Product Monograph

Including Patient Medication Information

PrTAKHZYRO®

lanadelumab injection

solution for subcutaneous injection; Prefilled Syringes (1 mL and 2 mL), Prefilled Pen (2 mL) and Vials (2 mL)

150 mg/1 mL of lanadelumab

Monoclonal antibody inhibitor of plasma kallikrein

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Part 1: Healthcare Professional Information

1. Indications

TAKHZYRO (lanadelumab injection) is indicated for:

- routine prevention of attacks of hereditary angioedema (HAE) in adults and pediatric patients aged 2 years and older.

TAKHZYRO is not intended for acute treatment of HAE attacks.

1.1. Pediatrics

≥2 years of age and older: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TAKHZYRO in pediatric patients aged ≥2 years and weighing ≥10 kg have been established. Therefore, Health Canada has authorized an indication for pediatric use.

<2 years of age: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for this age range (see 7.1.3. Pediatrics).

1.2. Geriatrics

Geriatrics (≥65 years of age): The safety and efficacy of TAKHZYRO were evaluated in subjects 65 years of age and older (n=11). Results of the subgroup analysis by age were consistent with overall study results.

2. Contraindications

TAKHZYRO (lanadelumab injection) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.2. Recommended Dose and Dosage Adjustment

Adults and Pediatric Patients (aged 12 Years and older): The recommended dose of TAKHZYRO is 300 mg administered subcutaneously every 2 weeks. A dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack-free) for more than 6 months.

Pediatric Patients (2 to <12 years of age): The recommended dose of lanadelumab is based on body weight (see Table 1).

Table 1. Recommended Dose in Children 2 to Less Than 12 Years of Age

Body Weight (kg)	Recommended Starting Dose	Dose Adjustment
10 to <20 kg	150 mg lanadelumab every 4 weeks	A dose increase to 150 mg lanadelumab every 3 weeks may be considered in patients with insufficient control of attacks
≥ 20 kg	150 mg lanadelumab every 2 weeks	A dose reduction to 150 mg lanadelumab every 4 weeks may be considered in patients who are stably attack free on treatment

The prefilled pen has not been studied in children 2 to <12 years of age and should not be used in these patients.

Patients with a body weight of 20 to <40 kg who are stably attack free may continue with the same dose when reaching 12 years of age.

4.4. Administration

TAKHZYRO is administered subcutaneously only.

TAKHZYRO is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self-inject TAKHZYRO, or the patient's caregiver may administer TAKHZYRO, if their healthcare professional determines that it is appropriate.

- **Adult and pediatric patients 12 years of age and older**: TAKHZYRO may be administered by the patient, health care professional or caregiver.
- **Pediatric patients 2 to less than 12 years of age**: TAKHZYRO should be administered by a healthcare professional or caregiver.

TAKHZYRO is provided as a ready-to-use solution that does not require additional reconstitution or dilution for administration.

Instructions for single-use prefilled syringe or single-use prefilled pen

Inspect the prefilled syringe or prefilled pen for any damage.

Do not use the prefilled syringe or prefilled pen if the solution appears discoloured or contains visible particles. Avoid vigorous agitation of the prefilled syringe or prefilled pen.

For the TAKHZYRO prefilled syringe, remove from the refrigerator approximately 15 minutes before injecting to allow the solution to come to room temperature.

For the TAKHZYRO prefilled pen, remove from the refrigerator approximately 30 minutes before injecting to allow the solution to come to room temperature.

Inject TAKHZYRO prefilled syringe or prefilled pen subcutaneously into the abdomen or thigh. Inject subcutaneously into the upper arm only if a healthcare provider or caregiver is giving the injection. Healthcare providers, caregivers or patients should inject the complete dose as prescribed.

For detailed instructions on the preparation and administration of TAKHZYRO see either the 1 mL or 2 mL prefilled syringe or the 2 mL prefilled pen Patient Medication Information.

Instructions for single-use vial

Do not use the vial if the solution appears discoloured or contains visible particles. Avoid vigorous agitation of the vial.

Remove the TAKHZYRO vial from the refrigerator approximately 15 minutes before injecting to allow the solution to come to room temperature.

Using aseptic technique, withdraw the prescribed dose of TAKHZYRO from the vial using an 18 gauge needle. Change the needle on the syringe to a 27 gauge ½-inch pointed tip needle or other needle suitable for subcutaneous injection.

Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm. Patients should inject the complete dose as prescribed by their health professional.

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 (2°C to 8°C) but must be used within 8 hours.

Discard any unused portions of the drug remaining in the vial and syringe.

For detailed instructions on the preparation and administration of TAKHZYRO see vial Patient Medication Information.

4.5. Missed Dose

If a dose of TAKHZYRO is missed,

- **Adult and pediatric patients 12 years of age and older**: instruct the patient to administer the dose as soon as possible, ensuring at least 10 days between the doses.
- **Pediatric patients 2 to <12 years of age weighing ≥ 20 kg**: instruct the caregiver to administer the dose as soon as possible, ensuring at least 10 days between the doses.
- **Pediatric patients 2 to <12 years weighing 10 kg to <20 kg**: instruct the caregiver to administer the dose as soon as possible, ensuring at least 24 days between the doses.

5. Overdose

There is no clinical experience with overdosage of TAKHZYRO. The highest dose tested in clinical trials was 400 mg.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2. Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
subcutaneous	solution; single-dose 300 mg lanadelumab in 2 mL single use vial	citric acid, L-histidine, polysorbate 80, sodium chloride, sodium phosphate, water for injection
	solution; single-dose 300 mg lanadelumab in 2 mL single use prefilled syringe	
	solution; single-dose 150 mg lanadelumab in 1 mL single use prefilled syringe	
	solution; single-dose 300 mg lanadelumab in 2 mL single use prefilled pen	

Description

TAKHZYRO (lanadelumab injection) is a colourless to slightly yellow solution, appearing either clear or slightly opalescent. The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

TAKHZYRO is a sterile, preservative-free solution available in the following presentations:

- **single-use prefilled syringe (300 mg / 2 mL):**

TAKHZYRO is a ready-to-use solution supplied in an individual packaged prefilled syringe with bromobutyl stopper, 27-gauge, ½-inch staked needle and rigid needle cap. Each carton contains one prefilled syringe.

- **single-use prefilled syringe (150 mg / 1 mL):**

TAKHZYRO is a ready-to-use solution supplied in an individual packaged prefilled syringe with bromobutyl stopper, 27-gauge, ½-inch staked needle and rigid needle cap. Each carton contains one prefilled syringe.

- **single-use prefilled pen (300 mg / 2 mL):**

TAKHZYRO is a ready-to-use solution supplied in an individual packaged prefilled pen with bromobutyl stopper, 27-gauge, ½-inch staked needle and rigid needle cap. Each carton contains one prefilled pen.

- **single-use vial (300 mg / 2 mL):**

TAKHZYRO is a ready-to-use solution supplied in an individual packaged glass vial with chlorobutyl rubber stopper, aluminum crimp seal and polypropylene flip-off cap. Each vial contains a slight overfill. Each carton contains one vial.

Note: Not all presentations may be marketed.

7. Warnings and Precautions

General

TAKHZYRO (lanadelumab injection) 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.

Driving and Operating Machinery

Patients should be advised not to drive or operate machinery if they feel dizzy after use.

Reproductive Health

- Fertility

There have been no studies of the effects of TAKHZYRO on human fertility.

Sensitivity/Resistance

Hypersensitivity reactions have been observed with TAKHZYRO. In case of a severe hypersensitivity reaction, discontinue TAKHZYRO administration and institute appropriate treatment.

7.1. Special Populations

7.1.1. Pregnancy

TAKHZYRO has not been studied in pregnant women.

In an enhanced pre- and post-natal developmental study conducted in pregnant cynomolgus monkeys, no lanadelumab-related adverse effects on pre- and post-natal development were observed. Lanadelumab was present at measurable levels in infant plasma, indicating that lanadelumab crossed the placental barrier (see 16. Non-Clinical Toxicology).

Animal studies are not always predictive of human response; therefore, it is unknown whether TAKHZYRO can cause fetal harm when administered to a pregnant woman.

7.1.2. Breastfeeding

TAKHZYRO has not been studied in lactating women.

It is unknown if lanadelumab is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

Available pharmacokinetic data from the enhanced pre- and post-natal developmental study conducted in cynomolgus monkeys demonstrated low excretion of lanadelumab in milk at approximately 0.2% of the maternal plasma level (see 16. Non-Clinical Toxicology).

7.1.3. Pediatrics

Pediatrics (<2 years): The safety and efficacy of TAKHZYRO in pediatric patients <2 years of age and weighing <10 kg have not been studied; therefore, Health Canada has not authorized an indication.

Pediatrics (≥2 years of age): Warnings applicable to adults are also relevant to pediatric use.

7.1.4. Geriatrics

Geriatrics (≥65 years of age): The safety and efficacy of TAKHZYRO were evaluated in subjects 65 years of age and older (n=11). Results of the subgroup analysis by age were consistent with overall study results.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Adult and Pediatric Patients 12 Years of Age and Older

Two hundred and fifty seven (257) unique subjects (233 patients with HAE and 24 healthy participants) were exposed to at least one dose of lanadelumab in two (2) Phase 1 and two (2) Phase 3 clinical trials (the HELP study [DX-2930-03] and the HELP study extension [DX-2930-04]).

Of the patients treated with lanadelumab in Phase 3 trials (excluding the waiting period in the HELP study extension), 58.6% experienced at least 1 acute HAE attack (see 14. Clinical Trials). Most patients (89.1%) treated with lanadelumab also experienced adverse events other than HAE attacks (see 8.2. Clinical Trial Adverse Reactions).

The most commonly observed adverse reactions associated with lanadelumab in patients with HAE were injection site reactions (ISR), including injection site pain (39.5%), injection site erythema (13.2%) and injection site bruising (7.7%). Most were of mild intensity and resolved within 1 day after onset. Hypersensitivity reactions have been observed in clinical trials with lanadelumab.

In Phase 3 clinical trials with exposure up to 19.6 months, 2.7% of subjects discontinued due to an adverse event other than a HAE attack, 12.3% who had severe adverse events, and 5.0% who had serious adverse events.

Pediatric Patients 2 to <12 Years of Age

The safety of lanadelumab was evaluated at 150 mg (150 mg q4wks for patients 2 to <6 years or 150 mg q2wks for patients 6 to <12 years, with the option for 150 mg q4wks if the patient was well-controlled for 6 months) in an open-label, multicentre study with 21 patients aged 2 to <12 years (SPRING Study). No new safety signals were observed in these patients.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Table 3 summarizes the adverse reactions occurring in >1% of patients observed in the double-blind placebo-controlled HELP study that included 84 subjects with HAE who received at least one dose of lanadelumab. In the HELP study, 70.4% of patients were female; 90.4% were white; 8.0% were black; the mean age was 40.7 years (range 12 to 73 years, n=10 patients <18 years); and the mean weight was 80.2 kg. Overall, 90.4% of patients had HAE Type I and 9.6% had Type II. The mean HAE attack rate at baseline was 3.7 attacks/month.

Table 3. Adverse Drug Reactions (ADRs) Observed in the Pivotal Clinical Trial (the HELP study; DX-2930-03) occurring in >1% of patients

System Organ Class / Preferred Term	Placebo	lanadelumab			
	(N=41)	150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)	Total (N=84)
	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions					
Injection site reactions[a]	14 (34)	16 (57)	13 (45)	15 (56)	44(52)
Immune system disorder					
Hypersensitivity[b]	0	0	0	1(4)	1(1)
Investigations					
Alanine aminotransferase increased	0	0	1(3)	1(4)	2(2)
Aspartate aminotransferase increased	0	0	1(3)	1(4)	2(2)
Musculoskeletal and connective tissue disorders					
Myalgia	0	1(4)	0	3(11)	4(5)
Nervous system disorders					
Dizziness	0	1(4)	3(10)	1(4)	5(6)
Skin and subcutaneous tissue disorder					
Rash maculo-papular	0	1(4)	0	1(4)	2(2)

N= Number of subjects, n = Number of subjects experiencing the event. Percentages are based on all subjects in the safety population. Percentages are rounded to the nearest integer.

q4wks: every 4 weeks, q2wks: every 2 weeks

SOC is presented in MedDRA International Order and MedDRA 20.0 version is used for ADRs.

[a]Injection site reactions include: pain, erythema, bruising, discomfort, hematoma, hemorrhage, pruritus, swelling, induration, paresthesia, reaction, warmth, edema and rash.

[b]Hypersensitivity includes: pruritus, discomfort and tingling of tongue.

