ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TAKHZYRO 300 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 300 mg of lanadelumab* in 2 mL solution.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

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

Missed doses

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

Special populations

Elderly

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

Hepatic impairment

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

Renal impairment

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

Paediatric population

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

Method of administration

TAKHZYRO is intended for subcutaneous (SC) administration only.

Each TAKHZYRO vial is intended for single use only (see section 6.6).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity reactions

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

General

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

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

Interference with coagulation test

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

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly (52.4%) observed adverse reaction associated with TAKHZYRO was injection site reactions (ISR) including injection site pain, injection site erythema and injection site bruising. Of these ISRs, 97% were of mild intensity, 90% resolved within 1 day after onset with a median duration of 6 minutes.

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

Tabulated list of adverse reactions

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

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

Table 1: Adverse reactions reported with lanadelumab

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

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

Paediatric population

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

Immunogenicity

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

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

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

Clinical efficacy and safety

HELP study

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

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

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

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

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

Note: CI=confidence interval; LS=least squares.
[a] Results are from a Poisson regression model accounting for over dispersion with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the treatment period as an offset variable in the model.
[b] Model-based treatment period HAE attack rate (attacks/4 weeks).
[c] % reduction relative to placebo corresponds to 100% * (1-rate ratio). The rate ratio is ratio of the model-based treatment period HAE attack rates.
[d] Adjusted p-values for multiple testing.

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

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

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

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

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

Health related Quality of Life

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

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

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

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

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

HELP study extension

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

A total of 212 adult and adolescent subjects with symptomatic type I or II HAE received at least one dose of lanadelumab in this study, including 109 subjects who entered as rollover subjects from the HELP study and 103 new or non-rollover subjects (including 19 subjects from Phase1b study) who

had an historical baseline attack rate of ≥1 attack per 12 weeks Subjects were allowed to initiate self-administration after receiving the first 2 doses from a health care professional in clinic and completing appropriate training. Interim analysis indicates that the effect was sustained up to one year of treatment.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with TAKHZYRO in one or more subsets of the paediatric population in the prevention of hereditary angioedema attacks.

5.2 Pharmacokinetic properties

The single and multiple dose pharmacokinetics of lanadelumab have been studied in patients with HAE. Pharmacokinetics of lanadelumab showed linear dose-exposure response with doses up to 400 mg and reproducible exposure following subcutaneous administration up to 12 months. The absolute bioavailability of lanadelumab after subcutaneous administration has not been determined. In the HELP study, patients treated with 300 mg q2 wks presented mean (SD) area under the curve over the dosing interval at steady-state (AUCtau,ss), maximum concentration at steady-state (Cmax,ss) and minimum concentration at steady-state (Cmin,ss) of 408 µg*day/ml (138), 34.4 µg/mL (11.2), and 25.4 µg/mL (9.18), respectively. The anticipated time to reach steady state concentration was approximately 70 days.

Absorption

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

Distribution

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

Elimination

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

Special populations

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

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

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

Renal and hepatic impairment

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

Accordingly, in a population pharmacokinetic analysis, renal impairment (estimated GFR: 60 to 89 ml/min/1.73 m^2 [mild, N=98] and 30 to 59 ml/min/1.73m^2 [moderate, N=9]) had no effect on the clearance or volume of distribution of lanadelumab.

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

Vials may be stored below 25°C for a single period of 14 days, but not beyond the expiry date. Do not return TAKHZYRO to refrigerated storage after storage at room temperature.

6.5 Nature and contents of container

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

Each pack also contains the following items:

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

6.6 Special precautions for disposal and other handling

Lanadelumab is provided in single use vials.

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

Avoid vigorous agitation.

Administration steps

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

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

Discard the vial with any unused contents.

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

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

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Blocks 2 & 3 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
Ireland
Tel: +44(0)1256 894 959
E-mail: medinfoEMEA@shire.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1340/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
Rentschler Biopharma SE
Erwin-Rentschler-Strasse 21
D-88471 Laupheim
GERMANY

Name and address of the manufacturer(s) responsible for batch release

Shire Pharmaceuticals Ireland Limited
Blocks 2 and 3 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
IRELAND

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAKHZYRO 300 mg solution for injection
lanadelumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg lanadelumab.

