration. Each TAKHZYRO vial is intended for single use only. Do not use the vial if it appears discoloured or contains visible particles. Avoid vigorous agitation of the vial.

TAKHZYRO may be administered by a healthcare professional or by the patient/caregiver. The decision on the use of home treatment for an individual patient should be made by the treating physician, who should ensure that appropriate training is provided. The patient or caregiver should receive clear instructions and adequate training on how to perform subcutaneous administration. A healthcare professional should review the self-administration method at intervals to ensure the continued appropriate administration.

Detailed instructions for administration are provided in the Consumer Medicine Information that is included as a package insert and may be used as a training guide.

If a dose of TAKHZYRO is missed, instruct the patient or caregiver to administer the dose as soon as possible ensuring at least 10 days between the doses.

Administration steps

An aseptic technique must be used. The 18 gauge needle is used to withdraw the TAKHZYRO dose from the vial and the 27 gauge needle is used to administer the complete dose as prescribed subcutaneously. TAKHZYRO may be administered into the abdomen, thigh, or upper arm. Any unused portions of drug remaining in the vial should be discarded.

TAKHZYRO should be administered within 2 hours of preparing the dosing syringe at room temperature. After the dosing syringe is prepared, it can be refrigerated at 2°C to 8°C and must be used within 8 hours.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

TAKHZYRO should not be used to treat an acute attack. Patients and caregivers should continue to be prepared to treat attacks with acute HAE treatments when necessary.

There are no available clinical data on the use of TAKHZYRO in HAE patients with normal C1 esterase inhibitor activity.

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, discontinue TAKHZYRO administration and institute appropriate treatment.

Use in hepatic impairment

No dedicated study has been conducted in subjects with hepatic impairment.

Use in renal impairment

No dedicated study has been conducted in subjects with renal impairment (see Section 5.2 Pharmacokinetic Properties – Special Populations).

Use in the elderly

The clinical studies included 11 subjects aged ≥65 years, with 5 included in the main efficacy study. Results of the subgroup analysis by age were consistent with overall study results (see Section 5.1 Pharmacodynamic Properties – Clinical Trials).

Paediatric use

The safety and efficacy of TAKHZYRO in children has not been established. No data are available for children aged less than 12 years. Treatment in children aged <12 years is not recommended. There are limited data for children aged 12 to <18 years – the clinical studies included 23 subjects aged 12 to <18 years, with 10 included in the main efficacy study. Results of the subgroup analysis were consistent with overall study results for all subjects (see Section 5.1 Pharmacodynamic Properties – Clinical Trials).

Effects on laboratory tests

Coagulation tests:
TAKHZYRO can increase activated partial thromboplastin time (aPTT) due to an interaction of TAKHZYRO 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 TAKHZYRO 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

TAKHZYRO effect on fertility has not been evaluated in humans.

In a 13-week study, once weekly subcutaneous administration at doses of 10 or 50 mg/kg (highest dose tested) lanadelumab had no effects on semen sample weight, total sperm count, sperm density, motility and morphology, testicular measurements, spermatogenesis staging, menstrual cycle length, or reproductive organs (organ weights, macroscopic and microscopic findings). Exposures in sexually mature cynomolgus monkeys were approximately 18-fold greater than that noted at 300 mg every 2 weeks based on AUC.

Use in pregnancy

Australian Pregnancy Categorisation: Category B1

TAKHZYRO has not been studied in pregnant women. There are no or limited amount of data from the use of lanadelumab in pregnant women. A risk to the pregnant woman or developing fetus cannot be excluded. A decision should be made whether to initiate or discontinue treatment with TAKHZYRO, taking into account the risk/benefit of therapy.

The effects of lanadelumab were evaluated in an enhanced pre- and postnatal developmental (ePPND) toxicity study. In the ePPND study in pregnant cynomolgus monkeys administered once weekly doses of 10 or 50 mg/kg (highest dose tested) from gestation day 20 to delivery, there were no lanadelumab-related effects on pregnancy and parturition, embryo-fetal development, as well as survival, growth, and/or postnatal development of offspring. Exposures in the ePPND study were approximately 28-fold greater than that noted at 300 mg every 2 weeks based on AUC.

