

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAKHZYRO® safely and effectively. See full prescribing information for TAKHZYRO®.

TAKHZYRO® (lanadelumab-flyo) injection, for subcutaneous use
Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1) 02/2023
Dosage and Administration (2) 02/2023

INDICATIONS AND USAGE

TAKHZYRO is a plasma kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older. (1)

DOSAGE AND ADMINISTRATION

For subcutaneous use only.

Recommended Dosage:

- Adult and pediatric patients 12 years of age and older: administer 300 mg every 2 weeks by the patient or caregiver. Dosing interval every 4 weeks may be considered in some patients. (2.1)
- Pediatric patients 6 to less than 12 years of age: administer 150 mg every 2 weeks by a healthcare provider or caregiver. Dosing interval every 4 weeks may be considered in some patients. (2.2)
- Pediatric patients 2 to less than 6 years of age: administer 150 mg every 4 weeks by a healthcare provider or caregiver. (2.2)
- See Full Prescribing Information for Administration Instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection:

- 150 mg/1 mL (150 mg/mL) solution in a single-dose prefilled syringe. (3)
- 300 mg/2 mL (150 mg/mL) solution in a single-dose prefilled syringe. (3)
- 300 mg/2 mL (150 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity reactions have been observed. In case of a severe hypersensitivity reaction, discontinue TAKHZYRO administration and institute appropriate treatment. (5.1)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are injection site reactions, upper respiratory infections, headache, rash, dizziness, diarrhea, and myalgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No dedicated drug interaction studies have been conducted. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TAKHZYRO® is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 2 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adult and Pediatric Patients 12 Years of Age and Older

The recommended starting dosage in adult and pediatric patients 12 years of age and older is 300 mg administered subcutaneously every 2 weeks (q2wks). A dosing interval of 300 mg every 4 weeks (q4wks) is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.

2.2 Recommended Dosage for Pediatric Patients 2 to Less Than 12 Years of Age

Pediatric Patients 6 to Less Than 12 Years of Age

The recommended starting dosage in pediatric patients 6 to less than 12 years of age is 150 mg administered subcutaneously q2wks. A dosing interval of 150 mg q4wks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.

Pediatric Patients 2 to Less Than 6 Years of Age

The recommended dosage in pediatric patients 2 to less than 6 years of age is 150 mg administered subcutaneously q4wks.

2.3 Preparation and Administration Instructions

TAKHZYRO is administered subcutaneously only.

TAKHZYRO is intended for administration by a healthcare provider, patient or caregiver.

The patient or caregiver should be trained in subcutaneous injection technique by a healthcare professional.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use TAKHZYRO if the solution appears discolored or contains visible particles. TAKHZYRO is a clear to slightly opalescent, colorless to slightly yellow solution.

Administration Instructions for Single-Dose Prefilled Syringes

Instruct patients and/or caregiver on proper use of the TAKHZYRO prefilled syringe and assess that they are well trained in subcutaneous injection technique prior to administration by patient and/or caregiver.

Avoid vigorous agitation of the prefilled syringe.

Take the TAKHZYRO prefilled syringe out of the refrigerator 15 minutes before injecting to allow it to equilibrate to room temperature

Using aseptic technique, inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm.

Discard any unused portion of drug remaining in the prefilled syringe.

For detailed instructions on the preparation and administration of TAKHZYRO see Instructions for Use for either single-dose 1 mL prefilled syringe or single-dose 2 mL prefilled syringe.

Administration Instructions for Single-Dose Vial

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

Instruct patients and/or caregivers on proper use of TAKHZYRO from a vial and assess that they are well trained in subcutaneous injection technique prior to administration by patient and/or caregiver.

Avoid vigorous agitation of the vial.

Take the TAKHZYRO vial out of the refrigerator 15 minutes before injecting to allow it to equilibrate 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 needle or other needle suitable for subcutaneous injection. Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm. In clinical studies, the majority of patients self-administered TAKHZYRO over 10 to 60 seconds.

TAKHZYRO should be administered within 2 hours of preparing the dosing syringe. After the dosing syringe is prepared, it can be refrigerated at 36°F to 46°F (2°C to 8°C) and must be used within 8 hours.

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

For detailed instructions on the preparation and administration of TAKHZYRO see single-dose vial Instructions for Use.

3 DOSAGE FORMS AND STRENGTHS

TAKHZYRO is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution available in the following presentations.

- Injection: 150 mg/1 mL (150 mg/mL) solution in a single-dose prefilled syringe
- Injection: 300 mg/2 mL (150 mg/mL) solution in a single-dose prefilled syringe
- Injection: 300 mg/2 mL (150 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult and Pediatric Patients 12 Years of Age and Older

The safety of TAKHZYRO is primarily based on a 26-week, randomized, double-blind, parallel-group and placebo-controlled study (Trial 1) in 125 patients with Type I or II HAE. Eligible patients were also able to participate in an open-label extension study (Trial 2) up to 130 weeks. In Trial 1, a total of 84 patients with HAE aged 12 years and older received at least one dose of TAKHZYRO. Overall, 70% of patients were female and 90% of patients were Caucasian with a mean age of 41 years. The proportion of patients who discontinued study drug prematurely due to adverse events was 1.2% for TAKHZYRO-treated patients and 4.9% for placebo-treated patients. No deaths occurred in the trial.

