Drug Monograph

Takhzyro® (Lanadelumab-flyo) injection / Plasma Kallikrein Inhibitor; Hereditary Angioedema

Drug/Drug Class:

Prepared for: MO HealthNet
Prepared by: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Takhzyro® is available as a sterile, preservative-free 300 mg/ 2 mL solution in a single-dose glass vial. Distributed by: Dyax Corp., Lexington, MA 02421
Summary of Findings:	Takhzyro® is the first monoclonal antibody that provides targeted inhibition of plasma kallikrein, an enzyme which is uncontrolled in people with hereditary angioedema, to help prevent attacks. Takhzyro® is indicated for prophylaxis to prevent attacks of HAE in patients 12 years and older. In a multicenter, randomized, double-blind, placebo-controlled parallel-group study, Takhzyro® reduced the number of monthly HAE attacks an average of 87% vs. placebo when administered at 300 mg every 2 weeks and 73% vs. placebo when administered at 300 mg every 4 weeks. The most commonly observed adverse reactions associated with Takhzyro® were injection site reactions, upper respiratory infection and headache.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Non-Preferred Agent ☐ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,3]

Hereditary angioedema (HAE) is a rare genetic condition that occurs in about 1 in 10,000 to 1 in 50,000 people. HAE is characterized by recurrent episodes of severe swelling (angioedema) that most commonly occur on the limbs, face, intestinal tract, and airway. Minor trauma or stress may trigger an attack, but swelling often occurs without a known trigger. Episodes involving the intestinal tract cause severe abdominal pain, nausea, and vomiting. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. Symptoms of HAE typically begin in childhood and worsen during puberty. On average, untreated individuals have an attack every 1 to 2 weeks, and most episodes last for about 3 to 4 days.

Dosage Form [1,4]

Takhzyro® is available as a sterile, preservative-free 300 mg/ 2 mL solution in a single-dose glass vial.

Manufacturer [1]

Distributed by: Dyax Corp., Lexington, MA 02421

Indication(s) [1]

Takhzyro® is indicated for prophylaxis to prevent attacks of HAE in patients 12 years and older.

Clinical Efficacy [1,4,5] (mechanism of action/pharmacology, comparative efficacy)

Takhzyro® is a fully human monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity. Resultant decreases in plasma kallikrein activity controls excess bradykinin generation in patients with HAE. Bradykinin is a potent vasodilator that increases vascular permeability resulting in the localized swelling, inflammation and pain associated with HAE.

Pharmacokinetics:

	Takhzyro®
Time to Peak	4.11 to 5.17 days
Volume of Distribution	14.1 to 16.6 L
Clearance	0.667 to 0.809 L/day
Half-life	14.2 to 15 days

Clinical Trials:

HELP (Hereditary Angioedema Long-term Prophylaxis) Study

STUDY DESIGN	Global, multicenter, randomized, double-blind placebo-controlled parallel group trial evaluating the efficacy and safety of subcutaneously administered Takhzyro® versus placebo over 26 weeks (N=125).
INCLUSION CRITERIA	Males and females 12 years of age or older at time of screening. Documented diagnosis of HAE, Type I or II. Baseline rate of at least 1 HAE attack per 4 weeks.
EXCLUSION CRITERIA	Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema, idiopathic angioedema, or recurrent angioedema associated with urticaria. Treatment with any other investigational drug or exposure to an investigational device within 4 weeks prior screening. Exposure to angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications within 4 weeks prior to screening. Exposure to androgens within 2 weeks prior to entering the run-in period. Use of long-term prophylactic therapy for HAE within 2 weeks prior to entering the run-in period. Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period (Note: Although patient's ≥18 years of age were required to discontinue other prophylactic HAE medications prior to entering the study; all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks). Any of the following liver function test abnormalities: alanine aminotransferase (ALT) > 3x upper limit of normal, or aspartate aminotransferase (AST) > 3x upper limit of normal, or total bilirubin > 2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome). Pregnancy or breastfeeding.
TREATMENT REGIMEN	Patients were randomized into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, Takhzyro® 150 mg every 4 weeks, Takhzyro® 300 mg every 4 weeks, or Takhzyro® 300 mg every 2 weeks by subcutaneous injection) for the 26-week treatment period.
RESULTS	The primary endpoint was the number of HAE attacks over the entire 26-week study duration. Takhzyro® reduced the mean monthly number of attacks across all three treatment arms studied (Adjusted P<0.001 for all comparisons). • Takhzyro® 300 mg every 2 weeks reduced the number of mean monthly HAE attacks by 87% vs. placebo. • Takhzyro® 150 mg every 4 weeks reduced the number of mean