Use in lactation

TAKHZYRO has not been studied in lactating women. It is not known whether lanadelumab is present in human milk therefore a risk to the newborns/infants cannot be excluded. The developmental and health benefits of breastfeeding should be taken into consideration along with the mother's medical need for TAKHZYRO as well as any potential adverse effects on both the infant and the mother.

Available pharmacokinetic data from the ePPND study in cynomolgus monkeys have shown low excretion of lanadelumab in milk at approximately 0.2% of the maternal plasma level.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of lanadelumab was evaluated in 4 clinical studies: a Phase 1a, randomised, double-blind, placebo-controlled study in healthy subjects; a Phase 1b, randomised, double-blind, placebo-controlled, multiple-ascending dose study in subjects with HAE; a pivotal Phase 3, randomised, double-blind, and placebo-controlled study (HELP study) in subjects with HAE; and an open-label extension study (HELP study extension), which includes both subjects from the HELP study (rollover) and additional non-rollover HAE subjects. Two hundred and fifty-

seven (257) unique subjects (233 subjects with HAE and 24 healthy subjects) were exposed to at least one dose of lanadelumab.

The safety data described below reflect exposure to TAKHZYRO in the HELP study and in the HELP study extension; in total, 220 subjects received treatment with lanadelumab in one or both of the studies.

Treatment-emergent adverse events that occurred in ≥5% of lanadelumab-treated subjects (overall) in the HELP study are presented in Table 1.

Table 1. Treatment-Emergent Adverse Events (TEAE) Reported in ≥5% Lanadelumab-Treated Subjects (Overall) by Preferred Term-Safety Population in the HELP Study

Preferred Term	Placebo (N=41) n (%)	Lanadelumab			
		150 mg q4wks (N=28) n (%)	300 mg q4wks (N=29) n (%)	300 mg q2wks (N=27) n (%)	Total (N=84) n (%)
Any TEAE	31 (75.6)	25 (89.3)	25 (86.2)	26 (96.3)	76 (90.5)
Injection site pain	12 (29.3)	13 (46.4)	9 (31.0)	14 (51.9)	36 (42.9)
Viral upper respiratory tract infection	11 (26.8)	3 (10.7)	7 (24.1)	10 (37.0)	20 (23.8)
Headache	8 (19.5)	3 (10.7)	5 (17.2)	9 (33.3)	17 (20.2)
Injection site erythema	1 (2.4)	4 (14.3)	2 (6.9)	2 (7.4)	8 (9.5)
Injection site bruising	0 (0.0)	3 (10.7)	2 (6.9)	1 (3.7)	6 (7.1)
Dizziness	0 (0.0)	1 (3.6)	3 (10.3)	1 (3.7)	5 (6.0)

N: number of subjects; n: number of subjects experiencing the event.
Percentages are based on all subjects in the Safety Population.
Subjects were counted once per preferred term.

Table 2 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 reaction listed in Table 2 is defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 2. Adverse Reactions Reported with Lanadelumab

System Organ Class (Frequency)	Adverse Drug Reaction
Immune system disorders Common	Hypersensitivity*
Nervous system disorders Common	Dizziness
Skin and subcutaneous tissue disorders Common	Rash maculopapular
Musculoskeletal and connective tissue disorders Common	Myalgia
General disorders and administration site conditions Very common	Injection site reactions**
Investigations Common	Alanine aminotransferase increased, Aspartate aminotransferase increased
* 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.	

In the HELP study, the most commonly observed adverse reaction associated with TAKHZYRO in subjects with HAE 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 Special Warnings and Precautions for Use – Hypersensitivity Reactions).

Safety data from an interim analysis of HELP study extension is consistent with safety data from the HELP study (described in Table 2). Data on long-term use (>12 months) are limited.

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 thus indicating that safety and tolerability of lanadelumab in children (aged 12 years and above) compared with adults is similar.