The safety profile of TAKHZYRO was generally similar across all subgroups of patients, including analysis by age, sex, and geographic region.

Table 1 shows adverse reactions occurring in $\geq 10\%$ of patients in any TAKHZYRO treatment group that also occurred at a higher rate than in the placebo treatment group in Trial 1.

Table 1 Adverse Reactions Observed in $\geq 10\%$ of Patients Treated with TAKHZYRO in Trial 1

Adverse Reaction	Placebo (N=41)	TAKHZYRO			
		150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)	Total (N=84)
	n (%)	n (%)	n (%)	n (%)	n (%)
Injection site reactions ^a	14 (34)	16 (57)	13 (45)	15 (56)	44 (52)
Upper respiratory infection ^b	13 (32)	3 (11)	9 (31)	12 (44)	24 (29)
Headache ^c	9 (22)	3 (11)	6 (21)	9 (33)	18 (21)
Rash ^d	2(5)	2 (7)	3 (10)	1 (4)	6 (7)
Dizziness	0	1 (4)	3 (10)	1 (4)	5 (6)
Diarrhea	2 (5)	3 (11)	0	1 (4)	4 (5)
Myalgia	0	1 (4)	0	3 (11)	4 (5)

N= number of patients; n=number of patients experiencing the event; q2wks = every 2 weeks; q4wks = every 4 weeks

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

^b Includes upper respiratory infection, viral upper respiratory infection

^c Includes headache, tension headache, sinus headache

^d Includes rash, rash maculopapular, rash erythematous

Injection site reactions primarily consisted mainly of pain, erythema, and bruising at the injection site. There was no meaningful difference in injection site reactions with self-administration.

Less Common Adverse Reactions

Other adverse reactions that occurred at a higher incidence in TAKHZYRO-treated patients compared to placebo include hypersensitivity (1% vs 0%), increased aspartate transaminase (2% vs 0%), and increased alanine transaminase (2% vs 0%).

Safety data from the open-label extension study, consisting of 109 rollover patients from Trial 1 and 103 non-rollover HAE patients, is consistent with controlled safety data from Trial 1.

Laboratory Abnormalities

Transaminase elevations

During the placebo-controlled treatment period in Trial 1, the number of TAKHZYRO-treated patients with maximum transaminase (ALT or AST) levels >8, >5, or >3 times the upper limit of normal (ULN) was 1 (1.2%), 0 (0%), or 3 (3.6%) respectively, compared to 0 in the placebo-treated patients. These transaminase elevations were asymptomatic and transient. No patients had elevated total bilirubin >2x ULN. One TAKHZYRO-treated patient permanently discontinued treatment due to elevated transaminases (4.1x ULN AST). None of the patients were reported to have serious adverse reactions of elevated transaminases.

Pediatric Patients 2 to Less Than 12 Years of Age

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

7 DRUG INTERACTIONS

No dedicated drug interaction studies have been conducted [*see Clinical Pharmacology (12.3)*].

7.1 Drug-Laboratory Test Interactions

Coagulation tests

TAKHZYRO can increase activated partial thromboplastin time (aPTT) due to an interaction of TAKHZYRO with the aPTT assay. The reagents used in the aPTT laboratory test initiate intrinsic coagulation through the activation of plasma kallikrein in the contact system. Inhibition of plasma kallikrein by TAKHZYRO can increase aPTT in this assay. In Trial 1, prolongation of aPTT (>1x ULN) was observed at one or more time points in 3, 9, and 11 patients treated with TAKHZYRO 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks, respectively, compared to 5 placebo-treated patients. Only one patient in the 300 mg q2wks treatment group experienced transient aPTT prolongation $\geq 1.5x$ ULN which was confounded by ongoing heparin therapy. None of the increases in aPTT in patients treated with TAKHZYRO were associated with abnormal bleeding adverse events. There were no differences in INR values between treatment groups.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TAKHZYRO use in pregnant women to inform any drug associated risks. Monoclonal antibodies such as lanadelumab-flyo are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. An enhanced pre-and postnatal development (ePPND) study conducted in pregnant monkeys at doses resulting in exposures of up to 33 times the exposure achieved (on an AUC basis) at the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In the ePPND study, pregnant cynomolgus monkeys were administered lanadelumab-flyo once weekly at subcutaneous doses resulting in up to 33 times the exposure at the MRHD (on an AUC basis with maternal subcutaneous doses up to 50 mg/kg/week) from gestation day 20, at the beginning of organogenesis, through to parturition. There were no lanadelumab-flyo-related effects on maintenance of pregnancy or parturition. Maternal lanadelumab-flyo treatment had no effects on embryo-fetal development, survival, growth, or postnatal development of offspring through 3 months of age. Lanadelumab-flyo crossed the placenta in monkeys. Offspring were exposed to lanadelumab-flyo at approximately 50% of the maternal plasma concentration out to postnatal day 21 (PND 21). Lanadelumab-flyo concentrations were approximately equivalent in maternal and offspring plasma at PND 90.