3. LIST OF EXCIPIENTS

Disodium phosphate, dihydrate
Citric acid monohydrate
Histidine
Sodium chloride
Polysorbate 80
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial of 2 ml

This pack also contains:
3 ml syringe
18 gauge access needle
Injection needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Blocks 2 & 3 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
IRELAND
Tel: +44(0)1256 894 959
E-mail: medinfoEMEA@shire.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1340/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TAKHZYRO 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TAKHZYRO 300 mg solution for injection
lanadelumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

TAKHZYRO 300 mg solution for injection

lanadelumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TAKHZYRO is and what it is used for

TAKHZYRO contains the active substance lanadelumab.

What TAKHZYRO is used for

TAKHZYRO is a medicine used in adults, and adolescents aged 12 years and older to prevent angioedema attacks, in patients with HAE.

What hereditary angioedema (HAE) is

HAE is a condition which runs in families. With this condition your blood does not have enough of a protein called ‘C1 inhibitor’, or C1 inhibitor does not work properly. This leads to too much ‘plasma kallikrein’, which in turn produces higher levels of ‘bradykinin’ in your bloodstream. Too much bradykinin leads to symptoms of HAE like swelling and pain on the,

- hands and feet
- face, eyelids, lips or tongue
- voice-box (larynx), which may make breathing difficult
- genitals

How TAKHZYRO works

TAKHZYRO is a type of protein that blocks the activity of plasma kallikrein. This helps to reduce the amount of bradykinin in your bloodstream and prevents symptoms of HAE.

2. What you need to know before you use TAKHZYRO

Do not use TAKHZYRO:

If you are allergic to lanadelumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Talk to your doctor, pharmacist or nurse before using TAKHZYRO.
- If you have a severe allergic reaction to TAKHZYRO with symptoms such as a rash, a tight chest, wheezing, or a fast heart beat, tell your doctor, pharmacist or nurse **immediately.**

Keeping a record

It is strongly recommended that every time you have a dose of TAKHZYRO, you write down the name and batch number of the medicine. This is so that you keep a record of the batches used.

Laboratory tests

Tell your doctor if you are using TAKHZYRO before you have laboratory tests to measure how well your blood is clotting. This is because TAKHZYRO in the blood may interfere with some laboratory tests, leading to inaccurate results

Children and adolescents

TAKHZYRO is not recommended for use in children under 12 years of age. This is because it has not been studied in this age group.

Other medicines and TAKHZYRO

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

TAKHZYRO is not known to affect other medicines or be affected by other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before starting to use Takhzryo. There is limited information on the safety of TAKHZYRO use during pregnancy and breast-feeding. As a precautionary measure, it is preferable to avoid the use of lanadelumab during pregnancy and breast-feeding. Your doctor will discuss with you the risks and benefits of taking this medicine.

Driving and using machines

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

TAKHZYRO contains sodium

The medicine contains less than 1 mmol sodium (23 mg) per ml of solution, that is to say essentially ‘sodium-free’.

3. How to use TAKHZYRO

TAKHZYRO is provided in single-use vials as ready-to-use solution. Your treatment will be started and managed under the supervision of a doctor experienced in the care of patients with HAE.

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure or have any further questions on the use of this medicine.

How much TAKHZYRO to use

The recommended starting dose is 300 mg every 2 weeks. If you have not had an attack for a long period, your doctor may change the dose to 300 mg every 4 weeks, especially if you have a low body weight.

How to inject TAKHZYRO

If you inject TAKHZYRO yourself or if your caregiver injects it, you or your caregiver must carefully read and follow the instructions in section 7, "Instructions for use".

- TAKHZYRO is for injection under the skin ('subcutaneous injection').
- The injection can be given either by yourself or a caregiver.
- A doctor, pharmacist or nurse should show you how to prepare and inject TAKHZYRO properly before you use it for the first time. Do not inject yourself or someone else until you have been trained to inject the medicine.
- Insert the needle into the fatty tissue in the tummy (abdomen), thigh or upper arm.
- Inject the medicine in a different place each time.
- Use each vial of TAKHZYRO only once.