In the HELP study, 1.2% of lanadelumab-treated patients and 2.4% of placebo-treated patients discontinued due to an adverse event other than a HAE attack. Severe and serious adverse events were reported in 9.5% and 4.8% of lanadelumab-treated patients and 9.8% and 0% of placebo-treated patients, respectively.

Safety data from all adult and adolescent patients treated with lanadelumab in Phase 3 trials (double-blind and open label) for up to 19.6 months (mean 10.35 months) were consistent with data in Table 3, but data on long-term use (>12 months) are limited.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Adolescents (12–17 years of age): The safety of lanadelumab in the subgroup of adolescent patients (n=23 in double-blind and open-label Phase 3 trials) was similar to the overall safety profile in Table ***3***.Approximately 85% of adolescent patients experienced non-HAE attack adverse events and approximately half of patients had treatment-related adverse reactions, mainly ISRs. No adolescent patient discontinued study treatment due to adverse events.

Pediatrics (2-<12 years of age): The safety of lanadelumab was evaluated at 150 mg/mL (150 mg q4wks for patients 2 to <6 years [N=4] or 150 mg q2wks for patients 6 to <12 years [N=17]) in the open-label, multicentre, 52-week SPRING study (in two 26-week periods; Treatment Periods A and B) that enrolled 21 patients with Type I or Type II HAE aged 2 to less than 12 years. The youngest patient included in the study was 3.5 years old. Well-controlled (attack-free) patients receiving 150 mg q2wks (6 to <12 years) had the option to reduce the dose to 150 mg q4wks in Treatment Period B (after 26 weeks). Seven patients switched to 150 mg q4wks during Treatment Period B, and one patient (enrolled in the 2 to <6 years age group) turned 6 years of age during Treatment Period A and switched to 150 mg q2wks during Treatment Period B after experiencing recurrent attacks.

The total exposure during the overall treatment period (including patients who switched dosing regimens) was 5.55 patient-years in the q4wks dosing regimen group and 14.47 patient-years in the q2wks dosing regimen group.

The only adverse reactions related to lanadelumab were injection site reactions, and consisted of injection site pain (28.6%), injection site erythema (14.3 %), injection site swelling (4.8%), administration site pain (4.8%), and injection site reaction (4.8%). The majority of injection site reactions were mild and resolved within 30 minutes of administration. One patient experienced multiple events of injection site erythema greater than 50 mm that resolved within 1 hour.

No patient discontinued treatment due to adverse events.

No new safety signals were observed in these patients. Safety and tolerability results for pediatric patients (2 to <12) were consistent with overall study results for all participants. Data are very limited in patients 2 to <6 years of age.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

One adult patient in the 300 mg q4wks group of the HELP study discontinued from the trial due to concurrent asymptomatic, transient, severe ADRs of elevated AST (4.1 x ULN) and ALT (3.5 x ULN).

8.5. Post-Market Adverse Reactions

The following ADR has been observed in postmarketing experience for which the frequency is unknown:

General disorders and administration site conditions: Injection site urticaria

9. Drug Interactions

9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

Based on population pharmacokinetic analysis, the use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications did not appear to affect the clearance and volume of distribution of TAKHZYRO.

For breakthrough HAE attacks, use of rescue medications such as C1-esterase inhibitor, icatibant or ecallantide did not appear to affect the clearance and volume of distribution of TAKHZYRO.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Prolongation of activated partial thromboplastin time (aPTT) is an indirect effect of plasma kallikrein inhibition and is a laboratory test phenomenon that has not been associated with impaired *in vivo* hemostasis. In clinical trials with lanadelumab in adult patients, there was an increase in aPTT values as compared to placebo. The majority of values for treated patients remained within the normal range. One patient experienced transient aPTT prolongation ≥1.5 x ULN while on concomitant heparin therapy. Increases in aPTT were not associated with abnormal bleeding events.

10. Clinical Pharmacology

10.1. Mechanism of Action

Lanadelumab is a fully human monoclonal antibody (IgG1 / κ-light chain) that binds plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in the swelling and pain associated with HAE. In patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction, uncontrolled increase in plasma kallikrein activity results in angioedema attacks. Lanadelumab decreases plasma kallikrein activity to control bradykinin generation in patients with HAE.

10.2. Pharmacodynamics

In adult and pediatric (12 to <18 years) patients, concentration-dependent inhibition of plasma kallikrein, measured as reduction of cHMWK levels, was demonstrated after subcutaneous administration of lanadelumab 150 mg q4wks, 300 mg q4wks or 300 mg q2wks in subjects with HAE.

For pediatric patients 2 to less than 6 years (150 mg q4wks) and 6 to less than 12 years (150 mg q2wks), the observed mean percent change from baseline cHMWK levels was similar to that observed in adult and pediatric (12 to less than 18 years) patients (300 mg q2wks or 300 mg q4wks).

Cardiac Electrophysiology

Lanadelumab did not prolong the QT/QTc interval.

10.3. Pharmacokinetics

Population Pharmacokinetic Analysis

The information contained in 10.3 Pharmacokinetics is derived from population pharmacokinetic analysis.

The pharmacokinetics of lanadelumab was approximately dose proportional in the dose range of 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks. The anticipated time to reach steady state concentration was approximately 70 days in HAE patients. The pharmacokinetic properties and steady-state exposure of lanadelumab in patients with HAE, following subcutaneous administration of 150 mg q4wks, 300 mg q4wks and 300 mg q2wks (pivotal HELP study), are provided in Table 4.

Table 4. Summary of lanadelumab Pharmacokinetic Parameters in Adult Patients with HAE

Pharmacokinetic Parameters Mean (SD)	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.

Absorption

Following subcutaneous administration of lanadelumab, the time to maximum concentration is approximately 5 days with an absorption rate of 0.0208/h. The site of subcutaneous injection (thigh, arm, or abdomen) did not affect the absorption of lanadelumab.

Distribution

The mean (SD) apparent volume of distribution of lanadelumab in patients with HAE is 14.5 (4.53) L.

Metabolism

Similar to other monoclonal antibodies, lanadelumab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids.

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 and Conditions

Based on population pharmacokinetic analysis, age, gender, and race did not appear to affect the pharmacokinetics of lanadelumab after correcting for body weight. Body weight was identified as an important covariate describing the variability of clearance and volume of distribution; however, dose adjustment according to body weight is not required for adult and adolescent (≥12 years of age) patients based on consistent efficacy and safety profiles across this study population. Dose adjustment maybe considered for pediatric (2 to <12 years of age) patients (see 4.2. Recommended Dose and Dosage Adjustment).

Table 5. Summary of Lanadelumab Pharmacokinetic Parameters in Pediatrics (2 to <12 years of age) and Adolescents (12 to 17 years of age)

Age group (dose)	Pharmacokinetic Parameters (Steady State) Mean (SD)						
	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	t_{max} (day)	$t_{1/2}$ (day)	$AUC_{tau,ss}$ (µg*day/mL)	CL/F (L/day)	Vc/F (L)
2 to <12 years of age							
• 10 to <20 kg (150 mg q4wk)	47.2 (17.2)	9.79 (4.56)	4.19 (1.32)	9.63 (2.17)	748 (249)	0.222 (0.0711)	3.01 (0.973)
• ≥20 kg (150 mg q2wk)	40.3 (14.7)	23.7 (8.63)	3.42 (0.842)	11.7 (2.64)	463 (162)	0.365 (0.131)	6.10 (2.53)
12 to 17 years of age							
• 12 to 17 years of age (300 mg q2wk)	46.6 (14.8)	31.5 (10.4)	3.82 (0.315)	14.6 (1.90)	567 (182)	0.588 (0.208)	11.8 (4.79)

- **Pediatrics:** Following subcutaneous administration of 150 mg q4wks (10 to <20 kg) and 150 mg q2wks (20 to <40 kg), the model-predicted overall exposure (i.e., Cavg,ss) to lanadelumab was similar compared with adult patients who received lanadelumab 300 mg q2wks (ratios relative to adults were 0.76 and 0.96 for subjects aged 2 to <12 years weighing 10 to <20 kg and 20 to <40 kg, respectively).
- **Adolescents:** Based on population pharmacokinetic analysis, the mean AUCtau,ss in adolescents (12-17 years of age) was approximately 37% higher relative to the AUCtau,ss in adults following the 300 mg q2wks dose regimen, likely due to lower body weight of the adolescent subjects. Dose adjustment is not required based on consistent efficacy and safety observed between adults and adolescents. (See 8.2.1. Clinical Trial Adverse Reactions – Pediatrics and 14. Clinical Trials.)

- **Hepatic Insufficiency:** No dedicated studies have been conducted to evaluate the pharmacokinetics of lanadelumab in patients with hepatic impairment.
- **Renal Insufficiency:** No dedicated studies have been conducted to evaluate the pharmacokinetics of lanadelumab in patients with renal impairment. Based on population pharmacokinetic analysis, mild (estimated GFR 60-89 mL/min/1.73m^2) and moderate (estimated GFR 30-59 mL/min/1.73m^2) renal impairment did not appear to affect the clearance and volume of distribution of lanadelumab.

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

In the HELP study, 10 (12%) lanadelumab-treated and 2 (5%) placebo-treated adult subjects had at least 1 anti-drug antibody (ADA)-positive sample during the 26-week treatment period. Two subjects receiving 150 mg q4wks had antibodies classified as neutralizing.

In the open-label SPRING study, conducted in pediatric patients 2 to less than 12 years of age, 3/20 (15%) lanadelumab-treated patients developed ADAs during the 52-week treatment period, all of whom were in the 6 to ≤12 years age group. None of these patients had pre-existing antibodies, and the ADA response was transient in all 3 patients. One patient had neutralizing antibodies.

The development of ADA, including neutralizing antibodies, against lanadelumab did not appear to adversely affect the pharmacokinetic (PK), pharmacodynamics (PD), safety or clinical response in any patient. Definitive conclusions of the impact of ADAs, including neutralizing antibodies, against lanadelumab, on the pharmacokinetics, safety, and efficacy of in pediatric patients (2 to <12 years) is limited by the small number of pediatric patients evaluated.

11. Storage, Stability and Disposal

Temperature:

Store TAKHZYRO (lanadelumab injection) under refrigeration (2°C to 8°C). Do not freeze.

Prefilled syringes or prefilled pens removed from refrigeration should be stored below 25°C and used within 14 days. Do not return prefilled syringes or prefilled pens to refrigerated storage after storage at room temperature.

Vials removed from refrigeration should be stored below 25°C and used within 14 days. After storage at room temperature, unopened vials may be returned to the refrigerator. Cumulative storage time at room temperature should not exceed 14 days.

Light:

Keep the prefilled syringe, prefilled pen or vial in the original carton to protect TAKHZYRO from light.

Other:

Do not shake.

Keep out of reach and sight of children under 12 years of age.

Disposal:

Dispose of used prefilled syringes, pre-filled pens and used vials with the needle still inside in a sharps disposal container in accordance with local requirements. Discard unused portions of drug remaining in the syringe or vial.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug product(s): lanadelumab

Chemical name**:** lanadelumab (USAN, INN)

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

Structure: Amino acid sequences of the light and heavy chains are shown below. Amino acid sequences (one letter code) were based on the translation of the confirmed DNA sequence in the expression vector. The underlined residue in the heavy chain sequence is a predicted site of N- glycosylation.

Light Chain:

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASTLESGVPSRFSGSGSGTEFTLTISSLQPD
DFATYYCQQYNTYWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYIMMWVRQAPGKGLEWVSGIYSSGGITVYADSVKGRFTISRDNSKNT
LYLQMNSLRAEDTAVYYCAYRRIGVPRRDEFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

Physicochemical properties: a colourless to slightly yellow solution, appearing either clear or slightly opalescent. The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg

Product Characteristics: lanadelumab is a non-plasma derived, recombinant, fully human, monoclonal antibody (IgG1/ κ-light chain) produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology.