8.2 Lactation

Risk Summary

There are no data on the presence of lanadelumab-flyo in human milk, its effects on the breastfed infant, or its effects on milk production. Lanadelumab-flyo was detected in the milk of lactating cynomolgus monkeys at approximately 0.2% of the maternal plasma concentration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAKHZYRO and any potential adverse effects on the breastfed infant from TAKHZYRO or from the underlying maternal condition.

Data

Animal Data

Available pharmacokinetic data in cynomolgus monkeys have shown excretion of lanadelumab-flyo in milk at approximately 0.2% of the maternal plasma level.

8.4 Pediatric Use

The safety and effectiveness of TAKHZYRO for prophylaxis to prevent attacks of hereditary angioedema (HAE) have been established in pediatric patients 2 years of age and older.

Use of TAKHZYRO for this indication in patients 12 years of age and older was supported by a subgroup analysis by age of 10 patients aged 12 to <18 years in Trial 1 (a randomized, double-blind, placebo-controlled parallel-group study in adult and pediatric patients 12 years of age and older with HAE). Results of the subgroup analysis by age were consistent with overall study results. An additional 13 pediatric patients aged 12 to <18 years were enrolled in the open-label extension study [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14)*].

Use of TAKHZYRO for this indication in patients 2 to less than 12 years of age was supported by extrapolation of efficacy data from Trial 1, an adequate and well controlled study in adult and pediatric (12 to less than 18 years of age) patients, with additional pharmacokinetic analyses showing similar drug exposures between adults (>18 years of age) and pediatric patients (2 to less than 12 years of age), and safety and pharmacodynamic data from an open-label, multicenter study in pediatric patients with HAE aged 2 to less than 12 years that enrolled 21 patients (4 patients were aged 2 to less than 6 years and 17 patients were 6 to less than 12 years of age) [*see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)*]. The pharmacodynamic response observed in this trial for pediatric patients 2 to less than 12 years of age was similar to that seen in adult and pediatric patients 12 years of age and older [*see Clinical Pharmacology (12.2)*].

The safety and effectiveness of TAKHZYRO in pediatric patients less than 2 years of age have not been established.

8.5 Geriatric Use

The safety and effectiveness of TAKHZYRO were evaluated in a subgroup of patients (N=5) aged ≥ 65 years in Trial 1. Results of the subgroup analysis by age were consistent with overall study results [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)* and *Clinical Studies (14)*].

10 OVERDOSAGE

There is no clinical experience with overdosage of TAKHZYRO.

11 DESCRIPTION

Lanadelumab-flyo, a plasma kallikrein inhibitor, is a non-plasma derived, recombinant, fully human, monoclonal antibody (IgG1/ κ -light chain) produced in Chinese Hamster Ovary (CHO) cells. Based on the amino acid sequence, the molecular weight of the non-glycosylated lanadelumab-flyo is 146 kDa. The calculated molecular mass of the fully reduced light chain is 23 kDa. The calculated molecular mass of the fully reduced and non-glycosylated heavy chain is 49 kDa.

TAKHZYRO (lanadelumab-flyo) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous use.

Each mL of ready-to-use TAKHZYRO solution contains 150 mg of lanadelumab-flyo, citric acid monohydrate (4.1 mg), L-histidine (7.8 mg), polysorbate 80 (0.1 mg), sodium chloride (5.3 mg), sodium phosphate dibasic dihydrate (5.3 mg), and Water for Injection, USP. The solution has a pH of approximately 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lanadelumab-flyo 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 swelling and pain associated with HAE. In patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction, normal regulation of plasma kallikrein activity is not present, which leads to uncontrolled increases in plasma kallikrein activity and results in angioedema attacks. Lanadelumab-flyo decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

12.2 Pharmacodynamics

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

TAKHZYRO did not prolong the QT/QTc interval.

12.3 Pharmacokinetics

Following subcutaneous administration, the pharmacokinetics of lanadelumab-flyo was approximately dose-proportional in the therapeutic dose range in patients with HAE (Table 2). The pharmacokinetic properties

and exposure (steady state) of lanadelumab-flyo in HAE patients, following subcutaneous administration of 150 mg q4wks, 300 mg q4wks and 300 mg q2wks, are provided in **Table 2**. Following subcutaneous administration of TAKHZYRO, peak plasma concentrations are reached within 5 days, and terminal elimination half-life is ~2 weeks. The anticipated time to reach steady state concentration was approximately 70 days. At steady-state, the mean accumulation ratio is approximately 1.44, 1.42, and 2.43 for dosing regimen of 150 mg q4wks, 300 mg q4wks and 300 mg q2wks, respectively.

Table 2 Mean (SD) Pharmacokinetic Parameters of Lanadelumab-flyo Following Subcutaneous Administration (Trial 1)

Pharmacokinetic Parameters	Lanadelumab-flyo		
	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.

Specific Populations

Population pharmacokinetic analyses showed that age, gender and race did not meaningfully influence the pharmacokinetics of lanadelumab-flyo after correcting for body weight. Body weight was identified as an important covariate describing the variability of clearance and volume of distribution, resulting in higher exposure (AUC and C_{max}) in lighter patients. However, this difference is not considered to be clinically relevant and no dose adjustments are recommended for any of these demographics.