If you use more TAKHZYRO than you should

Tell your doctor, pharmacist or nurse if you take too much TAKHZYRO.

If you forget to use TAKHZYRO

If you miss a dose of TAKHZYRO, inject your dose as soon as possible but there must be at least 10 days between each dose. If you are not sure when to inject TAKHZYRO after a missed dose, ask your doctor, pharmacist or nurse.

If you stop using TAKHZYRO

It is important that you keep injecting TAKHZYRO as instructed by your doctor even if you feel better.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you have a severe allergic reaction to TAKHZYRO with symptoms such as a rash, tight chest, wheezing, or a fast heart beat, tell your doctor, pharmacist or nurse **immediately.**

Tell your doctor, pharmacist or nurse if you notice any of the following side effects.

Very common (may affect more than 1 in 10 people):

- Reactions where the injection is given – symptoms include pain, skin redness, bruising, discomfort, swelling, bleeding, itching, hardening of skin, tingling, warmth and rash.

Common (may affect up to 1 in 10 people):

- Allergic reactions including itching, discomfort and tingling of the tongue
- Dizziness, feeling faint
- Raised skin rash
- Muscle pain
- Blood tests showing liver changes

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side affects you can help provide more information on the safety of this medicine.

5. How to store TAKHZYRO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Vials may be stored below 25°C for a single period of 14 days, but not beyond the expiry date.
Do not return TAKHZYRO to refrigerated storage after storage at room temperature.

Do not use this medicine if you notice signs of deterioration such as particles in the vial or changed colour of the injection solution.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TAKHZYRO contains

- The active substance is lanadelumab. Each vial contains 300 mg of lanadelumab in 2mL.
- The other ingredients are disodium phosphate dihydrate, citric acid monohydrate, histidine, sodium chloride, polysorbate 80 and water for injections – see section 2 "TAKHZYRO contains sodium"

What TAKHZYRO looks like and contents of the pack

TAKHZYRO is presented as a clear, colourless to slightly yellow solution for injection in a glass vial.

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

Each pack also contains the following items:

- Empty 3 ml syringe
- 18 gauge blunt tip vial access needle
- 27 gauge ½ inch (0.4 x 13 mm) pointed tip administration (injection) needle.

Marketing Authorisation Holder and Manufacturer

Shire Pharmaceuticals Ireland Limited
Blocks 2 & 3 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
IRELAND
Tel: +44(0)1256 894 959
E-mail: medinfoEMEA@shire.com

This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

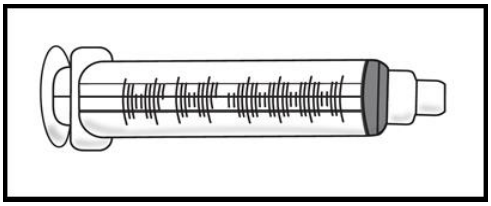
This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

7. Instructions for use

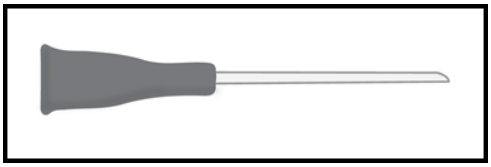
Be sure that you read, understand and follow the step-by-step instructions for injecting TAKHZYRO. Contact your doctor, pharmacist or nurse if you have any questions.

In addition to the vial, each TAKHZYRO pack also contains:

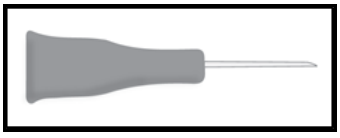
- One empty 3 ml syringe.



- One 18 gauge blunt tip vial access needle.
  Used to draw medicinal solution from the vial into the syringe.



- One 27 gauge ½-inch (0.4 x 13 mm) pointed tip injection needle.
  Used for injection under the skin (subcutaneous).



Only use the syringes, blunt-tip vial access needles and pointed-tip injection needles in this pack or which your doctor has prescribed.

Only use the syringes, blunt-tip vial access needles and pointed-tip injection needles one time. Place all used syringes and needles in the sharps container.