14. Clinical Trials

14.1. Clinical Trials by Indication

Prevention of Attacks of Hereditary Angioedema (HAE)

Table 6. Summary of Patient Demographics for Clinical Studies in the Prevention of Attacks of Hereditary Angioedema

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median Age (Range)	Sex
HELP Study (DX-2930-03) Phase 3	Multi-centre Randomized, double-blind, placebo-controlled	lanadelumab 300 mg SC q2wks, 300 mg SC q4wks 150 mg SC q4wks or placebo SC 26 week treatment period	300 mg SC q2wks (27) 300 mg SC q4wks (29) 150 mg SC q4wks (28) or placebo SC (41) N= 125 HAE Type I or II patients	42.4 years (12 – 73)	F = 88 (70.4%) M = 37 (29.6%)
HELP Study Extension (DX-2930-04) Phase 3	Multi-centre, open-label extension	lanadelumab 300 mg SC q2wks 132 week treatment period	Rollover[a]:109 Nonrollover[b]: 103 N = 212 HAE Type I or II patients	42.8 years (12 - 76)	F=143 (67.5%) M=69 (32.5%)
SPRING Study (SHP643-301) Phase 3	Multi-centre, open label	lanadelumab 150 mg SC q4wks 150 mg SC q2wks Treatment period A (26 week) Overall treatment period (52 week)	Treatment period A 150 mg SC q4wks (4) 150 mg SC q2wks (17) Overall treatment period 150 mg SC q4wks $(11)_c$ 150 mg SC q2wks (18)[c] N= 21 HAE Type I or II patients	8.7 years (3.5 – 10.9)	F = 12 (57.1%) M = 9 (42.9%)

[a]Rollover subjects (subjects who participated in DX-2930-03) received their first open-label dose on Day 0 with their second dose administered after their first HAE attack. Subsequent doses for rollover subjects were administered every 2 weeks.

[b]Nonrollover subjects (subjects who did not participate in DX-2930-03) received lanadelumab every 2 weeks.

[c]Seven patients received a dose reduction from q 2wks to q 4wks after attack-free for more than 26 weeks. One patient received a dose modification from q4wks to q2wks due to recurrent attacks. These patients were counted in both regimens.

The efficacy and safety of TAKHZYRO in preventing acute HAE attacks in adults/adolescents (≥12 years) and pediatrics (2 to <12 years) with Type I or Type II HAE were evaluated in the HELP Study (DX-2930-

03) and the SPRING study (SHP643-301), respectively. The HELP study was followed by an open-label, uncontrolled extension study (HELP Study Extension; DX-2930-04).

HAE in Adults and Adolescents (≥12 years)

The pivotal HELP study was a multi-centre, randomized, double-blind, placebo-controlled, parallel-arm study that included adult (n=115, 92.0%) and adolescent (n=10, 8.0%) subjects with Type I or Type II HAE who experienced at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period. Subjects who 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 q4wks, lanadelumab 300 mg q4wks, or lanadelumab 300 mg q2wks each by subcutaneous injection) for the 26-week treatment period. Randomization was stratified by baseline attack rate observed during the run-in period into the following groups: 1 to <2 attacks per 4 weeks, 2 to <3 attacks per 4 weeks, and ≥3 attacks per 4 weeks. Patients were required to discontinue other long-term prophylactic HAE treatments prior to the study run-in period. The use of rescue medications for treatment of acute HAE attacks, including C1 esterase inhibitors, was allowed during the study.

During the study, subjects (or caregivers in the circumstance that a subject was <18 years of age) were instructed to notify and report details of an attack to the study site within 72 hours of the onset of an HAE attack. Subjects were asked to provide specific details characterizing the attack, including severity and whether the attack required acute treatment.

The primary efficacy endpoint was the number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182). Key secondary endpoints included the number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182), and the number of moderate to severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182).

Overall, 90.4% of patients had Type I HAE. A history of laryngeal angioedema attacks was reported in 64.8% (81/125) of subjects and 56.0% (70/125) were on prior long term prophylaxis (LTP). During the study run-in period, attack rates of ≥3 attacks/month were observed in 52.0% (65/125) of subjects.

All TAKHZYRO treatment arms reported statistically significant reductions in the mean HAE attack rate compared to placebo across the primary and key secondary endpoints in the Intent-to-Treat population (ITT) (Table 7).

Table 7. Results of Primary and Key Secondary Efficacy Endpoints in Subjects with HAE in the HELP Study – ITT Population

Endpoint Statistic	Placebo (N=41)	TAKHZYRO		
		150 mg 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]		75.6 (61.2,84.6)	73.3 (59.5, 82.4)	86.9 (76.2, 92.8)
p-value[d]		<0.001	<0.001	<0.001

Endpoint Statistic	Placebo (N=41)	TAKHZYRO		
		150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)
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]		80.8 (66.1, 89.2)	74.2 (59.0, 83.7)	87.3 (75.2, 93.5)
p-value[d]		<0.001	<0.001	<0.001
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]		70.5 (49.7, 82.7)	73.3 (54.5, 84.3)	83.4 (67.1, 91.6)
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 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.

[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 utilized to control the global family-wise type I error rate at 0.05. Within a family, hypotheses were tested at $\alpha/3$ or 0.0167 significance level.

Additional pre-defined exploratory endpoints included the proportion of subjects who achieved a pre-specified reduction from the run-in period in the investigator-confirmed HAE attack rate (i.e., responder analyses). The percentage of responders with a ≥50% reduction in HAE attack rates over the 26 week treatment period was 100% of patients on 300 mg q2wks or q4wks compared to 31.7% of placebo patients. The percentage of responders with a 100% reduction in HAE attack rate (i.e. attack-free) over the 26 week treatment period was 44.4% of patients on 300 mg q2wks and 31.0% of patients on 300 mg q4wks compared to 2.4% of placebo subjects.

The proportion of subjects who achieved an improvement in quality of life as measured by the angioedema quality of life (AE-QoL) questionnaire (minimally important clinical difference (MCID) ≥6 in the AE-QoL total score) was 80.8% and 63.0% for TAKHZYRO 300 mg q2wks and 300 mg q4wks, and 36.8% for the placebo arm.

Long Term Extension Study (DX-2930-04)

The HELP Study Extension was an open-label uncontrolled study to evaluate the long-term safety and efficacy of TAKHZYRO for the prevention of HAE attacks.

A total of 212 adult and adolescent (≥12 years) subjects received at least one dose of 300 mg q2wks TAKHZYRO in the HELP Study Extension, including 109 subjects who entered as rollover subjects from the HELP Study. Rollover subjects, regardless of randomization group in the HELP Study, received a single dose of TAKHZYRO 300 mg at study entry and did not receive additional treatment until the occurrence of an HAE attack. After the first HAE attack, all subjects received open-label treatment with TAKHZYRO 300 mg q2wks. The majority of subjects self-administered TAKHZYRO over 10 to 60 seconds (64.4% of 929 injections).

At week 4 post-dose, 80.0% of subjects who had been in the 300 mg q2wks treatment group (n=25) in the HELP Study remained attack-free. These exploratory results should be interpreted with caution as they reflect a select cohort that completed 26-weeks of exposure to lanadelumab (HELP Study) and selectively enrolled in the open-label extension study.

HAE in Pediatric Patients (2 to <12 years of age)

The safety and efficacy of TAKHZYRO for the prevention of HAE attacks in children 2 to <12 years of age were evaluated in the pivotal, open-label, multicentre, phase 3 SPRING study.

The study enrolled 21 pediatric subjects with a confirmed diagnosis of HAE Type I or Type II and who had a baseline attack rate of ≥1 attacks per 12 weeks. The overall treatment period was 52 weeks, equally divided into Treatment Periods A and B.

In Treatment Period A, subjects aged 2 to <6 years (n=4) and 6 to <12 years (n=17) received lanadelumab 150 mg q4wks and 150 mg q2wks, respectively. One participant in the 150 mg q4wks group withdrew from the study prematurely due to withdrawal by the parent/guardian. In Treatment Period B, subjects in the 2 to <6 years age group continued the dosing regimen, while subjects in the 6 to <12 years age group were permitted to switch to 150 mg q4wks if they were well-controlled (e.g., attack-free) for the previous 26 weeks with lanadelumab treatment.

The median age (min, max) of the study population was 8.7 years (3.5, 10.9); 57.1% were female; 95.2% were white; 95.2% had a diagnosis of HAE Type I; the median age at HAE onset (min, max) was 2.0 years (0, 9); 23.8% had a history of laryngeal attacks; and 23.8% had previously used LTP therapy (C1-INH).

Efficacy results for the SPRING study at the end of Treatment Period A (26 weeks of treatment) are summarized in Table 8.

Table 8. HAE Attack Rate Reduction in Pediatric Subjects (2 to <12 years) with HAE in the SPRING Study (descriptive statistics)*

Criteria	Lanadelumab		
	150 mg q4wks[a] (2 to <6 years)	150 mg q2wks[a] (6 to <12 years)	Total
Treatment Period A (26 weeks)			
n	4	17	21
Baseline attack rate (attacks/month[b]), mean (SD)	1.9 (1.0)	1.8 (1.6)	1.8 (1.5)
On-treatment attack rate (attacks/month[b]), mean (SD)	0.2 (0.3)	0.1 (0.2)	0.1 (0.2)
Attack-free subjects, n (%)	3 (75.0)	14 (82.4)	17 (81.0)

*Data derived from the safety set.

[a] The actual treatment received during the given study period.

[b] Month is defined as 28 days. Attack rates (confirmed by the Investigator) at baseline and on-treatment were calculated over the 4-12 week observation period and the 26-week Treatment Period A, respectively.

Seven subjects aged 6 to <12 years switched to 150 mg q4wks during Treatment Period B, and one subject (enrolled in the 2 to < 6 years age group) turned 6 years of age and switched to 150 mg q2wks during Treatment B after experiencing recurrent attacks.

Similar results were observed for the overall 52-week treatment period.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology

In a 6-month repeat-dose toxicity study evaluating once weekly subcutaneous injection in cynomolgus monkeys, lanadelumab was well-tolerated at doses of up to and including 50 mg/kg (highest dose tested) with no organs of toxicity identified. At the no-observed-adverse-effect level (NOAEL) of 50 mg/kg, exposures were approximately 15- and 20-fold greater than human adolescent and adult simulated exposures (AUC) noted at 300 mg q2wks, respectively.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of lanadelumab.

Carcinogenicity

Animal studies have not been performed to evaluate the carcinogenic potential of lanadelumab.

Reproductive and Developmental Toxicology

The effects of lanadelumab on fertility were evaluated in a 13-week study conducted in sexually mature cynomolgus monkeys. Once weekly subcutaneous administration of lanadelumab had no adverse effects on male or female fertility-related endpoints at doses of 10 and 50 mg/kg (highest dose tested). Lanadelumab did not affect semen sample weight, total sperm count, sperm density, percent sperm motility, sperm morphology, testicular measurements, or menstrual cycle length. There were also no

lanadelumab-related adverse effects on reproductive organs, including no adverse histopathological findings. At the NOAEL of 50 mg/kg, exposures were approximately 19-fold greater than human adult simulated exposures (AUC) noted at 300 mg q2wks, respectively.

The developmental effects of lanadelumab were evaluated in an ePPND toxicity study in which pregnant cynomolgus monkeys were subcutaneously administered lanadelumab at doses of 10 or 50 mg/kg (highest dose tested), beginning on gestation day 20 and once weekly thereafter until parturition. There were no lanadelumab-related effects on pregnancy, parturition, embryo-fetal development, survival, growth, or postnatal development of offspring up to 3 months of age. At the NOAEL of 50 mg/kg exposures were approximately 29-fold greater than human adult simulated exposures (AUC) noted at 300 mg q2wks, respectively. Lanadelumab was detected in infant plasma, indicating that lanadelumab crossed the placental barrier; lanadelumab concentrations in infant plasma were approximately 50% of those in maternal plasma on post-natal days 7 and 21 and approximately equivalent to those in maternal plasma on post-natal day 90. Low levels of lanadelumab were also detected in milk at concentrations approximately 0.2% of the maternal plasma level.

Juvenile Toxicity

No juvenile toxicity studies have been conducted with lanadelumab.

Patient Medication Information (2 mL Prefilled Syringe)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

(tak-ZYE-roe)

Pr**TAKHZYRO®**

lanadelumab injection

Single-use 2 mL prefilled syringe

This Patient Medication Information is written for the person who will be taking **TAKHZYRO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TAKHZYRO**, talk to a healthcare professional.

What TAKHZYRO is used for:

- to prevent attacks of hereditary angioedema (HAE) in adults and children (12 years and older).

TAKHZYRO should not be used to treat an acute HAE attack. In the event of an acute attack, seek medical attention.

How TAKHZYRO works:

In HAE, uncontrolled production of a substance called plasma kallikrein occurs. This leads in the release of too much bradykinin in your bloodstream. Too much bradykinin leads to symptoms like swelling and pain. TAKHZYRO is a type of protein that blocks the activity of plasma kallikrein. This helps to limit the production of bradykinin in your bloodstream and can prevent the swelling associated with HAE.

The ingredients in TAKHZYRO are:

Medicinal ingredient: lanadelumab

Non-medicinal ingredients: citric acid, L-histidine, polysorbate 80, sodium chloride, sodium phosphate, water for injection.