	monthly HAE attacks by 76% vs. placebo. • Takhzyro® 300 mg every 4 weeks reduced the number of mean monthly HAE attacks by 73% vs. placebo. Secondary endpoints included: the number of attacks requiring acute treatment and the number of attacks assessed as moderate or severe. Overall, each Takhzyro® treatment arm demonstrated statistically significant attack rate reductions compared with placebo for all secondary efficacy endpoints (Adjusted P<0.001 for all comparisons). • Takhzyro® reduced the number of mean HAE attacks requiring acute treatment by 87%, 81%, and 74% vs. placebo for the 300 mg every 2 weeks,150 mg every 4 weeks and 300 mg every 4 weeks groups, respectively. • Takhzyro® reduced the number of mean HAE attacks assessed as moderate or severe by 83%, 73%, and 70% vs. placebo for the 300 mg every 2 weeks,300 mg every 4 weeks and 150 mg every 4 weeks groups, respectively.
SAFETY	The most frequent adverse events occurring in >10% of patients taking Takhzyro® were injection site reactions, followed by upper respiratory infection, and headache. No anaphylaxis reactions were observed.

Contraindications (1)

- There are no contraindications listed per the manufacturer labeling.

Warnings and Precautions (1,4)

- Hypersensitivity reactions have been reported. In case of a severe hypersensitivity reaction, discontinue therapy and institute appropriate treatment.

Adverse Effects (1)

Most common, ≥ 1%	Placebo (N=41)	Takhzyro®		
		300 mg q4wks (N=29)	300 mg q2wks (N=27)	Total (N=84)
Injection site reactions	34%	45%	56%	52%
Upper respiratory infection	32%	31%	44%	29%
Headache	22%	21%	33%	21%
Rash	5%	10%	4%	7%
Myalgia	0	0	11%	5%
Dizziness	0	10%	4%	6%
Diarrhea	5%	0	4%	5%

Drug Interactions [4]

- There are no known significant drug interactions.

Dosage and Administration [1,4]

Dosage: Initial: 300 mg subcutaneously every 2 weeks; dosing every 4 weeks may be considered in well-controlled patients (attack free) for more than 6 months.

Administration: Takhzyro® is intended for subcutaneous injection only into the abdomen, thigh, or upper arm. Remove Takhzyro® vial from refrigerator 15 minutes before injection to allow it to reach room temperature. Before preparing dose, gently invert vial 3 to 5 times to mix; do not shake. Use an 18-gauge transfer needle to withdraw dose and a 27-gauge, ½-inch needle or other needle suitable for subcutaneous injection to administer dose. Rotate injection sites; injection site should be ≥2 inches (5 cm) away from any scars or navel. Do not inject in an area that is bruised, swollen, or painful. Takhzyro® should be administered within 2 hours of preparing the dosing syringe. After the dosing syringe is prepared, it can be refrigerated at 36ºF to 46ºF (2°C to 8°C) and must be used within 8 hours. Discard any unused portions of drug remaining in the vial and syringe.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ vial
Lanadelumab-flyo	Takhzyro®	Dyax	300 mg/ 2 mL	$22,070

** Wholesale Acquisition Cost

Conclusion

Takhzyro® is the first and only monoclonal antibody that provides targeted inhibition of plasma kallikrein to help prevent attacks of HAE in patients 12 years and older. Data from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 125 patients with HAE demonstrated that patients who received Takhzyro® had clinically meaningful and statistically significant reductions in the rate of HAE attacks compared to placebo over a 6-month treatment period. The most commonly observed adverse reactions associated with Takhzyro® were injection site reactions, upper respiratory infection, and headache.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1) Product Information: Takhzyro® (lanadelumab-flyo). Dyax Corp., Lexington, MA 02421
2) HAE Disease. US Hereditary Angioedema Association. https://www.haea.org/HAEdisease.php. Accessed October 17, 2018.
3) Hereditary angioedema - Genetics Home Reference – NIH. U.S. National Library of Medicine. https://ghr.nlm.nih.gov/condition/hereditary-angioedema. Accessed October 17, 2018.
4) Lanadelumab-flyo: Drug Information (Lexicomp) Wolters Kluwer Health.

5) Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02586805. Accessed October 18, 2018.

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