Do not use any syringes, blunt-tip vial access needles and pointed-tip injection needles that appear damaged.

You will also need:

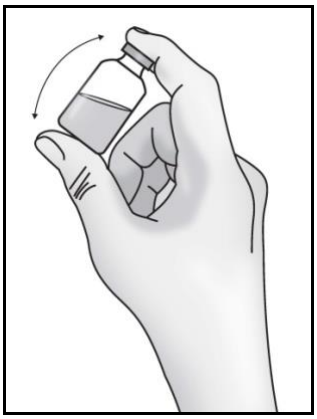
- Alcohol wipes
- A sharps container for used vials, needles and syringes

You can get supplies from your doctor, pharmacist or nurse.

The injection of TAKHZYRO can be summarised 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 injection needle**
4. **Select and prepare injection site**
5. **Inject TAKHZYRO**

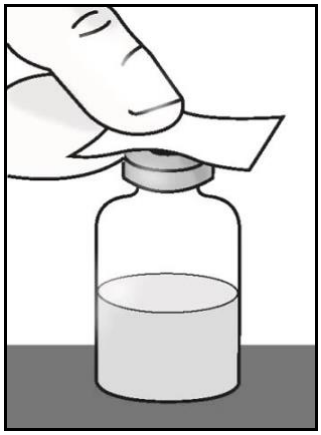
Step 1: Prepare the vial of TAKHZYRO



a) Take the vial out of the refrigerator 15 minutes before use to allow it to reach room temperature (15°C to 25°C) before preparing an injection.
b) Clean your work area and wash your hands before preparing your dose. Do not touch any surface or your body, especially your face, after washing your hands before injection.
c) Gather your TAKHZYRO and supplies and place them on your well-lit work surface.
d) Remove the vial from the packaging. Do not use the vial if the cap covering the stopper is missing.
e) **Gently invert the vial 3 to 5 times to ensure the solution is mixed. Do not shake the vial as this can cause foaming.**
f) Check the solution in the vial for particles or a change in the colour (normally it is colourless to slightly yellow). Do not use if you see particles or a change in colour.

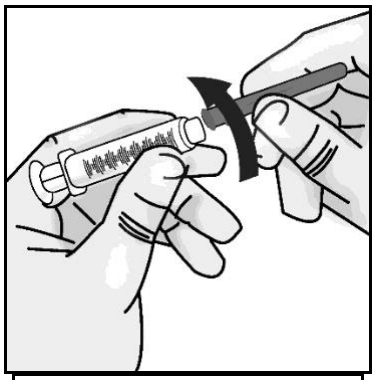
Important: Do not shake.

g) Remove the plastic cap from the vial. Do not remove the vial rubber stopper.



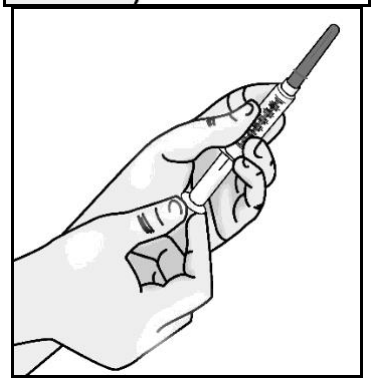
h) Place the vial on a flat surface. Clean the vial rubber stopper with an alcohol wipe and allow it to dry.

Step 2: Attach blunt tip vial access needle to syringe

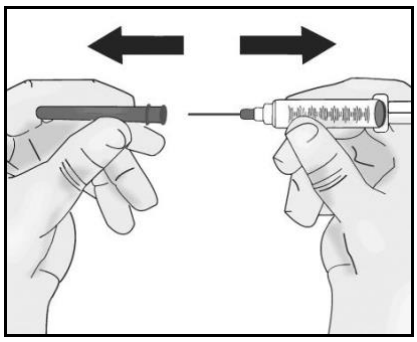


a) Screw the 18 gauge blunt tip vial access needle to the 3 ml syringe.

