SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TAKHZYRO 300 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One unit (pre-filled pen) 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 2 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

Adults and Adolescents 12 to less than 18 years of age

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

In patients with a body weight less than 40 kg, a starting dose of 150 mg lanadelumab every 2 weeks may also be considered. In patients who are stably attack free on treatment, a dose reduction to 150 mg lanadelumab every 4 weeks may be considered.

Children 2 to less than 12 years of age

The recommended dose of lanadelumab for children 2 to less than 12 years of age is based on body weight (see table below) and should only be administered via a pre-filled syringe or vial.

The pre-filled pen has not been studied in children 2 to less than 12 years of age and therefore should not be used.

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

Table 1. Recommended dose in children 2 to less than 12 years of age

Body Weight (kg)	**Recommended Starting Dose**	**Dose Adjustment**
10 to less than 20 kg	150 mg lanadelumab every 4 weeks	A dose increase to 150 mg lanadelumab every 3 weeks may be considered in patients with insufficient control of attacks
20 to less than 40 kg	150 mg lanadelumab every 2 weeks	A dose reduction to 150 mg lanadelumab every 4 weeks may be considered in patients who are stably attack free on treatment
40 kg or more	300 mg lanadelumab every 2 weeks	A dose reduction to 300 mg lanadelumab every 4 weeks may be considered in patients who are stably attack free on treatment

Consideration should be given to discontinuing treatment in patients with HAE with normal C1 esterase inhibitor (nC1-INH) who have shown insufficient reduction in attacks after 3 months of treatment (see section 4.4 and 5.1).

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 or caregiver should be instructed to administer the dose as soon as possible. The subsequent dosing schedule may need adjustment according to the intended dosing frequency to ensure:

- at least 10 days between doses for patients on every 2 weeks dosing regimen,
- at least 17 days between doses for patients on every 3 weeks dosing regimen,

- at least 24 days between doses for patients on every 4 weeks dosing regimen.

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 2 years have not been established. No data are available.

Method of administration

TAKHZYRO is intended for subcutaneous (SC) administration only.

Each TAKHZYRO pre-filled pen 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.

For adults and adolescents (12 to less than 18 years of age), TAKHZYRO may be self-administered or administered by a caregiver only after training on subcutaneous injection technique by a healthcare professional.

For children (2 to less than 12 years of age), TAKHZYRO should only be administered by a caregiver after training on subcutaneous 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 is limited clinical data on the use of lanadelumab in HAE patients with normal C1-INH (see section 5.1).
Patients with HAE nC1-INH having mutations that are not associated with the kallikrein-kinin system (KKS) pathway are not expected to respond to TAKHZYRO. It is recommended to perform genetic testing, if available, according to the current HAE guidelines and to discontinue the treatment if clinical response is not observed (see section 4.2 and 5.1).

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 pre-filled pen, 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 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 no or negligible influence on the ability to drive and 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 2 summarises adverse reactions observed in the HELP study that included 84 subjects with HAE, who received at least one dose of TAKHZYRO.

The frequency of adverse reactions listed in Table 2 is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10 000 to < 1/1,000); very rare (< 1/10 000).

Table 2: Adverse reactions reported with lanadelumab

System organ class	**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.

Safety data available from the HELP study extension are consistent with the safety data from the HELP study (described in Table 2).

Paediatric population

The safety of TAKHZYRO 300 mg/2 ml was evaluated in a subgroup of 23 subjects 12 to less than 18 years of age in the HELP and HELP study extension. In the SPRING study, safety of TAKHZYRO was also evaluated at 150 mg/1 ml in 21 subjects 2 to less than 12 years of age (see section 5.1). No subject below the age of 3.5 years was receiving lanadelumab in the study. No new adverse reactions were identified. Safety and tolerability results for paediatric subjects were consistent with overall study results for all subjects.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 proteolysis of high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, which is associated with inflammation and swelling in HAE attacks.

Pharmacodynamic effects

In adult and adolescent (12 to less than 18 years of age) patients, concentration-dependent inhibition of plasma kallikrein, measured as reduction of cHMWK levels, was demonstrated after subcutaneous administration of TAKHZYRO 150 mg every 4 weeks, 300 mg every 4 weeks or 300 mg every 2 weeks in subjects with HAE.

The pharmacokinetic-pharmacodynamic (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% and the TAKHZYRO concentration associated with the 50% inhibition(IC_{50}) was5705 ng/ml.