TAKHZYRO comes in the following dosage forms:

- Glass single-use prefilled syringe containing 300 mg/2 mL lanadelumab solution.
- Glass single-use prefilled syringe containing 150 mg/1 mL lanadelumab solution.
- Single-use prefilled pen containing 300 mg/2 mL lanadelumab solution.
- Glass single-use vials containing 300 mg/2 mL lanadelumab solution.

Note: Not all presentations may be marketed.

Do not use TAKHZYRO if:

- you are allergic to any ingredients in TAKHZYRO (see "**The ingredients in TAKHZYRO are**").
- you are pregnant or planning to become pregnant. It is not known if TAKHZYRO can harm your unborn baby.
- you are breastfeeding or plan to breastfeed. It is not known if TAKHZYRO passes into your milk and if it can harm your baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAKHZYRO. Talk about any health conditions or problems you may have, including if you:

- are pregnant or breastfeeding.

Other warnings you should know about:

Acute HAE attacks: TAKHZYRO should not be used to treat an acute HAE attack (when symptoms of HAE appear rapidly). Patients and their caregivers should be prepared to treat such attacks when needed.

Driving and using machines: Taking TAKHZYRO may cause you to feel dizzy after use. Do not drive or operate machinery if you have these symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TAKHZYRO:

Do not inject yourself or someone else until you have been trained by your healthcare professional.

Be sure that you read, understand, and follow the step-by-step instructions for injecting TAKHZYRO. A healthcare professional will show you how to prepare and inject TAKHZYRO properly before you inject yourself for the first time. Contact your healthcare professional if you have any questions.

- You should always follow the specific instructions given by your healthcare professional. The steps listed below are general guidelines for using TAKHZYRO. If you are unsure of the steps, contact your healthcare professional before using TAKHZYRO.

Preparation

- Collect all supplies listed below to prepare and give your injection.
- Inspect the supplies for damage. Do not use if they appear damaged.

TAKHZYRO is a ready-to-use solution for injection under the skin (subcutaneous injection). It is supplied in a single-use prefilled syringe at a dosage of 300 mg/2 mL solution.

Parts of your TAKHZYRO prefilled syringe before use (Figure A).

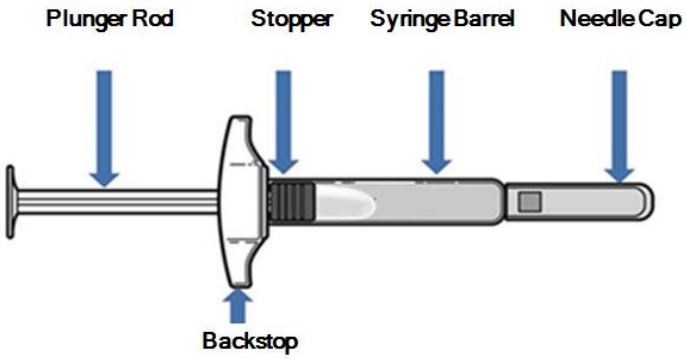


Figure A

Step 1: Prepare for your injection

a. Gather an alcohol swab, cotton ball/gauze pad, adhesive bandage, sharps disposal container (**Figure B**) and place on a clean, flat, surface in a well lit area. These supplies are not included in the TAKHZYRO packaging.

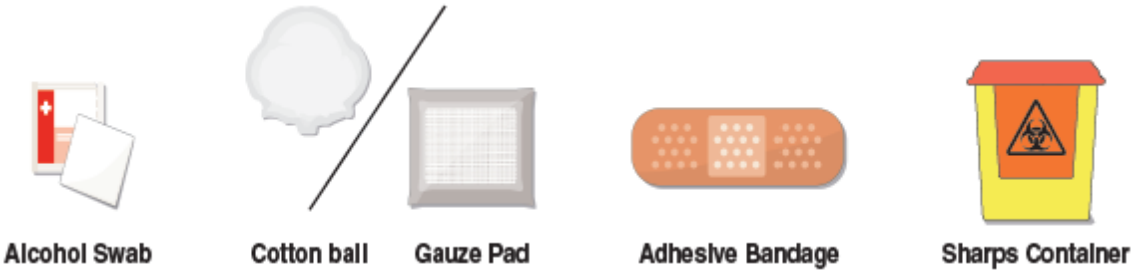


Figure B

b. Remove TAKHZYRO from refrigerator, open the carton box and remove the TAKHZYRO prefilled syringe from the tray.
   - **Before you prepare your injection, allow the prefilled syringe to come to room temperature for at least 15 minutes.**
   - Your medicine is sensitive to warm temperatures. **Do not** use external heat sources such as hot water to warm your TAKHZYRO prefilled syringe.
   - **Do not** remove the needle cap until you are ready to inject.

c. Wash your hands with soap and water. Dry your hands completely (**Figure C**).

Figure C

d. Check **the expiration date** on the label (**Figure D**).
   - **Do not** use the TAKHZYRO prefilled syringe if the expiration date has passed.

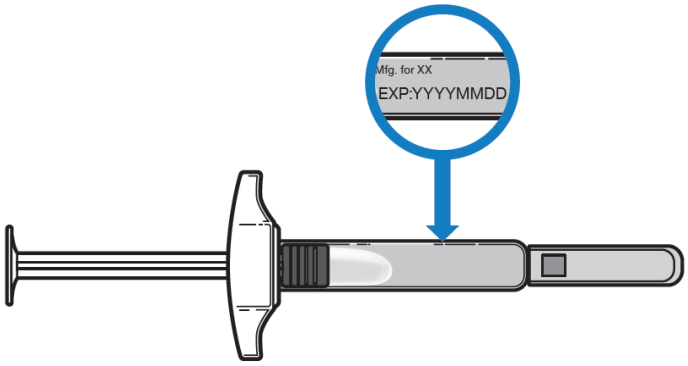


Figure D

e. Visually inspect the TAKHZYRO prefilled syringe for any damage and make sure the medicine is colourless to slightly yellow.
   - Do not use product if syringe is damaged – e.g., cracked syringe.
   - Do not administer if the medicine is discoloured, cloudy or has flakes or particles in it.
   - You might see air bubbles in the TAKHZYRO prefilled syringe. This is normal and will not affect your dose.

Step 2: Select and prepare injection site

a. TAKHZYRO should be injected into your stomach (abdomen) or thigh. If given by a caregiver, TAKHZYRO may also be injected in the upper arm. (**Figure E**).
   - It is important to rotate injection sites to keep skin healthy. Each new injection should be given at least 2 inches (5 cm) from the last site you used.
   - **Do not** inject into an area of your body where the skin is irritated, reddened, bruised, or infected.
   - The area you choose for injection should be at least 2 inches (5 cm) away from any scars or your belly button (navel).

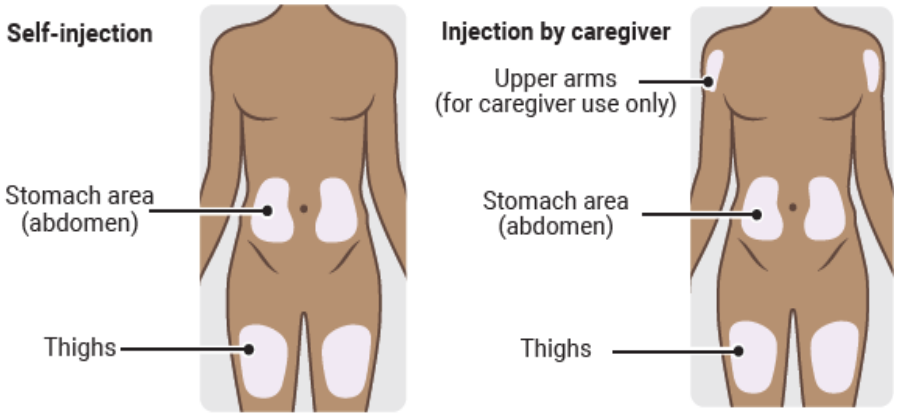


Figure E

b. Clean the injection site with an alcohol swab and allow it to dry.
   - **Do not** fan or blow on the clean site.

- **Do not** touch this area again before giving your injection.

c. Remove needle cap from the TAKHZYRO prefilled syringe. Gently pull the needle cap straight off with one hand and firmly hold the middle of the TAKHZYRO prefilled syringe with the other hand. Throw away the needle cap (**Figure F**).
   - **Do not** recap your TAKHZYRO prefilled syringe.
   - **Do not** use the TAKHZYRO prefilled syringe if it has been dropped without the needle cap on or if the needle looks damaged or bent.
   - **Do not** touch the needle or allow the needle to touch anything.

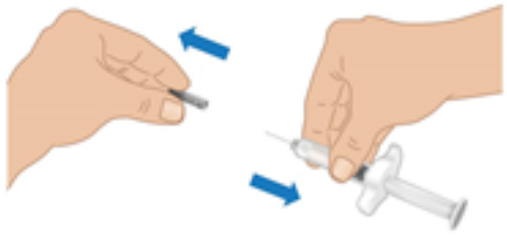


Figure F

Step 3: Inject TAKHZYRO

a. Grip the TAKHZYRO prefilled syringe in one hand like a pencil. Avoid touching the needle or pushing on the plunger (**Figure G**).

Figure G

b. With your other hand, gently pinch a 1-inch (2.5 cm) fold of skin at the cleaned injection site.
c. Using a quick dart-like motion, insert the needle. Make sure to keep the needle in place (**Figure H**).

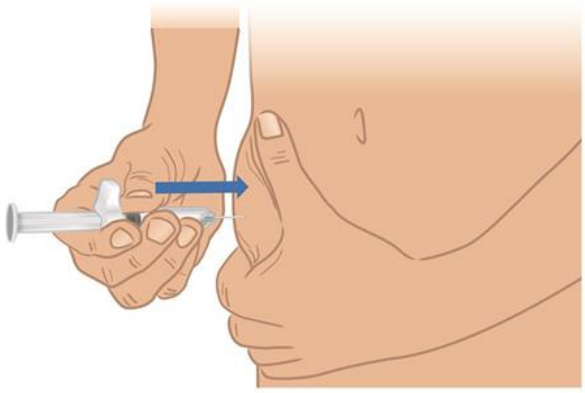


Figure H

d. **Slowly push** the plunger until all of the liquid is injected and the syringe is empty, then gently let go of your skin.
e. Slowly withdraw needle while maintaining the syringe at the same angle (**Figure I**).

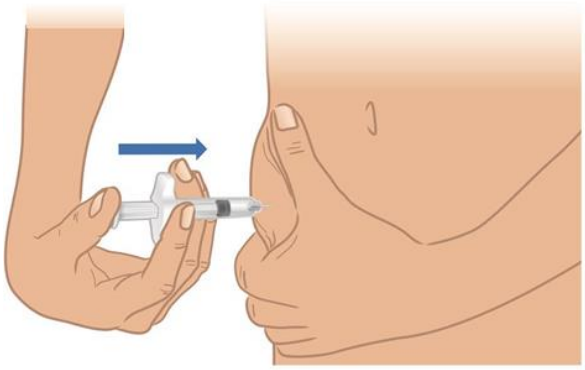


Figure I

f. Press cotton ball or gauze pad over injection site if needed and hold for 10 seconds.
   - **Do not** rub the injection site. You may have a minor bleeding. This is normal.
   - Cover injection site with an adhesive bandage if needed.
g. Put your used TAKHZYRO prefilled syringes in a sharps disposal container right away after use.
   - **Do not** touch the needle.
   - To avoid a needle-stick injury, **do not** recap the needle.
   - **Do not reuse** the TAKHZYRO prefilled syringe and any of your injection supplies.

There may be provincial, territorial, and local laws about the right way to throw away used syringes. Ask your healthcare professional how to throw away used syringes.

Usual dose:

Your healthcare professional will tell you how much TAKHZYRO to take and how often to take it.

TAKHZYRO is given as an injection under your skin (subcutaneous injection) by you or a caregiver.

If you have side effects or your condition is under control, your dose may be lowered or you may administer it less often.

Overdose:

If you think you, or a person you are caring for, have taken too much TAKHZYRO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose of TAKHZYRO, take your dose as soon as possible, making sure there are at least 10 days between doses. Do not administer a missed dose at the same time as your scheduled dose. If you are not sure when to administer TAKHZYRO after a missed dose, ask your healthcare professional.

Possible side effects from using TAKHZYRO:

These are not all the possible side effects you may have when taking TAKHZYRO. If you experience any side effects not listed here, tell your healthcare professional.