Pediatric Population

Based on population pharmacokinetics (PK) analyses, the geometric mean lanadelumab-flyo average concentration at steady state (C_{ave}) was approximately 25% higher following subcutaneous administration of TAKHZYRO 300 mg q2wks in pediatric patients 12 to less than 18 years of age than the mean C_{ave} in adult patients under the same dosing regimen, due to lower body weight in pediatric patients. Lanadelumab-flyo exposures in pediatric patients 2 to less than 12 years of age receiving TAKHZYRO 150 mg q2wks or q4wks are comparable to those in adult patients receiving TAKHZYRO 300 mg q2wks. The geometric mean lanadelumab-flyo C_{ave} was approximately 7% higher following subcutaneous administration of TAKHZYRO 150 mg q2wks in pediatric patients 6 to less than 12 years of age compared to the mean C_{ave} in adult patients

receiving 300 mg q2wks. The mean lanadelumab-flyo C_{ave} was approximately 14% lower following subcutaneous administration of TAKHZYRO 150 mg q4wks in pediatric patients 2 to less than 6 years of age compared to the mean C_{ave} in adult patients receiving 300 mg q2wks.

Renal Impairment

No dedicated studies have been conducted to evaluate the PK of lanadelumab-flyo in renal impairment patients. Based on population pharmacokinetic analysis, renal impairment (estimated GFR: 60 to 89 mL/min/1.73m², [mild, N=98] and 30 to 59 mL/min/1.73m², [moderate, N=9]) had no effect on the clearance or volume of distribution of lanadelumab-flyo.

Concomitant medications

The use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on clearance and volume of distribution of lanadelumab-flyo.

For breakthrough HAE attacks, use of rescue medications such as plasma-derived and recombinant C1-INH, icatibant or ecallantide had no effects on clearance and volume of distribution of lanadelumab-flyo.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of lanadelumab-flyo or of other lanadelumab products.

In Trial 1 with adult and pediatric patients 12 years of age and older, 10 (12%) lanadelumab-flyo-treated and 2 (5%) placebo-treated patients had at least 1 anti-drug antibody (ADA)-positive sample during the 26-week treatment period; antibody titers were low (range: 20 to 1280). The ADA response observed was transient in 2/10 lanadelumab-flyo and 1/2 placebo-treated patients. Pre-existing low titer antibodies were observed in 3 lanadelumab-flyo-treated patients and 1 placebo-treated patient with ADAs. Two patients receiving 150 mg q4wks had low titer antibodies classified as neutralizing.

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

The development of ADA including neutralizing antibodies against lanadelumab-flyo did not appear to adversely affect pharmacokinetics (PK), pharmacodynamics (PD), safety or clinical response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of lanadelumab-flyo. Published literature supports bradykinin, which is elevated in HAE, as a pro-tumorigenic molecule. However, the malignancy risk in humans from an antibody that inhibits plasma kallikrein activity, such as lanadelumab-flyo, which lowers bradykinin levels, is currently unknown.

Male and female fertility were unaffected based upon no observed adverse histopathological findings in the reproductive organs from sexually mature cynomolgus monkeys that received lanadelumab-flyo for 13 weeks at subcutaneous doses up to 50 mg/kg/week (resulting in approximately 22 times the exposure at the MRHD on an AUC basis).

14 CLINICAL STUDIES

Trial 1 (NCT02586805)

The efficacy of TAKHZYRO for the prevention of angioedema attacks in patients 12 years of age and older with Type I or II HAE was demonstrated in a multicenter, randomized, double-blind, placebo-controlled parallel-group study (Trial 1).

The study included 125 adult and pediatric patients (12 years of age and older) with Type I or II HAE who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. Patients were randomized into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, lanadelumab-flyo 150 mg q4wks, lanadelumab-flyo 300 mg q4wks, or lanadelumab-flyo 300 mg q2wks by subcutaneous injection) for the 26-week treatment period. Patients ≥ 18 years of age were required to discontinue other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.

Overall, 90% of patients had Type I HAE. A history of laryngeal angioedema attacks was reported in 65% of patients and 56% were on prior long-term prophylaxis. During the study run-in period, attack rates of ≥ 3 attacks/month were observed in 52% of patients overall.

All TAKHZYRO treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate compared to placebo across all primary and secondary endpoints in the Intent-to-Treat population (ITT) as shown in **Table 3**.

Table 3 Results of Primary and Secondary Efficacy Measures-ITT Population

Endpoint Statistics	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		76 (61, 85)	73 (59, 82)	87 (76, 93)
Adjusted p-values ^d		<0.001	<0.001	<0.001
Number of HAE Attacks Requiring Acute Treatment from Day 0 to 182				
LS Mean (95% CI) monthly attack rate ^b	1.64 (1.34, 2.00)	0.31 (0.18, 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
% Reduction relative to placebo (95% CI) ^c		81 (66, 89)	74 (59, 84)	87 (75, 93)
Adjusted p-values ^d		<0.001	<0.001	<0.001

Endpoint Statistics	Placebo (N=41)	TAKHZYRO		
		150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)
Number of Moderate or Severe HAE Attacks from Day 0 to 182				
LS Mean (95% CI) monthly attack rate ^b	1.22 (0.97, 1.52)	0.36 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)
% Reduction relative to placebo (95% CI) ^c		70 (50, 83)	73 (54, 84)	83 (67, 92)
Adjusted p-values ^d		<0.001	<0.001	<0.001

CI=confidence interval; LS=least squares.