For children aged 2 to less than 6 years (150 mg every 4 weeks) and 6 to less than 12 years (150 mg every 2 weeks), the observed mean percent change from baseline in cHMWK levels was similar to that observed in adult and adolescent (12 to less than 18 years of age) patients.

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 randomised into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, lanadelumab 150 mg every 4 weeks [q4wks], lanadelumab 300 mg every 4 weeks [q4wks], or lanadelumab 300 mg every 2 weeks [q2wks] by subcutaneous 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 3).

Table 3. Results of primary and secondary efficacy measures-ITT population

Endpoint statistics[a]	**Placebo (N=41)**	**Lanadelumab**		
		150mg every 4 weeks (N=28)	**300 mg every 4 weeks (N=29)**	**300 mg every 2 weeks (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 4.

Table 4. Percentage of subjects who were attack free through treatment

Criteria	**Placebo**	**Lanadelumab**		
		150 mg every 4 weeks	**300 mg every 4 weeks**	**300 mg every 2 weeks**
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 every 2 weeks group, compared to 3% of patients in the placebo group.

100% of the subjects on 300 mg every 2 weeks or every 4 weeks and 89% on 150 mg every 4 weeks 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 5. 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 every 4 weeks, 300 mg every 4 weeks, and 300 mg every 2 weeks groups, respectively, compared to 37% of patients in the placebo group.

Table 5. 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, PK, and impact on health-related quality of life (HRQoL) of TAKHZYRO for prophylaxis to prevent HAE attacks were evaluated in an open-label uncontrolled HELP study extension.

A total of 212 adult and adolescent (≥ 12 years) subjects with symptomatic type I or II HAE received at least one dose of lanadelumab 300 mg every 2 weeks in this study, including 109 subjects who entered as rollover subjects from the HELP study. Rollover subjects, regardless of randomisation group in the HELP Study, received a single dose of lanadelumab 300 mg at study entry and did not receive additional treatment until the occurrence of an HAE attack. After the first HAE attack, all subjects received open-label treatment with lanadelumab 300 mg every 2 weeks. The study also included 103 new or non-rollover subjects (including 19 subjects from Phase1b study) who had a historical baseline attack rate of ≥1 attack per 12 weeks. The non-rollover subjects received lanadelumab 300 mg every 2 weeks at study entry.Subjects were allowed to initiate self-administration after receiving the first 2 doses from a health care professional in clinic and completing appropriate training.

The majority of subjects (173/212; 81.6%) who were treated in this study completed at least 30 months of treatment (either as a rollover or non-rollover subjects). The mean (SD) time in the HELP study extension was 29.6 (8.20) months. The majority of subjects self-administered lanadelumab (60.6% of 8,018 injections).

There was a sustained reduction in attack rates compared to baseline during the HELP study extension, with a similar response to TAKHZYRO observed in both rollover (92.4%) and non-rollover groups (82.0%) and an overall reduction rate of 87.4%. Though the magnitude of the attack rate reduction in the HELP study limited the potential for further reductions in the HELP extension study, mean attack rates for the rollover subjects decreased further at the time of the final analysis and ranged from 0.08 to 0.26 attacks per month. In addition, the mean (SD) percentage of attack-free days was 97.7 (6.0)% and the mean (SD) duration of the attack-free period was 415.0 (346.1) days. The proportion of patients with a maximum attack-free period of 6 months or more or 12 months or more was 81.8% and 68.9%, respectively.

CASPIAN study

The CASPIAN study was a multicenter, randomised, double-blind, placebo-controlled study in 77 adult subjects to evaluate the efficacy of lanadelumab in preventing acute attacks of non-histaminergic angioedema in subjects with normal C1-INH. Of the subjects enrolled, 5 (6.5%) were HAE nC1-INH subjects with known mutations (FXII, PLG), 13 (16.9%) were HAE nC1-INH subjects with a family history of angioedema but who did not have a known mutation, and 59 (76.6%) were subjects with idiopathic non-histaminergic angioedema who did not meet the clinical definition of HAE. No statistically significant treatment effect compared to placebo was observed in any subgroup.