- pain, redness, itching, hives and bruising at the site of the injection
- raised skin rash
- skin redness
- muscle pain
- dizziness

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Hypersensitivity / allergic reactions after taking this medicine: sudden wheeziness, difficulty breathing, swelling of the eyelids, face or lips, rash or itching (affecting the whole body), tight feeling in your chest			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in a refrigerator (2° C to 8° C). Do not freeze. Do not shake.
- Prefilled syringes removed from refrigeration should be stored at room temperature (below 25° C) and used within 14 days. Do not return prefilled syringes to refrigerated storage after storage at room temperature.
- Keep prefilled syringes in the original carton to protect the medicine from light.
- Dispose of any unused medicine.
- Keep out of reach and sight of children under 12.

If you want more information about TAKHZYRO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.takeda.com/en-ca/science/our-medicines/, or by calling 1-800-268-2772.

This leaflet was prepared by:

Takeda Canada Inc.
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3

Date of Authorization 2026-03-02

Patient Medication Information (1 mL Prefilled Syringe)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

(tak-ZYE-roe)

Pr**TAKHZYRO®**

lanadelumab injection

Single-use 1 mL prefilled syringe

This Patient Medication Information is written for the person who will be taking **TAKHZYRO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TAKHZYRO**, talk to a healthcare professional.

What TAKHZYRO is used for:

- to prevent attacks of hereditary angioedema (HAE) in adults and children (2 years and older who weigh more than 10 kg).

TAKHZYRO should not be used to treat an acute HAE attack. In the event of an acute attack, seek medical attention.

How TAKHZYRO works:

In HAE, uncontrolled production of a substance called plasma kallikrein occurs. This leads in the release of too much bradykinin in your bloodstream. Too much bradykinin leads to symptoms like swelling and pain. TAKHZYRO is a type of protein that blocks the activity of plasma kallikrein. This helps to limit the production of bradykinin in your bloodstream and can prevent the swelling associated with HAE.

The ingredients in TAKHZYRO are:

Medicinal ingredient: lanadelumab

Non-medicinal ingredients: citric acid, L-histidine, polysorbate 80, sodium chloride, sodium phosphate, water for injection.

TAKHZYRO comes in the following dosage forms:

- Glass single-use prefilled syringe containing 300 mg/2 mL lanadelumab solution.
- Glass single-use prefilled syringe containing 150 mg/1 mL lanadelumab solution.
- Single-use prefilled pen containing 300 mg/2 mL lanadelumab solution.
- Glass single-use vials containing 300 mg/2 mL lanadelumab solution.

Note: Not all presentations may be marketed.

Do not use TAKHZYRO if:

- you are allergic to any ingredients in TAKHZYRO (see "**The ingredients in TAKHZYRO are**").
- you are pregnant or planning to become pregnant. It is not known if TAKHZYRO can harm your unborn baby.

- you are breastfeeding or plan to breastfeed. It is not known if TAKHZYRO passes into your milk and if it can harm your baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAKHZYRO. Talk about any health conditions or problems you may have, including if you:

- are pregnant or breastfeeding

Other warnings you should know about:

Acute HAE attacks: TAKHZYRO should not be used to treat an acute HAE attack (when symptoms of HAE appear rapidly). Patients and their caregivers should be prepared to treat such attacks when needed.

Driving and using machines: Taking TAKHZYRO may cause you to feel dizzy after use. Do not drive or operate machinery if you have these symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TAKHZYRO:

Do not inject yourself or someone else until you have been trained by your healthcare professional.

Be sure that you read, understand, and follow the step-by-step instructions for injecting TAKHZYRO. A healthcare professional will show you how to prepare and inject TAKHZYRO properly before you inject yourself for the first time. Contact your healthcare professional if you have any questions.

- You should always follow the specific instructions given by your healthcare professional. The steps listed below are general guidelines for using TAKHZYRO. If you are unsure of the steps, contact your healthcare professional before using TAKHZYRO.

Preparation

- Collect all supplies listed below to prepare and give your injection.
- Inspect the supplies for damage. Do not use if they appear damaged.

TAKHZYRO is a ready-to-use solution for injection under the skin (subcutaneous injection). It is supplied in a single-use prefilled syringe at a dosage of 150 mg/1 mL solution.

Parts of your TAKHZYRO prefilled syringe before use (Figure A).

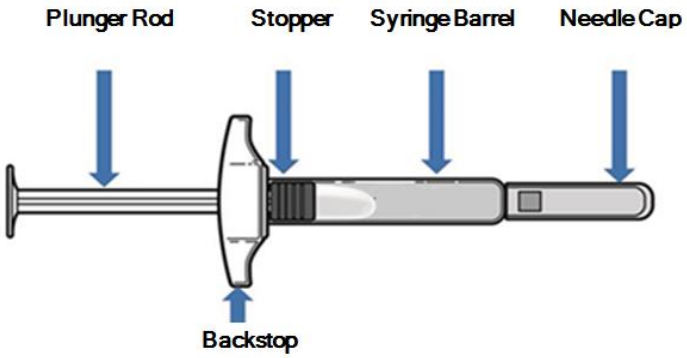


Figure A

Step 1: Prepare for your injection

a. Gather an alcohol swab, cotton ball/gauze pad, adhesive bandage, sharps disposal container (**Figure B**) and place on a clean, flat, surface in a well lit area. These supplies are not included in the TAKHZYRO packaging.

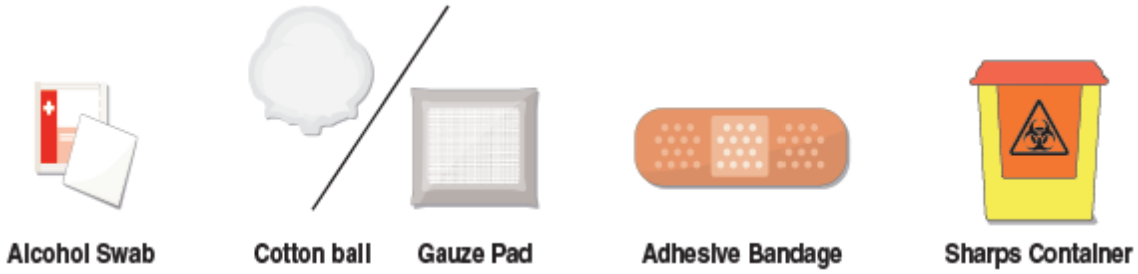


Figure B

b. Remove TAKHZYRO from refrigerator, open the carton box and remove the TAKHZYRO prefilled syringe from the tray.
   - **Before you prepare your injection, allow the prefilled syringe to come to room temperature for at least 15 minutes.**
   - Your medicine is sensitive to warm temperatures. **Do not** use external heat sources such as hot water to warm your TAKHZYRO prefilled syringe.
   - **Do not** remove the needle cap until you are ready to inject.

c. Wash your hands with soap and water. Dry your hands completely (**Figure C**).

Figure C

d. Check **the expiration date** on the label (**Figure D**).
   - **Do not** use the TAKHZYRO prefilled syringe if the expiration date has passed.

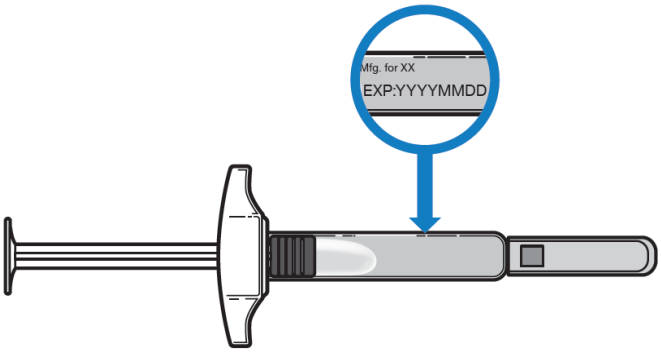


Figure D

e. Visually inspect the TAKHZYRO prefilled syringe for any damage and make sure the medicine is colourless to slightly yellow.
   - Do not use product if syringe is damaged – e.g., cracked syringe.
   - Do not administer if the medicine is discoloured, cloudy or has flakes or particles in it.
   - You might see air bubbles in the TAKHZYRO prefilled syringe. This is normal and will not affect your dose.

Step 2: Select and prepare injection site

a. TAKHZYRO should be injected into your stomach (abdomen) or thigh. If given by a caregiver, TAKHZYRO may also be injected in the upper arm. (**Figure E**).
   - It is important to rotate injection sites to keep skin healthy. Each new injection should be given at least 2 inches (5 cm) from the last site you used.
   - **Do not** inject into an area of your body where the skin is irritated, reddened, bruised, or infected.
   - The area you choose for injection should be at least 2 inches (5 cm) away from any scars or your belly button (navel).

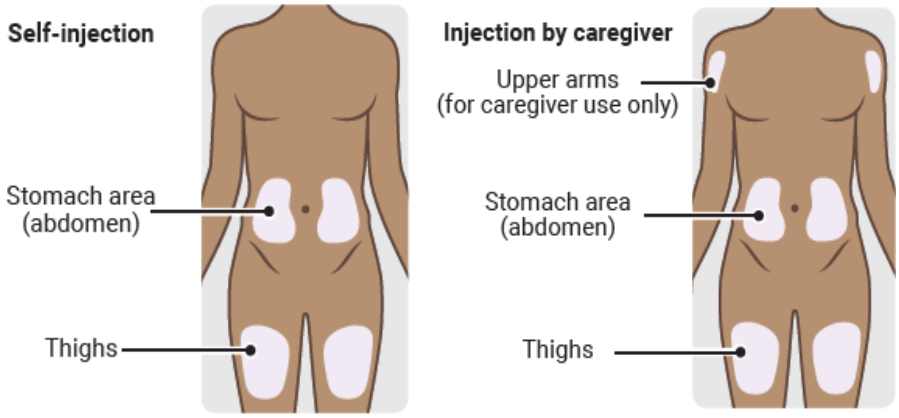


Figure E

b. Clean the injection site with an alcohol swab and allow it to dry.
   - **Do not** fan or blow on the clean site.
   - **Do not** touch this area again before giving your injection.

c. Remove needle cap from the TAKHZYRO prefilled syringe. Gently pull the needle cap straight off with one hand and firmly hold the middle of the TAKHZYRO prefilled syringe with the other hand. Throw away the needle cap (**Figure F**).
   - **Do not** recap your TAKHZYRO prefilled syringe.
   - **Do not** use the TAKHZYRO prefilled syringe if it has been dropped without the needle cap on or if the needle looks damaged or bent.
   - **Do not** touch the needle or allow the needle to touch anything.

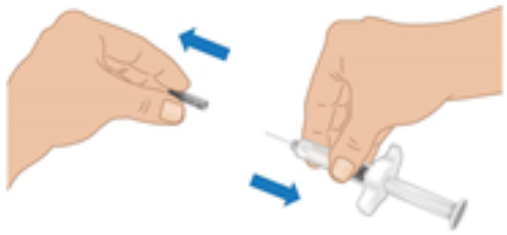


Figure F

Step 3: Inject TAKHZYRO

a. Grip the TAKHZYRO prefilled syringe in one hand like a pencil. Avoid touching the needle or pushing on the plunger (**Figure G**).

Figure G

b. With your other hand, gently pinch a 1-inch (2.5 cm) fold of skin at the cleaned injection site.
c. Using a quick dart-like motion, insert the needle. Make sure to keep the needle in place (**Figure H**).

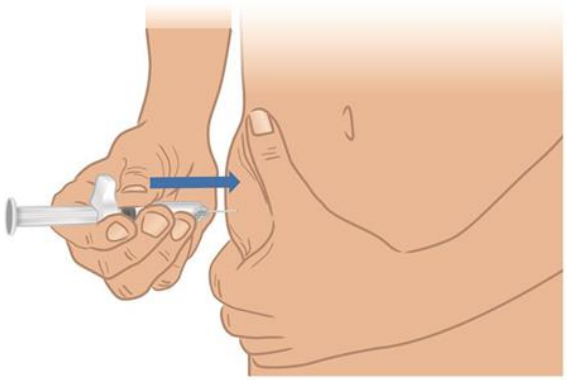


Figure H

d. **Slowly push** the plunger until all of the liquid is injected and the syringe is empty, then gently let go of your skin.
e. Slowly withdraw needle while maintaining the syringe at the same angle (**Figure I**).

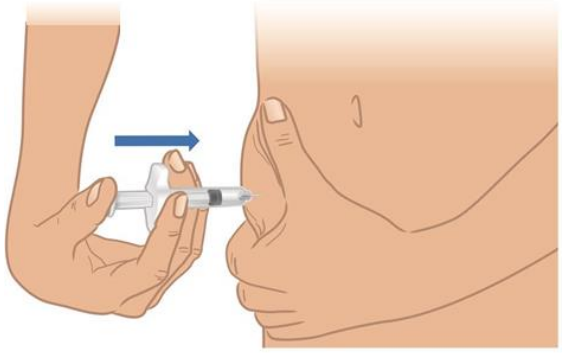


Figure I

f. Press cotton ball or gauze pad over injection site if needed and hold for 10 seconds.
   - **Do not** rub the injection site. You may have a minor bleeding. This is normal.
   - Cover injection site with an adhesive bandage if needed.
g. Put your used TAKHZYRO prefilled syringes in a sharps disposal container right away after use.
   - **Do not** touch the needle.
   - To avoid a needle-stick injury, **do not** recap the needle.
   - **Do not reuse** the TAKHZYRO prefilled syringe and any of your injection supplies.