Note: 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 patient 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 the ratio of the model-based treatment period HAE attack rates (lanadelumab/placebo) minus 1 multiplied by 100.

^d Adjusted p-values for multiple testing.

The mean reduction in HAE attack rate was consistently higher across the TAKHZYRO treatment arms compared to placebo regardless of the baseline history of prior long-term prophylaxis, laryngeal attacks, or attack rate during the run-in period.

Additional pre-defined exploratory endpoints included the percentage of patients who were attack free for the entire 26-week treatment period and the percentage of patients achieving threshold ($\geq 50\%$, $\geq 70\%$, $\geq 90\%$) reductions in HAE attack rates compared to run-in during the 26-week treatment period. A $\geq 50\%$ reduction in HAE attack rate was observed in 100% of patients on 300 mg q2wks or q4wks and 89% on 150 mg q4wks compared to 32% of placebo patients. A $\geq 70\%$ reduction in HAE attack rates was observed in 89%, 76%, and 79% of patients on 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks, respectively, compared to 10% of placebo patients. A $\geq 90\%$ reduction in HAE attack rates was observed 67%, 55%, and 64% of patients on 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks, respectively, compared to 5% of placebo patients.

The percentage of attack-free patients for the entire 26-week treatment period was 44%, 31%, and 39% in the TAKHZYRO 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks groups respectively, compared to 2% of placebo patients.

Trial 2 (NCT02741596)

Patients who completed Trial 1 were eligible to rollover into an open-label extension study. Rollover patients, regardless of randomization group in Trial 1, received a single dose of TAKHZYRO 300 mg at study entry and were followed until the first HAE attack occurred. All efficacy endpoints were exploratory in this uncontrolled, unblinded study. At week 4 post-dose, approximately 80% of patients who had been in the 300 mg q2wks treatment group (N=25) in Trial 1 remained attack-free. After the first HAE attack, all patients received open-label treatment with TAKHZYRO 300 mg q2wks.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TAKHZYRO (lanadelumab-flyo) injection is a ready-to-use, clear to slightly opalescent, colorless to slightly yellow solution supplied in the following presentations.

Single-dose prefilled syringe

- Supplied in a carton containing one single-dose prefilled syringe with a bromobutyl rubber stopper, 27-gauge, ½-inch staked needle and rigid needle cap.
- NDC 47783-645-01: 150 mg/mL prefilled syringe
- NDC 47783-646-01: 300 mg/2 mL (150 mg/mL) prefilled syringe

Single-dose vial

- Supplied in a carton containing one single-dose glass vial with chlorobutyl rubber stopper, aluminum crimp seal and polypropylene flip-off cap.
- NDC 47783-644-01: 300 mg/2 mL (150 mg/mL) vial

Storage and Handling

- Store the prefilled syringes and vials refrigerated at 36°F to 46°F (2°C to 8°C).
- Do not freeze. Do not shake.
- Keep the prefilled syringe and vial in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [*see Warnings and Precautions (5.1)*].

Self-Administration:

- Ensure that the patient or caregiver receives clear instructions and training on subcutaneous administration and has demonstrated the ability to perform a subcutaneous injection.
- Instruct patients or caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct patients or caregivers to dispose needles and syringes in a puncture-resistant container.

For more information, visit www.TAKHZYRO.com

Manufactured by

Takeda Pharmaceuticals U.S.A., Inc.

Lexington, MA 02421

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PATIENT INFORMATION

TAKHZYRO® (tak-ZYE-roe)

(lanadelumab-flyo)

injection, for subcutaneous use

Read this Patient Information before you start using TAKHZYRO and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is TAKHZYRO?

TAKHZYRO is a prescription medicine used to prevent attacks of Hereditary Angioedema (HAE) in people 2 years of age and older.

It is not known if TAKHZYRO is safe and effective in children under 2 years of age.

Before you use TAKHZYRO, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or planning to become pregnant. It is not known if TAKHZYRO can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TAKHZYRO passes into your breastmilk. Talk to your healthcare provider about the best way to feed your baby while using TAKHZYRO.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

How should I use TAKHZYRO?

- See the detailed Instructions for Use that comes with this patient information leaflet about the right way to prepare and inject TAKHZYRO.
- Use TAKHZYRO exactly as your healthcare provider tells you to use it.
- TAKHZYRO is given as an injection under your skin (subcutaneous) by you or a caregiver.
- Your healthcare provider should show you or your caregiver how to prepare and inject your dose of TAKHZYRO before you inject yourself for the first time.
- **Do not** try to inject TAKHZYRO unless you have been trained by your healthcare provider.
- Self-injection is not recommended in children (2 to less than 12 years).

What are the possible side effects of TAKHZYRO?