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

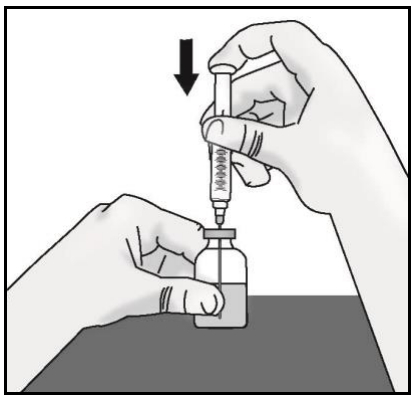


b) Pull back the plunger to fill the syringe with air equal to the amount of solution in the vial.

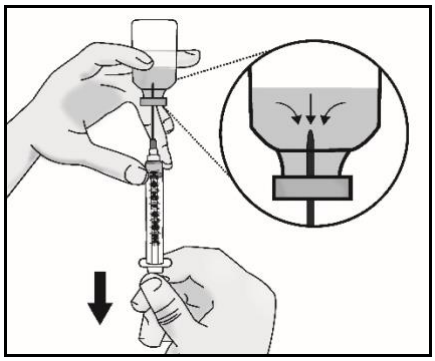


c) Pull off the needle cap straight away from the syringe without touching the needle. Do not pull on the plunger.

Step 3: Transfer TAKHZYRO into syringe and switch to the pointed-tip injection needle

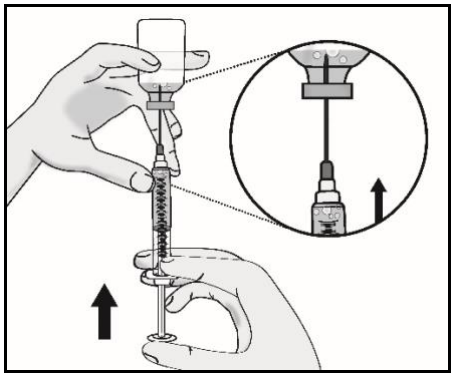


a) Insert the needle into the centre of the rubber stopper.
b) Push the plunger down to inject air into the vial and hold the plunger down.



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

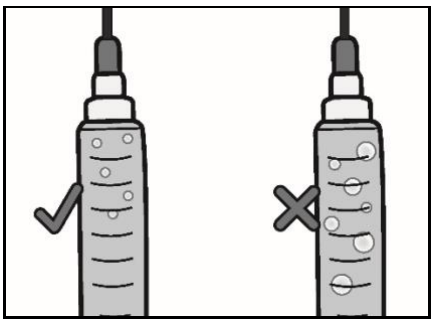
Important: Be sure to keep the tip of the needle in the liquid to avoid drawing air in as you pull back the plunger.



d) Remove large air bubbles by gently tapping on the syringe with your fingers until the bubbles rise to the top of the syringe.

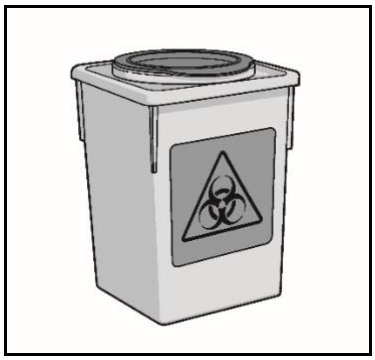
Slowly push the plunger, allowing air to go back into the vial, until the solution reaches the top of the syringe.

Repeat these steps until large air bubbles are removed.

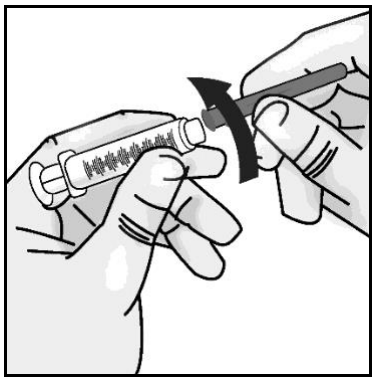


e) Without removing the needle from the vial, unscrew the syringe by holding the top of the needle and turning the syringe counter clockwise.

Return the syringe to an upright position.



f) Place the 18 gauge blunt-tip vial access needle and the vial in a sharps container.



g) Screw the 27 gauge ½-inch (0.4 x 13 mm) pointed-tip injection needle to the syringe.