There may be provincial, territorial, and local laws about the right way to throw away used syringes. Ask your healthcare professional how to throw away used syringes.

Usual dose:

Your healthcare professional will tell you how much TAKHZYRO to take and how often to take it.

TAKHZYRO is given as an injection under your skin (subcutaneous injection) by you or a caregiver.

If your condition changes or you have side effects, your healthcare professional may recommend a different dose or may change how often you use TAKHZYRO.

Overdose:

If you think you, or a person you are caring for, have taken too much TAKHZYRO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

- **Adults, children over 12 years of age and children under 12 years old who weigh more than 20 kg:** If you miss a dose of TAKHZYRO, administer the dose as soon as possible, making sure there are at least 10 days between doses.
- **Children under 12 years old who weigh between 10 and 20 kg:** If a dose is missed, give the missed dose as soon as possible, making sure there are at least 24 days between the doses.

Do not administer a missed dose at the same time as your scheduled dose. If you are not sure when to administer TAKHZYRO after a missed dose, ask your healthcare professional.

Possible side effects from using TAKHZYRO:

These are not all the possible side effects you may have when taking TAKHZYRO. If you experience any side effects not listed here, tell your healthcare professional.

- pain, redness, itching, hives and bruising at the site of the injection
- raised skin rash
- skin redness
- muscle pain
- dizziness

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Hypersensitivity / allergic reactions after taking this medicine: sudden wheeziness, difficulty breathing, swelling of the eyelids, face or lips, rash or itching (affecting the whole body), tight feeling in your chest			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in a refrigerator (2° C to 8° C). Do not freeze. Do not shake.
- Prefilled syringes removed from refrigeration should be stored at room temperature (below 25° C) and used within 14 days. Do not return prefilled syringes to refrigerated storage after storage at room temperature.
- Keep prefilled syringes in the original carton to protect the medicine from light.
- Dispose of any unused medicine.
- Keep out of reach and sight of children under 12.

If you want more information about TAKHZYRO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.takeda.com/en-ca/science/our-medicines/, or by calling 1-800-268-2772.

This leaflet was prepared by:

Takeda Canada Inc.
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3

Date of Authorization 2026-03-02

Patient Medication Information (2 mL Prefilled Pen)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

(tak-ZYE-roe)

Pr**TAKHZYRO®**

lanadelumab injection

Single-use 2 mL prefilled pen

This Patient Medication Information is written for the person who will be taking **TAKHZYRO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TAKHZYRO**, talk to a healthcare professional.

What TAKHZYRO is used for:

- to prevent attacks of hereditary angioedema (HAE) in adults and children (12 years and older).

TAKHZYRO should not be used to treat an acute HAE attack. In the event of an acute attack, seek medical attention.

How TAKHZYRO works:

In HAE, uncontrolled production of a substance called plasma kallikrein occurs. This leads in the release of too much bradykinin in your bloodstream. Too much bradykinin leads to symptoms like swelling and pain. TAKHZYRO is a type of protein that blocks the activity of plasma kallikrein. This helps to limit the production of bradykinin in your bloodstream and can prevent the swelling associated with HAE.

The ingredients in TAKHZYRO are:

Medicinal ingredient: lanadelumab

Non-medicinal ingredients: citric acid, L-histidine, polysorbate 80, sodium chloride, sodium phosphate, water for injection.

TAKHZYRO comes in the following dosage forms:

- Glass single-use prefilled syringe containing 300 mg/2 mL lanadelumab solution.
- Glass single-use prefilled syringe containing 150 mg/1 mL lanadelumab solution.
- Single-use prefilled pen containing 300 mg/2 mL lanadelumab solution.
- Glass single-use vials containing 300 mg/2 mL lanadelumab solution.

Note: Not all presentations may be marketed.

Do not use TAKHZYRO if:

- You are allergic to any ingredients in TAKHZYRO (see "**The ingredients in TAKHZYRO are**").
- You are pregnant or planning to become pregnant. It is not known if TAKHZYRO can harm your unborn baby.
- You are breastfeeding or plan to breastfeed. It is not known if TAKHZYRO passes into your milk and if it can harm your baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAKHZYRO. Talk about any health conditions or problems you may have, including if you:

- are pregnant or breastfeeding.

Other warnings you should know about:

Acute HAE attacks: TAKHZYRO should not be used to treat an acute HAE attack (when symptoms of HAE appear rapidly). Patients and their caregivers should be prepared to treat such attacks when needed.

Driving and using machines: Taking TAKHZYRO may cause you to feel dizzy after use. Do not drive or operate machinery if you have these symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TAKHZYRO:

Do not inject yourself or someone else until you have been trained by your healthcare professional.

Be sure that you read, understand, and follow the step-by-step instructions for injecting TAKHZYRO. A healthcare professional will show you how to prepare and inject TAKHZYRO properly before you inject yourself for the first time. Contact your healthcare professional if you have any questions.

- You should always follow the specific instructions given by your healthcare professional. The steps listed below are general guidelines for using TAKHZYRO. If you are unsure of the steps, contact your healthcare professional before using TAKHZYRO.

Preparation

- Collect all supplies listed below to prepare and give your injection.
- Inspect the supplies for damage. Do not use if they appear damaged.

TAKHZYRO is a ready-to-use solution for injection under the skin (subcutaneous injection). It is supplied in a single-use prefilled pen at a dosage of 300 mg/2 mL solution.

TAKHZYRO prefilled pen before and after use (Figure A).

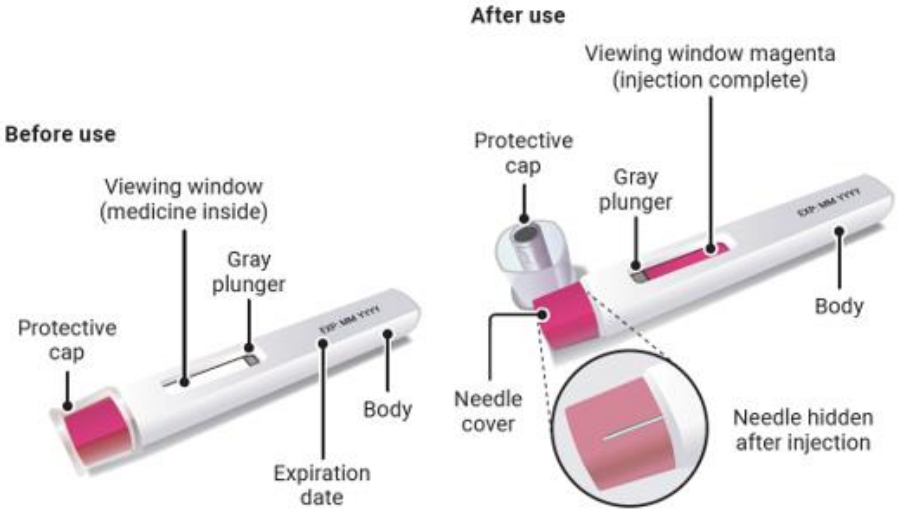


Figure A

Prepare for your injection

Step 1: Prepare your prefilled pen

Remove the TAKHZYRO prefilled pen carton from the refrigerator 30 minutes before injecting.

- **Do not** use if the seal on the carton is open or broken.
- Your medicine is sensitive to warm temperatures. **Do not** use heat sources such as a microwave or hot water to warm your TAKHZYRO prefilled pen.

Step 2: Gather supplies

Gather an alcohol swab, cotton ball or gauze pad, adhesive bandage, sharps disposal container (**Figure B**) and place the supplies on a clean, flat, surface in a well-lit area. These supplies are not included in the TAKHZYRO prefilled pen carton.

Figure B

Step 3: Remove prefilled pen

Open the carton. Hold the pen body and remove the TAKHZYRO prefilled pen from the tray (**Figure C**).

- **Do not** remove the protective cap until you are ready to inject.
- **Do not** touch or push the needle cover until you are ready to inject.

Figure C

Step 4: Wash hands

Wash your hands with soap and water (**Figure D**). Dry your hands completely.

- **Do not** touch any surface or body part after washing your hands before injection.

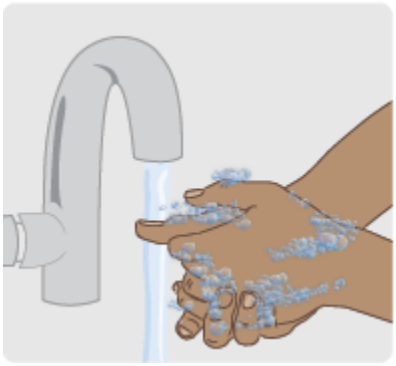


Figure D

Step 5: Check expiration date

Check the expiration date (EXP) on the pen body (**Figure E**).

- **Do not** use the TAKHZYRO prefilled pen if the expiration date has passed. If the TAKHZYRO prefilled pen is expired throw it away (dispose of) in a sharps disposal container and contact your healthcare provider.

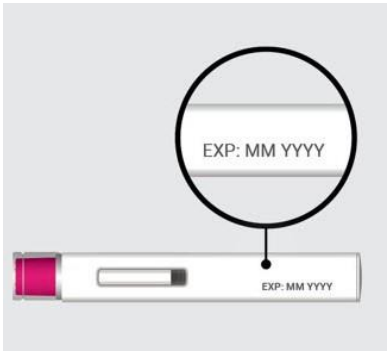


Figure E

Step 6: Inspect TAKHZYRO

Inspect the TAKHZYRO prefilled pen for any damage. Check the viewing window (**Figure F**) and make sure the medicine is colorless to slightly yellow.

- **Do not** use the TAKHZYRO prefilled pen if the pen is damaged or cracked.
- **Do not** use the TAKHZYRO prefilled pen if the medicine is discolored, cloudy, or has flakes or particles in it.
- You may see air bubbles in the TAKHZYRO prefilled pen viewing window. This is normal and will not affect your dose.

If you cannot use the prefilled pen, contact your healthcare provider.

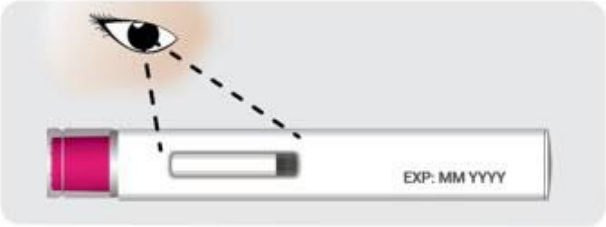


Figure F

Select and prepare injection site

Step 7: Select injection site

TAKHZYRO should be injected into the following sites only (**Figure G for self-injection and Figure H for caregiver injection**):

- stomach area (abdomen)
- thighs
- upper arms (only if a healthcare provider or caregiver is giving you the injection)

- **Do not** inject into an area of your body where the skin is irritated, red, bruised, or infected.
- The area you choose for injection should be at least 5 cm (2-inches) away from any scars or your belly button (navel).

Important:

- **Rotate injection sites** to keep skin healthy. Each new injection should be given at least 2.5 cm (1-inch) from the last site you used.

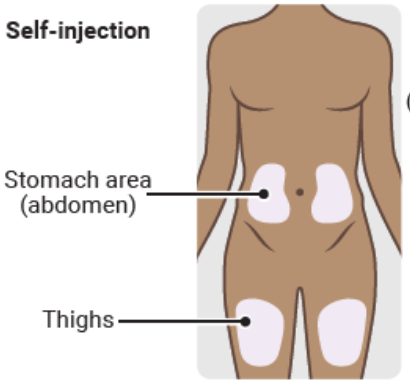


Figure G

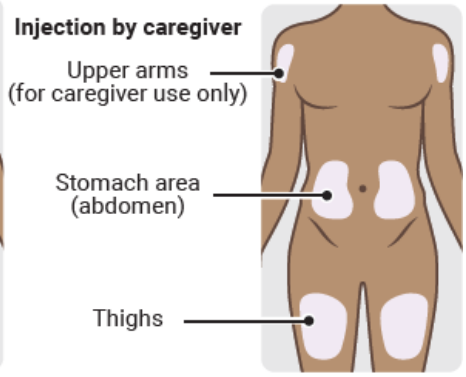


Figure H

Step 8: Clean injection site

Clean the injection site with an alcohol swab and allow it to dry completely (**Figure I**).