TAKHZYRO may cause serious side effects, including allergic reactions. Allergic reactions may happen with TAKHZYRO. Call your healthcare provider or get emergency help right away if you have any of the following symptoms:

- | | |
|------------------------|-------------|
| • wheezing | • faintness |
| • difficulty breathing | • rash |
| • chest tightness | • hives |
| • fast heartbeat | |

The most common side effects of TAKHZYRO are:

- injection site reactions (pain, redness, and bruising)
- upper respiratory infections
- headache
- rash
- dizziness
- diarrhea
- muscle aches

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of TAKHZYRO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TAKHZYRO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TAKHZYRO for a condition for which it is not prescribed. Do not give TAKHZYRO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TAKHZYRO that is written for health professionals.

What are the ingredients in TAKHZYRO?

Active ingredient: lanadelumab

Inactive ingredients: citric acid monohydrate, L-histidine, sodium chloride, sodium phosphate dibasic dihydrate and water for injection.

Manufactured by:

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For more information, visit www.TAKHZYRO.com or call 1-877-TAKEDA-7 (1-877-825-3327).

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: 02/2023

INSTRUCTIONS FOR USE

TAKHZYRO® (tak-ZYE-roe)

(lanadelumab-flyo)

injection, for subcutaneous use
single-dose 1 mL prefilled syringe

This Instructions for Use contains information on how to inject TAKHZYRO. Please make sure to read, understand, and follow the Instructions for Use before injecting TAKHZYRO.

A healthcare provider should show you how to prepare and inject TAKHZYRO properly before you use it for the first time. Contact your healthcare provider if you have any questions.

Important information:

- TAKHZYRO is a ready to use prefilled syringe (**Figure A**) for injection under the skin (subcutaneous) to be given to children by their healthcare provider or caregiver. **Self-injection is not recommended in children (2 to less than 12 years of age).**
- Each TAKHZYRO prefilled syringe contains one 150 mg/1 mL dose. **The TAKHZYRO prefilled syringe is for single use only.**

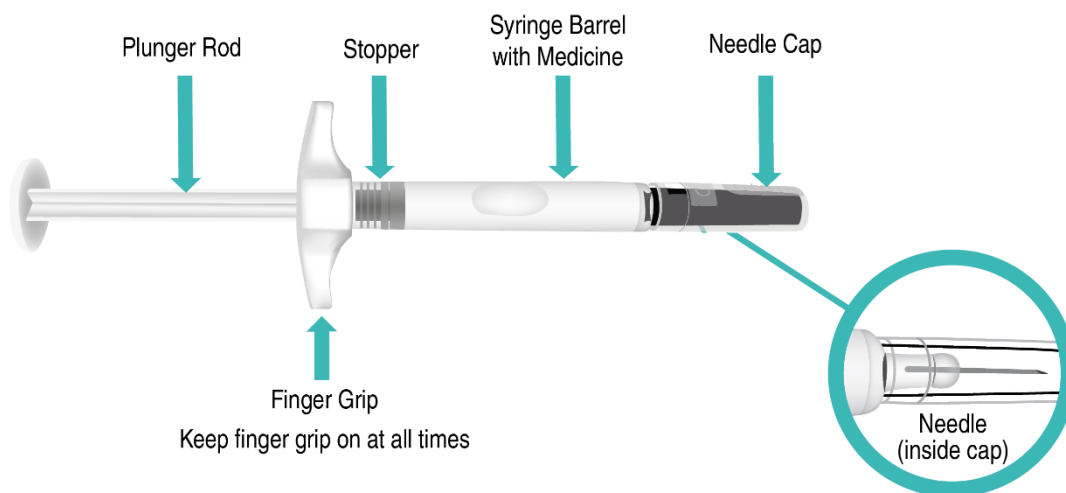


Figure A: TAKHZYRO prefilled syringe

Storing TAKHZYRO:

- Store the TAKHZYRO prefilled syringe in the refrigerator at 36°F to 46°F (2°C to 8°C).
Do not freeze.
- Store the TAKHZYRO prefilled syringe in the original carton to protect it from light.
- Throw away (discard) the TAKHZYRO prefilled syringe if it has been kept out of the refrigerator, frozen, or not kept in the original carton protected from light.
- **Do not** shake the TAKHZYRO prefilled syringe.

Keep the TAKHZYRO prefilled syringe and all medicines out of the reach of children.

Step 1: Prepare for your injection

- a. Gather an alcohol swab, cotton ball or gauze pad, adhesive bandage, and 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 carton.

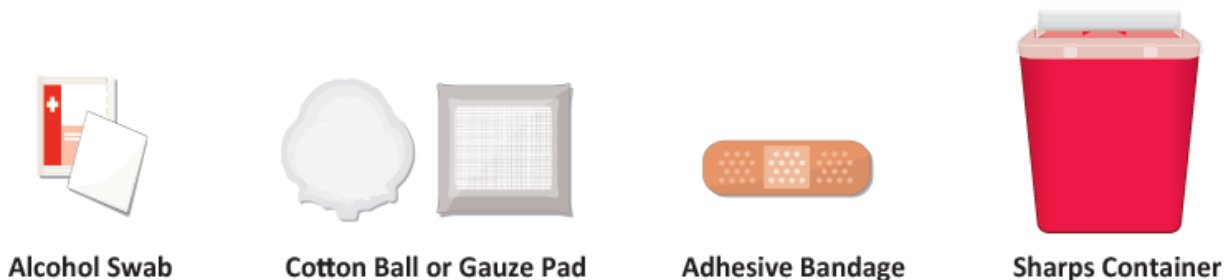


Figure B: Supplies

- b. Remove the TAKHZYRO prefilled syringe carton from the refrigerator 15 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 syringe.