Immunogenicity

In the HELP study, 10 (12%) lanadelumab-treated and 2 (5%) placebo-treated subjects had at least 1 anti-drug antibody (ADA)-positive sample during treatment period; antibody titres were

low (range: 20 to 1280). The ADA response observed was transient in 2 of 10 lanadelumab-treated and 1 of 2 placebo-treated subjects. Pre-existing low titre antibodies were observed in 3 lanadelumab-treated subjects and 1 placebo-treated subjects with ADAs. Two subjects receiving 150 mg every 4 weeks had low titre antibodies classified as neutralising.

The development of ADA including neutralising antibodies against TAKHZYRO did not appear to adversely affect pharmacokinetics, pharmacodynamics, safety or clinical response.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no clinical experience with overdosage of TAKHZYRO.

For information on the management of overdose, contact the Poisons Information Centre on 131126 in Australia, or the National Poisons Centre on 0800 POISON (0800 764766) in New Zealand.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs used in hereditary angioedema, monoclonal antibody, ATC code: B06AC05.

Mechanism of action

Lanadelumab is a fully human, monoclonal antibody (IgG1/κ-light chain) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Lanadelumab inhibits active plasma kallikrein proteolytic activity without binding prekallikrein, the inactive precursor found in the circulation. 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, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. It has been demonstrated that patients with HAE due to C1 esterase inhibitor deficiency or dysfunction have increased plasma kallikrein activity, as indirectly measured by amount of cHMWK, both during and in between HAE attacks. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in patients with HAE.

Pharmacodynamic effects

At pharmacokinetic steady-state, similar inhibition of plasma kallikrein, measured as reduction of cHMWK levels, was demonstrated after subcutaneous administration of TAKHZYRO 150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg every 2 weeks in subjects with HAE.

The pharmacokinetic-pharmacodynamic 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.

Serial 12 lead ECG monitoring in the clinical studies found that TAKHZYRO did not prolong the QT/QTc interval.

Clinical trials

HELP study

The HELP study investigated efficacy and safety of TAKHZYRO for routine prevention of attacks of HAE in subjects 12 years of age and older in a multicentre, randomised, double-blind, placebo-controlled parallel-group study.

The study included 125 subjects with symptomatic type I or II HAE, including 10 subjects aged 12 to 17 years and 5 subjects aged more than 65 years. Subjects were randomised 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 q4wks, or lanadelumab 300 mg every 2 weeks (q2wks) by subcutaneous injection) for the 26-week treatment period. The use of rescue medications for treatment of breakthrough HAE attacks was allowed for subjects receiving placebo or TAKHZYRO.

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, attack rates of ≥3 attacks/month were observed in 52% (65/125) of subjects overall.

All TAKHZYRO treatment arms produced clinically meaningful and 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 3).

Table 3. 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)
Number of HAE Attacks from Day 0 to 182[a]				
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)
p-value[d]		<0.001	<0.001	<0.001
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)
p-value[d]		<0.001	<0.001	<0.001

Table 3. 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)
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)
p-value[d]		<0.001	<0.001	<0.001

CI: confidence interval; ITT: intent-to-treat; LS: least squares.
Results are from a Poisson regression model accounting for over dispersion with fixed effects for treatment group (categorical) and normalised 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.
[a] Primary efficacy endpoint.
[b] Model-based treatment period HAE attack rate (attacks/4 weeks).
[c] Calculated as one minus the ratio of the model-based treatment period HAE attack rates (lanadelumab/placebo) multiplied by 100.
[d] P-values are adjusted for multiple testing. A general gatekeeping approach with families for each active treatment group to placebo group comparison was utilised to control the global family-wish type I error rate at 0.05. Within a family, hypotheses were tested at α/3 or 0.0167 significance level.

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.

During the anticipated pharmacokinetic steady-state period (Day 70 to Day 182), percentage reductions in the mean monthly HAE attack rate for TAKHZYRO-treated subjects compared to placebo was 78% in the 150 mg q4wks arm, 81% in the 300 mg q4wks arm, and 91% in the 300 mg q2wks arm.

The percentage of subjects who were attack free is provided in Table 4.