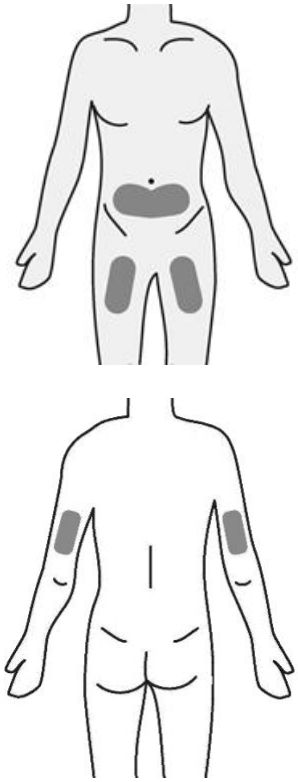
Important: Do not remove the needle cap from the needle when attaching to the syringe.

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

Step 4: Select and prepare injection site

a) Choose an injection site on your stomach (abdomen), thigh, or upper arm. The injection should be given subcutaneously.

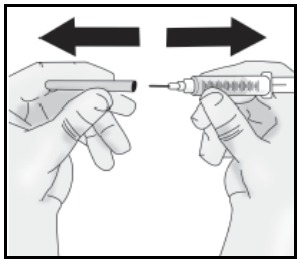
b) Clean your injection site with an alcohol wipe and allow the skin to dry completely.



Important:

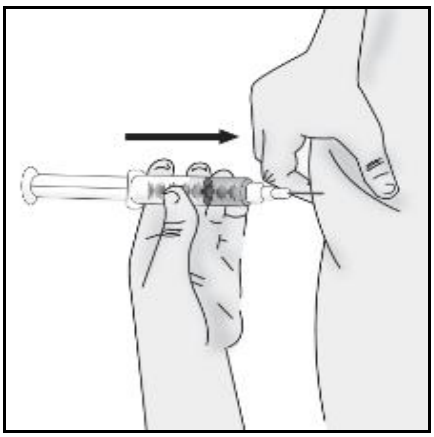
- It is important to use different injection sites to keep skin healthy.
- The area you choose for injection should be at least 5 cm away from any scars or your belly button (navel). Do not choose an area that is bruised, swollen, or painful.
- The outer area of the upper arm is not recommended if you are injecting yourself.

Step 5: Inject TAKHZYRO



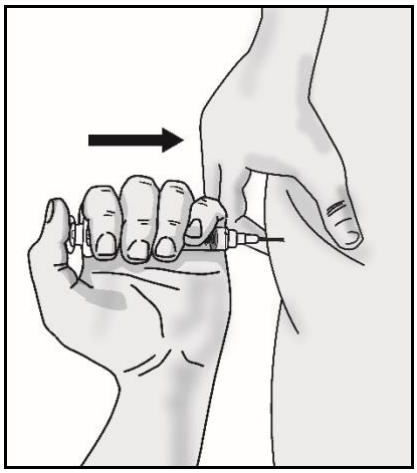
c) Pull off the needle cap straight from the syringe without touching the needle. Do not pull on the plunger. Do not touch the needle tip or allow it to touch any other surface.

Important: Inject TAKHZYRO within 2 hours of preparing the dosing syringe at room temperature. Alternatively, you can place the dosing syringe in a refrigerator at 2°C to 8°C and you must use it within 8 hours.

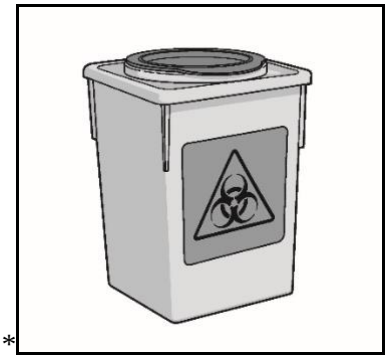


d) Gently pinch about 3 cm of skin at your cleaned injection site and insert the needle.

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



e) Push the plunger slowly until all the medicine has been injected. Release the skin fold and gently remove the needle. Do not recap the needle.



*

f) Place the 27 gauge ½-inch (0.4 x 13 mm) pointed-tip injection needle and the syringe in a sharps container.