- c. Open the carton. Hold the syringe barrel and remove the TAKHZYRO prefilled syringe from the tray (**Figure C**).
- **Do not** remove the needle cap until you are ready to inject.
 - **Do not** touch or push the plunger rod until you are ready to inject.

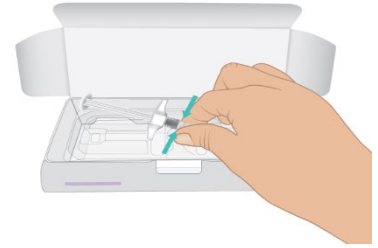


Figure C: Remove prefilled syringe

- d. 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 the injection.



Figure D: Wash hands

- e. **Check the expiration date (EXP)** on the syringe barrel (**Figure E**).
- **Do not** use the TAKHZYRO prefilled syringe if the expiration date has passed. If the TAKHZYRO prefilled syringe is expired throw it away (discard) in a sharps container and contact your healthcare provider.



Figure E: Location of expiration date

- f. **Inspect** the TAKHZYRO prefilled syringe for any damage. The medicine inside the syringe barrel should be colorless to slightly yellow (**Figure F**).
- **Do not** use the TAKHZYRO prefilled syringe if the syringe is damaged or cracked.
 - **Do not** use the TAKHZYRO prefilled syringe if the medicine is discolored, cloudy, or has flakes or particles in it.
 - You may see air bubbles in the TAKHZYRO prefilled syringe. This is normal and will not affect your dose.

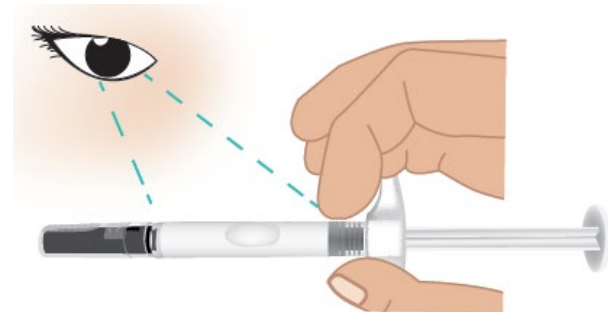


Figure F: Inspect the prefilled syringe

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

Step 2: Select and prepare injection site

- a. TAKHZYRO should be injected by a healthcare provider or caregiver into the following sites only (**Figure G**):
- stomach area (abdomen)
 - thighs
 - upper arms
- **Do not** inject into an area where the skin is irritated, red, bruised, or infected.
 - The area you choose for injection should be at least 2 inches away from any scars or belly button (navel).

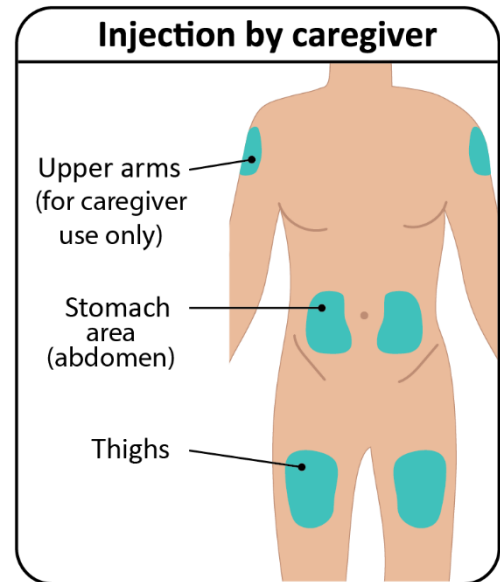


Figure G: Injection sites

Important:

Rotate injection sites to keep skin healthy. Each new injection should be given at least 1 inch from the last site you used.

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



Figure H: Clean injection site

- c. Firmly hold the middle of the TAKHZYRO prefilled syringe with one hand, and with the other hand, gently pull the needle cap straight off (**Figure I**).
- **Do not** touch or push the plunger rod until you are ready to inject.
 - **Do not** use the TAKHZYRO prefilled syringe if it has been dropped without the needle cap on.
 - **Do not** use the TAKHZYRO prefilled syringe if the needle looks damaged or bent.
 - **Do not** touch the needle or allow the needle to touch anything.

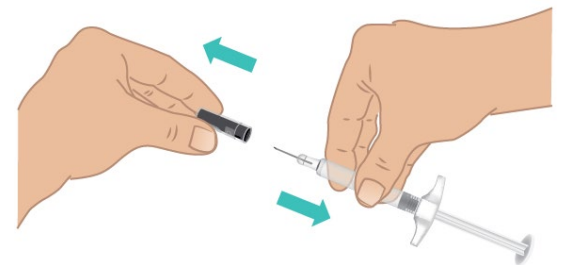


Figure I: Remove needle cap

You may see air bubbles, this is normal. **Do not** try to remove the air bubbles.

- d. Throw away the needle cap in your trash or in your sharps container.
 - **Do not** recap the needle to avoid a needle-stick injury.