Table 4. Percentage of Subjects who were Attack Free Through Treatment and Steady-state Periods

Criteria	Placebo (N=41)	Lanadelumab		
		150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)
Treatment Period (Day 0 to Day 182, 26 weeks)				
N	41	28	29	27
Attack free	2%	39%	31%	44%
Estimated Steady-State Period (Day 70 to Day 182, 16 weeks)				
n	37	28	29	26
Attack free	3%	54%	45%	77%

A responder was defined as achieving a 50% reduction in HAE attack rate compared to the run-in period. One hundred percent (100%) of subjects on 300 mg q2wks or q4wks and 89% on 150 mg q4wks responded to treatment. Table 5 shows the percentage of subjects achieving

pre-defined threshold (≥50%, ≥70%, ≥90%) reductions in HAE attack rates compared to run-in during the 26 week treatment period.

Table 5. Percentage of Subjects Achieving Pre-Defined Threshold Reductions in HAE Attacks

Criteria	Placebo (N=41) n (%)	Lanadelumab		
		150 mg q4wks (N=28) n (%)	300 mg q4wks (N=29) n (%)	300 mg q2wks (N=27) n (%)
≥50% Reduction	13 (32)	25 (89)	29 (100)	27 (100)
≥70% Reduction	4 (10)	22 (79)	22 (76)	24 (89)
≥90% Reduction	2 (5)	18 (64)	16 (55)	18 (67)

ITT: intent-to-treat; N: number of subjects; n: number of subjects experiencing the event.
Note: For each subject, the percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. The percentage reduction groups are not mutually exclusive, subjects may appear in more than one group as applicable based on their percentage reduction.

Health-related quality of life

The health-related quality of life (QoL) was investigated using a generic QoL questionnaire, EQ-5D-5L; and an angioedema-specific questionnaire, Angioedema Quality of Life (AE-QoL). The ED-5D-5L scores showed no differences between placebo and treatment groups. A higher proportion of TAKHZYRO treated subjects compared to placebo achieved a clinically meaningful improvement in QoL, as measured by a Minimal Clinically Important Difference (MCID) ≥6 for the AE-QoL total score; applying same MCID, a similar response was observed for functioning but not for fear/shame, fatigue/mood, and nutrition domains.

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 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 the Phase1b study) who had a historical baseline attack rate of ≥1 attack per 12 weeks and a confirmed diagnosis of type I or II HAE. The median (range) age of the study population was 43 (12 to 76) years with 67% female subjects. Rollover patients received a single dose of lanadelumab 300 mg and then did not receive another dose until the first HAE attack occurred ("dose-and-wait period"), after which they received lanadelumab 300 mg every 2 weeks. Non-rollover patients received lanadelumab 300 mg every 2 weeks from study entry. Subjects were allowed to self-administer and the majority of subjects self-administered TAKHZYRO over 10 to 60 seconds.

At the time of the interim analysis (including at least 12 months of lanadelumab exposure across both studies for lanadelumab rollover subjects), all subjects had a median attack rate of zero. At week 4 post-dose, approximately 80% of patients who had been in the 300 mg q2wks treatment group (N=25) in the HELP study remained attack-free. There was a 99% reduction in

the median attack rates observed in placebo rollover patients (N=33) after they received open label lanadelumab 300 mg q2wks for an average of 26 weeks. The mean AE-QoL total score was reduced (i.e. improved) for rollover and non-rollover subjects.

5.2 PHARMACOKINETIC PROPERTIES

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 pharmacokinetic (PK) properties and exposure (steady-state) of lanadelumab in HAE patients, following subcutaneous administration of 150 mg q4wks, 300 mg q4wks and 300 mg q2wks, are provided in Table 6. The anticipated population time to reach steady-state concentration was approximately 70 days.

