PDL DRUG REVIEW

Proprietary Name: Takhzyro®
Common Name: lanadelumab-flyo
PDL Category: Hereditary Angioedema Agents

Comparable Products	Preferred Drug List Status
Haegarda	Preferred with Conditions

Summary

Pharmacology/Usage: Lanadelumab-flyo, the active ingredient of Takhzyro®, is a recombinant, human monoclonal antibody (IgG1/k-light chain) produced in Chinese Hamster Ovary (CHO) cells. It 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 hereditary angioedema (HAE). In patients with HAE due to C1-inhibitor 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.

Indication: For prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on 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, thus potential effects on a fetus are likely to be greater during the 3rd trimester of pregnancy. The safety and efficacy of use in the pediatric population <12 years of age have not been established.

Dosage Forms: Preservative-free solution in a single-dose glass vial: 300mg/2ml (150mg/ml) solution. Store vials in refrigerator.

Recommended Dosage: For subcutaneous administration only and intended for self-administration or administration by a caregiver after trained by a healthcare professional. Inject into the abdomen, thigh, or upper arm. Remove vials from the refrigerator 15 minutes before injection to allow to get to room temperature. Start at 300mg every 2 weeks. A dosing interval of 300mg every 4 weeks is also effective and may be considered if the patients is well-controlled (e.g. attack free) for more than 6 months.

Drug Interactions: No drug interaction studies have been performed. 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 start intrinsic coagulation through the activation of plasma kallikrein in the contact system. Inhibition of plasma kallikrein by Takhzyro® can increase aPTT in this assay. None of the increases in aPTT in patients treated

with Takhzyro® were associated with abnormal bleeding adverse events, and there were no differences in the INR values between treatment groups in clinical trials as compared with placebo.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Takhzyro®) minus reported % incidence for placebo Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included injection site reactions (18%), upper respiratory infection (0%), headache (0%), rash (2%), myalgia (5%), dizziness (6%), and diarrhea (0%). Injection site reactions mainly consisted of pain, erythema, and bruising at the injection site. Less common adverse reactions included hypersensitivity (1%), increased aspartate transaminase (2%), and increased alanine transaminase (2%).

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Dyax Corp.

Analysis: The safety and efficacy of Takhzyro® for the prevention of angioedema in patients 12 years of age and older with Type I or II HAE were assessed in a multicenter, randomized, double-blind, placebo-controlled study. This study included subjects (N=125) who experienced at least 1 investigator-confirmed attack per 4 weeks during the run-in period. Subjects were randomized into 1 of 4 treatment arms, stratified by baseline attack rate, for the 26 weeks treatment period, and included placebo, lanadelumab-flyo 150mg Q4W, lanadelumab-flyo 300mg Q4W, or lanadelumab-flyo 300mg Q2W. Adults ≥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% had Type I HAE and a history of laryngeal angioedema attacks was reported in 65% of patients. During the study run-in period, attack rates of ≥3 attacks/month were observed in 52% of patients overall.

The primary efficacy endpoint was the number of HAE attacks from day 0 to 182. Results suggested that all Takhzyro® treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate as compared to placebo for all primary and secondary endpoints assessed. Results can be seen in the table below, which was adapted from the prescribing information.

Outcome	Placebo (N=41)	Takhzyro®		
		150mg Q4W (N=28)	300mg Q4W (N=29)	300mg Q2W (N=27)
Number of HAE attacks from day 0 to 182				
Least Squares (LS) mean monthly attack rate	1.97	0.48	0.53	0.26
% Reduction relative to placebo		76	73	87
Adjusted p-values		<0.001	<0.001	<0.001
Number of HAE attacks requiring acute treatment from day 0 to 182				
LS mean monthly attack rate	1.64	0.31	0.42	0.21
% Reduction relative to placebo		81	74	87
Adjusted p-value		<0.001	<0.001	<0.001
Number of moderate or severe HAE attacks from day 0 to 182				
LS mean monthly attack rate	1.22	0.36	0.32	0.20
% Reduction relative to placebo		70	73	83

Outcome	Placebo (N=41)	Takhzyro®		
		150mg Q4W (N=28)	300mg Q4W (N=29)	300mg Q2W (N=27)
Adjusted p-value		<0.001	<0.001	<0.001

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. The % of attack-free patients for the entire 26-week treatment period was 44%, 31%, and 39% in the Takhzyro® 300mg Q2W, 300mg Q4W, and 150mg Q4W groups, respectively, as compared to 2% of placebo. A ≥50% reduction in HAE attack rate was seen in 100% of patients on 300mg Q2W or Q4W and 89% on 150mg Q4W as compared to 32% of placebo patients. A ≥70% reduction in HAE attack rates was seen in 89%, 76%, and 79% of patients on 300mg Q2W, 300mg Q4W, and 150mg Q4W, respectively, as compared with 10% placebo. A ≥90% reduction in HAE attack rates was seen in 67%, 55%, and 64% of patients on 300mg Q2W, 300mg Q4W, and 150mg Q4W, respectively, as compared to 5% of placebo.

Patients who completed trial 1 were eligible to enroll into an open-label uncontrolled extension study. Regardless of their randomization group in trial 1, all patients in the extension study received a single dose of Takhzyro® 300mg at study entry and were followed until the first HAE attack occurred. At week 4 post-dose, about 80% of patients who had been in the 300mg Q2W treatment group (N=25) in trial 1 remained attack-free.

Place in Therapy: Takhzyro® is a self-administered subcutaneous injection indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. As compared with placebo in a clinical trial, the mean number of HAE attacks was significantly reduced with Takhzyro® from day 0 to 182.

There is no evidence at this time to support that Takhzyro® is safer or more effective than the currently available, more cost-effective medication. It is therefore recommended that Takhzyro® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on the recommended preferred medication.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Takhzyro [package insert]. Lexington, MA: Dyax Corp; 2018.