Step 3: Inject TAKHZYRO

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



Figure J: Grip prefilled syringe

- b. With your other hand, gently pinch a 1-inch fold of skin at the cleaned injection site.
 - Keep pinching until the injection is complete and the needle is removed (**Figure K**).

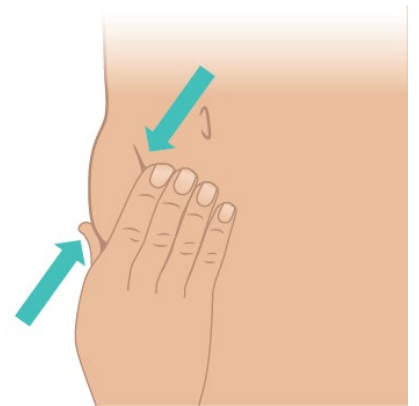


Figure K: Pinch a 1-inch fold of skin

- c. Using a quick dart-like motion, insert the needle at a 45-to-90-degree angle. Make sure to keep the needle in place (**Figure L**).

Important: Inject directly into the fatty layer under the skin (subcutaneous injection).

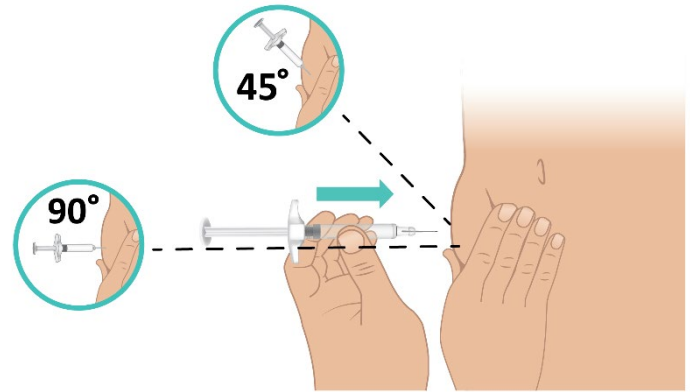


Figure L: Insert the needle

- d. Slowly push the plunger rod **all the way down until it stops** (**Figure M**).

Important: Do not remove the needle until all of the medicine is injected and the syringe barrel is empty.

When the injection is complete, you will see the stopper at the bottom of the syringe barrel (**Figure N**).

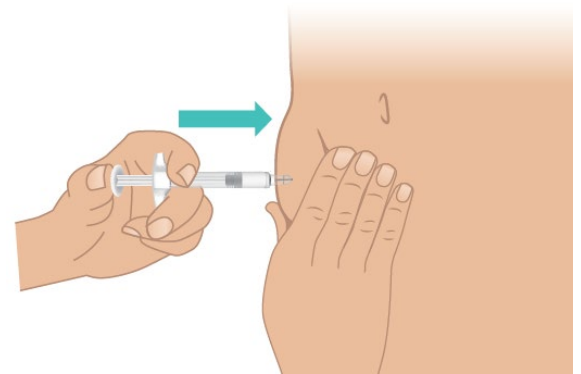


Figure M: Push the plunger rod all the way down

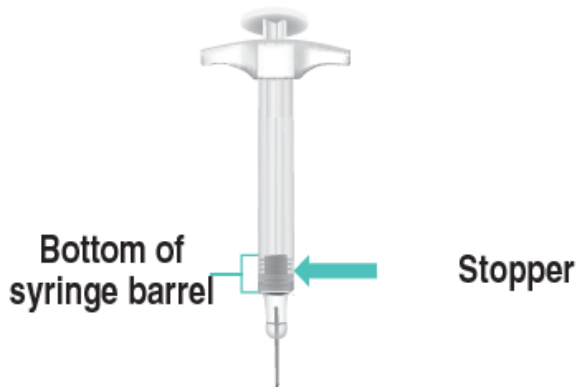


Figure N: Stopper at the bottom of the syringe barrel

- e. Slowly remove the needle while maintaining the syringe at the same angle. Gently release the fold of skin.
- f. Press a cotton ball or gauze pad over the injection site if needed and hold for 10 seconds.
- **Do not** rub the injection site. There may be a small amount of blood where you injected. This is normal.
 - Cover the injection site with an adhesive bandage if needed.

Step 4: Throw away (dispose of) TAKHZYRO prefilled syringe

- a. Put your used TAKHZYRO prefilled syringe in a sharps disposal container right away after use (**Figure O**).
 - **Do not** recap the needle to avoid a needle-stick injury.
 - **Do not** reuse the TAKHZYRO prefilled syringe or any of your injection supplies.
 - **Do not** throw away (dispose of) the TAKHZYRO prefilled syringe in your household trash.
 - **Do not** touch the needle.



Figure O: Dispose in a sharps container

FDA-cleared sharps containers are generally available through pharmacies, medical supply companies, healthcare providers, and online.

- If you do not have an FDA-cleared sharps container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at:
<http://www.fda.gov/safesharpsdisposal>.
- **Important:** Always keep the sharps disposal container out of the reach of children.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Questions?

For product or service-related questions, call 1-877-TAKEDA-7 (1-877-825-3327) or go to www.TAKHZYRO.com.

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