Paediatric population

SPRING study

The safety and efficacy of TAKHZYRO for prophylaxis to prevent HAE attacks in children were evaluated in an open-label, multicenter, Phase 3 SPRING study. Dosing regimens were based on the following pre-defined age groups: children from 2 to less than 6 years of age were to receive lanadelumab 150 mg every 4 weeks and children from 6 to less than 12 years of age were to receive lanadelumab 150 mg every 2 weeks. The overall treatment period was 52 weeks, equally divided into Treatment Period A and B. The study enrolled 21 paediatric subjects who had a baseline attack rate of ≥ 1 attack per 3 months (12 weeks) and a confirmed diagnosis of type I or II HAE.

In Treatment Period A, subjects aged 2 to < 6 years (n=4) and 6 to < 12 years (n=17) received lanadelumab 150 mg every 4 weeks and 150 mg every 2 weeks, respectively. The youngest patient included in the study was 3.5 years old.

In Treatment Period B, subjects receiving lanadelumab 150 mg every 2 weeks (i.e., subjects 6 to less than 12 years of age) could reduce dosing to 150 mg every 4 weeks if they were well-controlled (e.g., attack free) for 26 weeks with lanadelumab treatment. Seven subjects in the 6 to less than 12 years age group switched to 150 mg every 4 weeks during Treatment Period B, and one subject (enrolled in the 2 to less than 6 years age group) turned 6 years of age during Treatment Period A and switched to 150 mg every 2 weeks during Treatment Period B after experiencing recurrent attacks.

The total exposure was 5.5 patient-years in the “every 4 weeks”- dosing regimen group (age range 3.5-10.4 years) and 14.47 patient-years in the “every 2 weeks”-dosing regimen group (age range 6-10.9 years).
The TAKHZYRO dose regimen in both age groups produced reduction in mean HAE attack rate compared to baseline and an increased percentage of attack-free subjects in Treatment Period A (Table 6). Similar results were observed for the overall, 52-week treatment period.

Table 6. Results of efficacy measures

Criteria		**TAKHZYRO**	
150 mg every 4 weeks[a]	**150 mg every 2 weeks[a]**		**Total**
Treatment Period A (26 weeks)			
N	4	17	21
Baseline attack	1.9 (1.0)	1.8 (1.6)	1.8 (1.5)

rate (attacks/month[b]), mean (SD)			
On-treatment attack rate (attacks/month[b]), mean (SD)	0.2 (0.3)	0.1 (0.2)	0.1 (0.2)
Attack-free subjects N (%)	3 (75.0)	14 (82.4)	17 (81.0)

a The actual treatment received during the given study period.
b Month is defined as 28 days. Attack rates at baseline and on-treatment were calculated over the 4-12-week observation period and the 26-week treatment Period A, respectively.

Immunogenicity

Anti-drug antibodies (ADA) were very commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

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 every 2 weeks 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 subcutaneous administration, the time to maximum concentration is approximately 5 days. The site of subcutaneous 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 or pregnant women.

Population pharmacokinetic analyses showed that age, gender and race did not meaningfully influence the pharmacokinetics of lanadelumab. Body weight was identified as an important covariate describing the variability of clearance and volume of distribution of lanadelumab.Paediatric population

Following subcutaneous administration of 150 mg every 4 weeks (2 to less than 6 years of age) and 150 mg every 2 weeks (6 to less than 12 years of age), the overall exposure (i.e.,$_{Cavg,ss}$) to lanadelumab was similar compared with adult and adolescent (12 to less than 18 years of age) patients who received TAKHZYRO 300 mg every 2 weeks (ratio to adults ranged from 0.8 to 1.11).

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 subcutaneous 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 every 2 weeks 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 subcutaneous 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 at300 mg every 2 weeks 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 every 2 weeks 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the solution (pre-filledpen) in the outer carton in order to protect from light.

The solution (pre-filled pen) 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.

When one pre-filled pen from a multi-pack is removed from refrigeration, return the remaining pre-filled pen to the refrigerator until future use when needed.

6.5 Nature and contents of container

2 ml of solution in pre-filled syringe with a bromobutyl stopper, 27G x 13 mm staked needle and rigid needle cap contained within a pre-filled pen. TAKHZYRO is available as unit packs containing 1 or 2 pre-filled pens and in multipacks containing 6 (3 packs of 2) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Lanadelumab is provided in single use pre-filled pens.

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

Avoid vigorous agitation.

Administration steps

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

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

Disposal

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

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

7 MARKETING AUTHORISATION HOLDER

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