- **Do not** fan or blow on the clean site.
- **Do not** touch the clean site again before giving your injection.

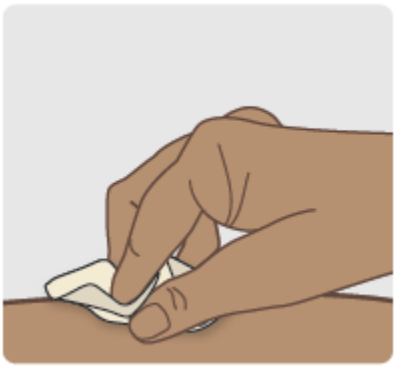


Figure I

Step 9: Remove protective cap

Firmly hold the middle of the TAKHZYRO prefilled pen with one hand, and with the other hand, pull the protective cap straight off (**Figure J**).

- The needle is protected by the needle cover.
- You may see a few drops of liquid come out of the needle. This is normal and will not affect your dose of TAKHZYRO.
- Your TAKHZYRO prefilled pen is ready to inject after the protective cap is removed.
- **Do not** touch or push the needle cover until you are ready to inject.
- **Do not** recap your TAKHZYRO prefilled pen.

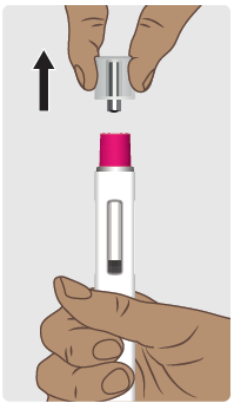


Figure J

Step 10: Dispose of protective cap

Throw away (dispose of) the protective cap in your trash or in your sharps disposal container (**Figure K**).

- **Do not** recap the pen to avoid a needle stick injury.

Figure K

Inject TAKHZYRO

Step 11: Hold the TAKHZYRO prefilled pen and pinch the skin

Hold the TAKHZYRO prefilled pen in one hand so that you can see the viewing window while giving the injection (**Figure L**).

With your other hand, gently pinch a 2.5 cm (1-inch) fold of skin at the cleaned injection site (**Figure M**).

- Keep pinching until the injection is complete and the needle is removed.
- **Do not** press the needle cover against your skin until you are ready to give the injection.

Figure L

Figure M

Step 12: Place pen on injection site

Place your TAKHZYRO prefilled pen on your skin at a 90-degree angle to the chosen injection site (Figure N).

- **Do not** push down on the pen until you are ready to inject.
- Hold your pen so you can see the viewing window.

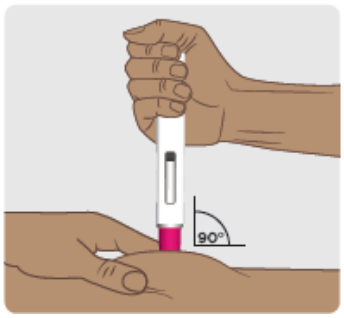


Figure N

Step 13: Inject TAKHZYRO pen

Firmly press your pen straight down and hold. This will insert the needle and start your injection (Figure O).

Your injection may take up to 25 seconds.

- You will hear a "click" sound when the injection starts.
- There will be a second "click" – **this is not the end of the injection**.
- Continue to hold down with constant pressure, until the v**iewing window is completely filled with the color magenta**.
- **Before you remove the pen from your skin, confirm that the viewing window is filled with magenta**. This means you have received your full dose (Figure O).
- The gray plunger is still visible in the viewing window after the injection is complete. This is normal and will not affect your dose.
- If the viewing window did not fill completely with magenta, contact your healthcare provider.

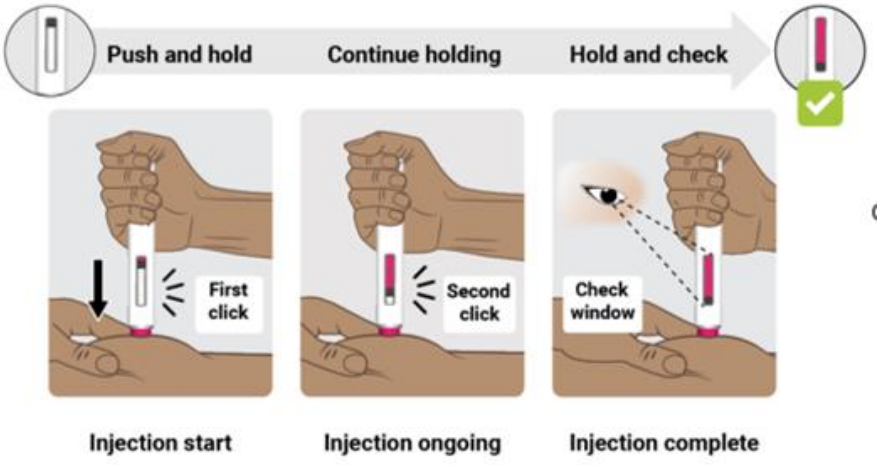


Figure O

Step 14: Remove pen

Slowly lift your pen straight away from the injection site. The needle cover will be covering all of the needle (**Figure P**).

- Release the fold of skin.
- **Do not** rub the injection site. There may be a small amount of blood where you injected. This is normal.
- Press a cotton ball or gauze pad over the injection site and cover with an adhesive bandage, if needed.

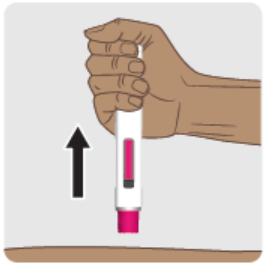


Figure P

Throw away (dispose of) the TAKHZYRO prefilled pen

Step 15: Dispose in a sharps disposal container

Put your used TAKHZYRO prefilled pen in a sharps disposal container right away after use (**Figure Q**).

- **Do not** recap the pen to avoid a needle-stick injury.
- **Do not** reuse the TAKHZYRO prefilled pen or any of your injection supplies.
- **Do not** throw away (dispose of) the TAKHZYRO prefilled pen in your household trash.
- **Do not** touch the needle.

Figure Q

There may be provincial, territorial and local laws about the right way to throw away used syringes. Ask your healthcare professional how to throw away used pens.

Usual dose:

Your healthcare professional will tell you how much TAKHZYRO to take and how often to take it.

TAKHZYRO is given as an injection under your skin (subcutaneous injection) by you or a caregiver.

If you have side effects or your condition is under control, your dose may be lowered or you may administer it less often.

The TAKHZYRO prefilled pen has only been studied in adults and children 12 years of age and older. It should only be used for these patients.

Overdose:

If you think you, or a person you are caring for, have taken too much TAKHZYRO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose of TAKHZYRO, take your dose as soon as possible, making sure there are at least 10 days between doses. Do not administer a missed dose at the same time as your scheduled dose. If you are not sure when to administer TAKHZYRO after a missed dose, ask your healthcare professional.

Possible side effects from using TAKHZYRO:

These are not all the possible side effects you may have when taking TAKHZYRO. If you experience any side effects not listed here, tell your healthcare professional.

- pain, redness, itching, hives and bruising at the site of the injection
- raised skin rash
- skin redness
- muscle pain
- dizziness

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Hypersensitivity / allergic reactions after taking this medicine: sudden wheeziness, difficulty breathing, swelling of the eyelids, face or lips, rash or itching (affecting the whole body), tight feeling in your chest			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in a refrigerator (2° C to 8° C). Do not freeze. Do not shake.
- Prefilled pen removed from refrigeration should be stored at room temperature (below 25° C) and used within 14 days. Do not return TAKHZYRO to refrigerated storage after storage at room temperature.
- Keep prefilled pens in the original carton to protect the medicine from light.
- Dispose of any unused medicine.
- Dispose of the TAKHZYRO prefilled pen in a sharps disposal container if it has been kept out of the refrigerator for more than 14 days, frozen, or not kept in the original carton protected from light.
- Keep out of reach and sight of children under 12.

If you want more information about TAKHZYRO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://www.takeda.com/en-ca/what-we-do/our-medicines/, or by calling 1-800-268-2772.

This leaflet was prepared by:

Takeda Canada Inc.
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3

Date of Authorization 2026-03-02

Patient Medication Information (Vial)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

(tak-ZYE-roe)

[Pr]TAKHZYRO®

lanadelumab injection

Single-use vial

This Patient Medication Information is written for the person who will be taking **TAKHZYRO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TAKHZYRO**, talk to a healthcare professional.

What TAKHZYRO is used for:

- to prevent attacks of hereditary angioedema (HAE) in adults and children (2 years and older who weigh more than 10 kg).

TAKHZYRO should not be used to treat an acute HAE attack. In the event of an acute attack, seek medical attention.

How TAKHZYRO works:

In HAE, uncontrolled production of a substance called plasma kallikrein occurs. This leads in the release of too much bradykinin in your bloodstream. Too much bradykinin leads to symptoms like swelling and pain. TAKHZYRO is a type of protein that blocks the activity of plasma kallikrein. This helps to limit the production of bradykinin in your bloodstream and can prevent the swelling associated with HAE.

The ingredients in TAKHZYRO are:

Medicinal ingredient: lanadelumab

Non-medicinal ingredients: citric acid, L-histidine, polysorbate 80, sodium chloride, sodium phosphate, water for injection.

TAKHZYRO comes in the following dosage forms:

- Glass single-use prefilled syringe containing 300 mg/2 mL lanadelumab solution.
- Glass single-use prefilled syringe containing 150 mg/1 mL lanadelumab solution.
- Single-use prefilled pen containing 300 mg/2 mL lanadelumab solution.
- Glass single-use vials containing 300 mg/2 mL lanadelumab solution.

Note: Not all presentations may be marketed.

Do not use TAKHZYRO if:

- you are allergic to any ingredients in TAKHZYRO (see "**The ingredients in TAKHZYRO are**").
- you are pregnant or planning to become pregnant. It is not known if TAKHZYRO can harm your unborn baby.

- you are breastfeeding or plan to breastfeed. It is not known if TAKHZYRO passes into your milk and if it can harm your baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAKHZYRO. Talk about any health conditions or problems you may have, including if you:

- are pregnant or breastfeeding.

Other warnings you should know about:

Acute HAE attacks: TAKHZYRO should not be used to treat an acute HAE attack (when symptoms of HAE appear rapidly). Patients and their caregivers should be prepared to treat such attacks when needed.

Driving and using machines: Taking TAKHZYRO may cause you to feel dizzy after use. Do not drive or operate machinery if you have these symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TAKHZYRO:

Do not inject yourself or someone else until you have been trained by your healthcare professional.

Be sure that you read, understand, and follow the step-by-step instructions for injecting TAKHZYRO. A healthcare professional will show you how to prepare and inject TAKHZYRO properly before you inject yourself for the first time. Contact your healthcare professional if you have any questions.

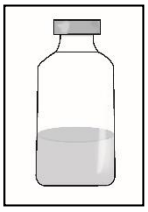
- You should always follow the specific instructions given by your healthcare professional. The steps listed below are general guidelines for using TAKHZYRO. If you are unsure of the steps, contact your healthcare professional before using TAKHZYRO.
- Only use the syringes, blunt tip vial access needles, and pointed tip administration (injection) needles that your healthcare professional prescribes.
- Only use the syringes, blunt tip vial access needles and pointed tip administration (injection) needles one time. Discard (throw away) any used syringes and needles in the proper disposal container.

Preparation

- Collect all supplies listed below to prepare and give your injection.
- Inspect the supplies for damage. Do not use if they appear damaged.

TAKHZYRO is a ready-to-use solution for injection under the skin (subcutaneous injection). It is supplied in a single-use, glass vial at a dosage of 300 mg/2 mL solution.

GATHER SUPPLIES



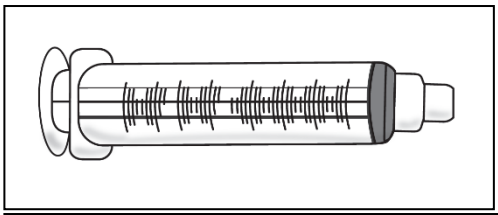
Vial containing TAKHZYRO

TAKHZYRO single-use vial Instructions for Use

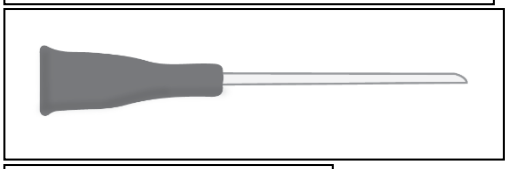
OTHER RECOMMENDED SUPPLIES

(For illustration purposes, not actual size)

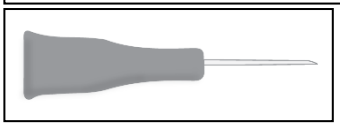
Gather an empty 3-mL syringe, 18 G blunt tip vial access needle, 27 1/2 G pointed tip administration (injection) needle. You will also need an alcohol swab, cotton ball/gauze pad, adhesive bandage, sharps disposal container. These supplies are not included in the TAKHZYRO packaging.