Table 6. Mean (SD) Pharmacokinetic Parameters of Lanadelumab Following Subcutaneous Administration (HELP Study)

Pharmacokinetic Parameters	Lanadelumab		
	150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)
CL/F (L/day)	0.667 (0.162)	0.742 (0.239)	0.809 (0.370)
Vc/F (L)	14.1 (2.93)	14.9 (4.45)	16.6 (4.79)
$AUC_{tau,ss}$ (µg*day/mL)	233 (56.6)	441 (137)	408 (138)
$C_{max,ss}$ (µg/mL)	12.0 (3.01)	23.3 (7.94)	34.4 (11.2)
$C_{min,ss}$ (µg/mL)	4.81 (1.40)	8.77 (2.80)	25.4 (9.18)
t_{max} (day)	5.17 (1.09)	5.17 (1.12)	4.11 (0.377)
$t_{1/2}$ (day)	14.9 (2.00)	14.2 (1.89)	15.0 (2.48)

CL/F: apparent clearance; Vc/F: apparent volume of distribution; $AUC_{tau,ss}$: area under the curve over the dosing interval at steady-state; $C_{max,ss}$: maximum concentration at steady-state; $C_{min,ss}$: minimum concentration at steady-state; t_{max}: time to maximum concentration; $t_{1/2:}$ terminal elimination half-life.

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.

Population PK analyses were performed, using data from rich sampling in two Phase 1 studies and sparse sampling in two Phase 3 (HELP and HELP extension) studies.

The population PK analyses found that patient body weight was an important covariate describing the variability of clearance and volume of distribution, resulting in higher exposure (AUC and C_{max}) in lighter patients. After correcting for body weight, no influence of gender was apparent on the clearance or volume of distribution of TAKHZYRO. No dose adjustment is required.

The population PK analyses for the effects of age, including 22 adolescents [aged 12 to 18], 226 adults [aged >18 and <65 years] and 9 elderly [aged >65 years]. The mean lanadelumab exposure under the same dosing regimen was found to be approximately 37% higher in adolescent patients compared to adult patients, due to lower body weight in adolescent patients.

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.

The population PK analysis of the effect of renal impairment that included estimated GFR: 60 to 89 mL/min/1.73m^2 [mild, N=98], 30 to 59 mL/min/1.73m^2 [moderate, N=9] and <30 mL/min/1.73m^2 [severe, N=0] found no effect on the clearance or volume of distribution. No dose adjustment is required for mild or moderate renal impairment. No dose recommendation can be made for severe renal impairment.

Concomitant medications

There have been no dedicated investigations of PK interactions (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Based on the population PK analysis of the Phase 3 data, the use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on clearance and volume of distribution of TAKHZYRO.

For breakthrough HAE attacks, use of rescue medications such as icatibant or plasma-derived C1esterase inhibitor had no effects on clearance and volume of distribution of TAKHZYRO.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Given that lanadelumab is a monoclonal antibody and therefore is not expected to interact directly with DNA or other chromosomal material, no genotoxicity evaluation has been conducted.

Carcinogenicity

Carcinogenicity has not been evaluated in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate dihydrate
Citric acid monohydrate
Histidine
Sodium chloride
Polysorbate 80
Water for injections

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 2°C to 8°C. Do not freeze.

Vials removed from refrigeration should be stored below 25°C and used within 14 days or returned to refrigeration until use.

Keep the vial in the original carton in order to protect vial from light.

6.5 NATURE AND CONTENTS OF CONTAINER

2 mL of solution in a vial (type I glass) with chlorobutyl rubber stopper and an aluminium crimp seal with violet flip-off cap. Pack size of 1 vial.

Each pack also contains the following administration ancillaries: one empty 3 mL syringe, one 18 gauge vial access needle, and one 27 gauge ½ inches needle (for subcutaneous injection).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

TAKHZYRO is a sterile, preservative-free, colourless to slightly yellow solution with a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

Chemical structure

Based on the amino acid sequence, the molecular weight of the non-glycosylated lanadelumab is 146 kDa. The calculated molecular mass of the fully reduced light chain is 23 kDa. The calculated molecular mass of the fully reduced and non-glycosylated heavy chain is 49 kDa.

CAS number

1426055-14-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8 SPONSOR

Shire Australia Pty Limited
Level 39
225 George Street
Sydney, NSW 2000
Australia
Telephone: 1800 012 612
www.shireaustralia.com.au

9 DATE OF FIRST APPROVAL

30 January 2019