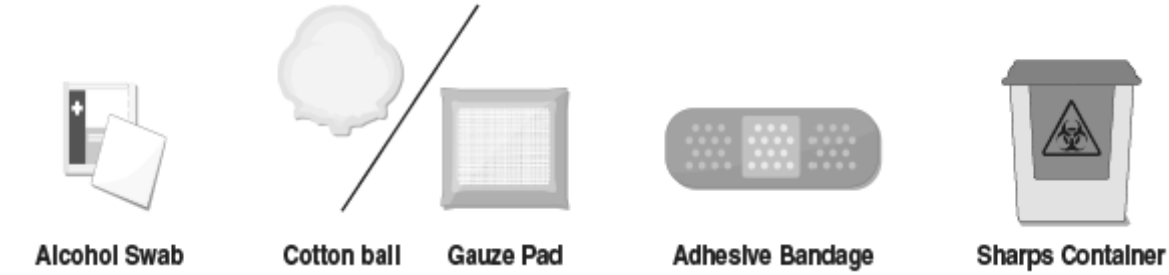
One (1) empty 3-mL syringe



One (1) 18G blunt tip vial access needle.
Used to draw drug from the vial into the syringe



One (1) 27G ½-inch pointed tip administration (injection) needle
Used for injection under the skin [subcutaneous]



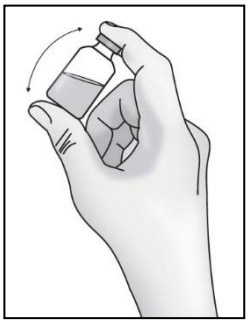
These are the recommended supplies. However, your healthcare professional may choose what is most appropriate for you.

The administration of TAKHZYRO can be summarized in 5 steps:

1. **Prepare the vial of TAKHZYRO**
2. **Attach blunt tip vial access needle to syringe**
3. **Transfer TAKHZYRO into syringe and switch to the pointed tip administration (injection) needle.**
4. **Select and prepare injection site**
5. **Inject TAKHZYRO**

Step 1: Prepare the vial of TAKHZYRO

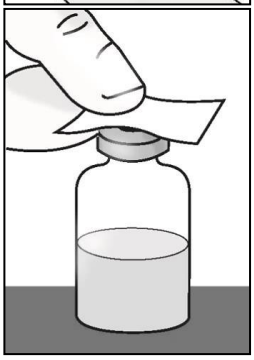
- Take the vial out of the refrigerator 15 minutes before use and allow it to reach room temperature before preparing an injection.
- Gather your TAKHZYRO and supplies and place them on your well-lighted work surface.



- Check the expiration date on the box, on the vial label. Do not use if the expiration date has passed.
- Clean your work area and wash your hands prior to preparing your dose. Do not touch any surface or body part, especially your face, after washing your hands before injection.
- Remove the vial from the packaging.
- Gently invert the vial 3 to 5 times to ensure the solution is mixed. Do not shake to avoid foaming.
- Look at the solution in the vial for visible particles or a change in the colour (normally colourless to slightly yellow). Do not use if you see particles or a change in colour.

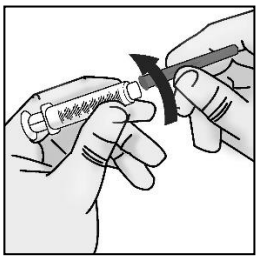
Important: Do not shake the vial.

- Remove the plastic cap from the drug vial. Do not remove the drug vial rubber stopper.



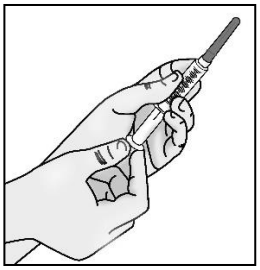
- Place the vial on a flat surface. Clean the drug vial rubber stopper with an alcohol wipe and allow it to dry.

Step 2: Attach blunt tip vial access needle to syringe

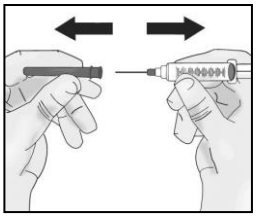


- Screw the 18G blunt tip vial access needle to the 3 mL syringe.

Important: Do not remove the needle cap from the needle when attaching to the syringe.

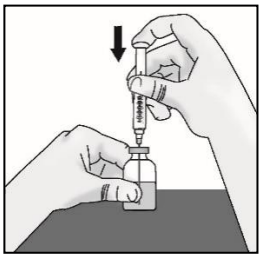


- Pull back the plunger to fill the syringe with air equal to the amount of drug in the vial.

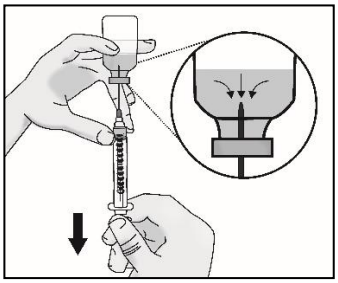


- Pull off the needle cap straight away from the syringe without touching the needle. Do not pull on the plunger.

Step 3: Transfer TAKHZYRO into syringe and switch to the pointed tip administration (injection) needle

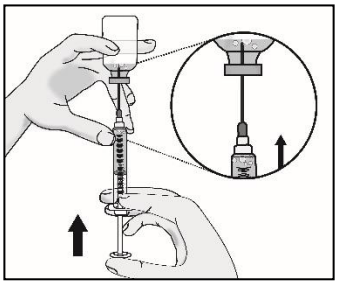


- Insert the needle into the center of the rubber stopper.
- Push the plunger down to inject air into the vial and hold the plunger down.

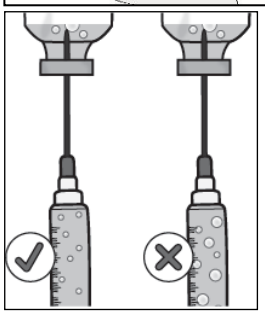


- Slowly turn the vial upside down with needle and syringe attached. Pull back on the plunger to withdraw the full dose in the vial.

Important: Be sure to keep the tip of the needle in the liquid to avoid drawing air in as you pull back the plunger.

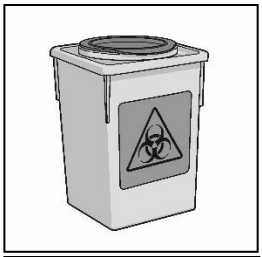


- Remove large air bubbles by gently tapping on the syringe with your fingers until the bubbles rise to the top of the syringe.
- Slowly push the plunger, allowing air to go back into the vial, until the drug reaches the top of the syringe.

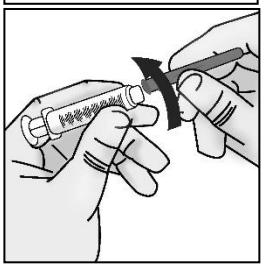


- Repeat these steps until large air bubbles are removed.

- Without removing the needle from the vial, unscrew the syringe by holding the needle hub and turning the syringe counter clockwise. Be careful not to press down on the plunger, as the drug will be pushed out.
- Return the syringe to an upright position.



- Discard the vial with the 18G needle still inside into a sharps container.



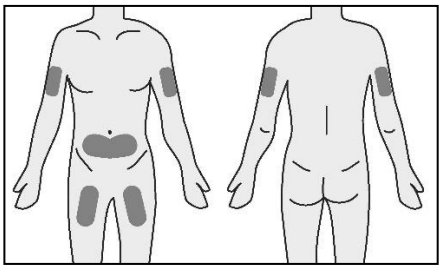
- Screw the 27G ½-inch administration (injection) needle to the syringe.

Important: Do not remove the needle cap from the needle when attaching to the syringe.

Do not use the blunt tip vial access needle to inject TAKHZYRO as this may cause harm such as pain and bleeding

Step 4: Select and prepare injection site

- Choose an injection site on your stomach (abdomen), thigh, or upper arm.

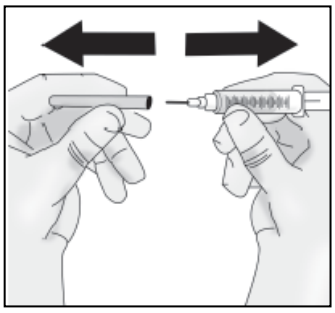


Important:

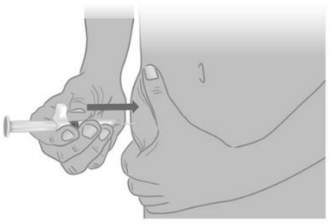
- Rotate injection sites to keep skin healthy.
- The area you choose for injection should be at least 2 inches (5 cm) away from any scars or your belly button (navel). Do not choose an area that is bruised, swollen, or painful.
- The outer area of the upper arm is not recommended for self- administration.
- TAKHZYRO must be administered within 2 hours of preparing your dosing syringe at room temperature. After the dosing syringe is prepared, it can be refrigerated (2°C to 8°C) and must be used within 8 hours of preparation. Take the prepared syringe out of the fridge 15 minutes before use to allow it to reach room temperature before injecting.

- Clean your injection site with an alcohol wipe and allow it to dry completely.

Step 5: Inject TAKHZYRO

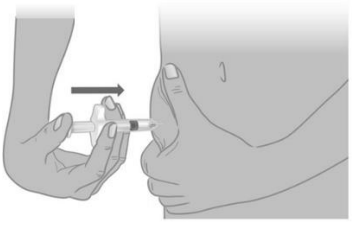


- Hold the syringe by the barrel with one hand and the needle cap with the other hand.
- Pull off the needle cap straight away from the syringe without touching the needle. Do not pull on the plunger. Do not touch the needle tip or allow it to touch any other surface.



- Gently pinch 1 inch/ 2.5 cm of skin at your cleaned injection site and insert the needle.

Important: Be sure to inject into a subcutaneous space that is not too shallow (skin layer) or too deep (muscle).



- Push the plunger slowly until no contents remain in the syringe. Release the skin fold and gently remove the needle. Do not recap the needle.
- Press cotton ball or gauze pad over injection site if needed and hold for 10 seconds.
  a. Do not rub the injection site. You may have a minor bleeding. This is normal.
  b. Cover injection site with an adhesive bandage if needed.
- Place the 27G ½-inch administration (injection) needle and the syringe in a sharps container

There may be provincial, territorial, and local laws about the right way to throw away used vials, syringes and needles. Ask your healthcare professional how to throw away used vials, syringes and needles.

Usual dose:

Your healthcare professional will tell you how much TAKHZYRO to use and how often to take it.

TAKHZYRO is given as an injection under your skin (subcutaneous injection) by you or a caregiver.

If your condition changes or you have side effects, your healthcare professional may recommend a different dose or may change how often you use TAKHZYRO.

Overdose:

If you think you, or a person you are caring for, have taken too much TAKHZYRO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

- **Adults, children over 12 years of age and children under 12 years old who weigh more than 20 kg:** If you miss a dose of TAKHZYRO, administer the dose as soon as possible, making sure there are at least 10 days between doses.
- **Children under 12 years old who weigh between 10 and 20 kg:** If a dose is missed, give the missed dose as soon as possible, making sure there are at least 24 days between the doses.

Do not administer a missed dose at the same time as your scheduled dose. If you are not sure when to administer TAKHZYRO after a missed dose, ask your healthcare professional.

Possible side effects from using TAKHZYRO:

These are not all the possible side effects you may have when taking TAKHZYRO. If you experience any side effects not listed here, tell your healthcare professional.

- pain, redness, itching, hives and bruising at the site of the injection
- raised skin rash
- skin redness
- muscle pain
- dizziness

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Hypersensitivity / allergic reactions after taking this medicine: sudden wheeziness, difficulty breathing, swelling of the eyelids, face or lips, rash or itching (affecting the whole body), tight feeling in your chest			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in a refrigerator (2° C to 8° C). Do not freeze. Do not shake.
- Vials removed from refrigeration should be stored at room temperature (below 25° C) and used within 14 days. After storage at room temperature, unopened vials may be returned to the refrigerator. The total length of time the medicine is stored at room temperature should not be more than 14 days.
- Keep vial in the original carton to protect the medicine from light.
- Dispose of any unused medicine.
- Keep out of reach and sight of children under 12.

If you want more information about TAKHZYRO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.takeda.com/en-ca/science/our-medicines/, or by calling 1-800-268-2772.

This leaflet was prepared by:

Takeda Canada Inc.
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Toronto Ontario M5H 4E3

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