Takhzyro (lanadelumab)
Policy Number: C15446-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
1/2019	6/17/2020	6/17/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J0593-Inj, lanadelumab-flyo, 1 mg (code may be used for medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered)	**RxPA**	**Q3 2020 20200722C15446-A**

PRODUCTS AFFECTED:
Takhzyro (lanadelumab-flyo)

DRUG CLASS:
Plasma Kallikrein Inhibitors- monoclonal antibodies

ROUTE OF ADMINISTRATION:
Subcutaneous, self-administered

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and member self-administered

AVAILABLE DOSAGE FORMS:
NDC: 47783-0644-01, 300 mg/2 ml vial

FDA-APPROVED USES:
Prophylaxis to prevent attacks of hereditary angioedema (HAE) in members 12 years and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
ICD-10 Diagnosis: D84.1 Defects in the complement system

REQUIRED MEDICAL INFORMATION:
A. PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (HAE):
1. Documentation of HAE diagnosis and subtype confirmed by ONE of the following:

(a) TYPE 1 OR 2 HAE; Presence of a mutation in the C1-INH gene altering protein synthesis and/or function
OR
(b) BOTH of the following: (documentation of TWO (2) separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):
(i) Low serum complement factor 4 (C4) level (< 14 mg/dL)
AND
(ii)Low C1 inhibitor (C1-INH) level (C1-INH < 19.9 mg/dL), OR Low C1-INH functional level (functional C1-INH < 72%)
AND

2. All other causes and potentially treatable triggers of HAE attacks (i.e. stress, trauma, infection, etc.) have been identified and optimally managed
3. Documentation of baseline record of the following aspects of HAE attacks: Severity, Duration and functional abilities in order to evaluate efficacy during re-authorization
AND
4. Concurrent therapies that may exacerbate HAE, have been evaluated and has been discontinued as appropriate, including: Estrogen-containing medications [e.g. hormone replacement therapy, contraceptives], ACE-inhibitor (ACEI), Angiotensin II receptor blockers
AND
5. Member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks (i.e. Haegarda, and Cinryze)
AND
6. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred/formulary alternatives for the given diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

B. HAE WITH NORMAL C1 INHIBITOR LEVELS (PREVIOUSLY CALLED TYPE III HAE):

1. Documented diagnosis HAE with normal C1 inhibitor levels as evidenced by normal C4 level and normal C1-INH levels AND any of the following: (i) Episodic angioedema affecting characteristic organs, without urticaria, (ii) a documented family history of angioedema, (iii) presence of a FXII (or possibly an angiopoietin-1 or plasminogen mutation) associated with the disease
AND
2. Documentation of baseline record of the following aspects of HAE attacks: Severity, duration and functional abilities in order to evaluate efficacy during re-authorization
AND
3. Member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks (i.e. Haegarda, and Cinryze)
AND
4. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred/formulary alternatives for the given diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s)

DURATION OF APPROVAL:
Initial authorization: 9 months, continuing authorization: 12 months

QUANTITY:
2 VIALS (4ml) per 28-day supply- If attack free for 6 months- 1 vial (2ml) per 28 days

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified allergist, immunologist, hematologist or dermatologist.

AGE RESTRICTIONS:

12 years of age and older

CONTINUATION OF THERAPY:

A. PREVENTION OF HAE ATTACKS:

1. Documentation of frequency and severity of attacks since starting Takhzyrotherapy
   AND
2. (a) If ZERO attacks have occurred within 6 months since starting Takhzyro therapy, documentation of member evaluation for extended dosing interval of 300mg every 4 weeks
   OR (b) If documentation provided show member is not attack free- must demonstrate improvement from baseline in severity, duration or frequency of attacks
   AND
3. Documentation that medication will be used for prophylaxis- not for acutetreatment
   AND
4. Takhzyro will not be used in combination with other approved treatments to PREVENT HAE attacks (i.e. Haegarda,Cinryze,)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Takhzyro (lanadelumab-flyo) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy.

OTHER SPECIAL CONSIDERATIONS:

Takhzyro is distributed by a limited network of 5 specialty pharmacies: Accredo, Briova, CVS Caremark, Option Care, Orsini.

The efficacy of Takhzyro for the prevention of angioedema attacks in members 12 years of age and older with Type I or II HAE was demonstrated in a multicenter, randomized, double-blind, placebo-controlled parallel- group study. The study included 125 adult and adolescent members with HAE who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. Members were randomized into 1 of 4 parallel treatment arms for the 26-week treatment period. All Takhzyro treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate compared to placebo across all primary and secondary endpoints in the intent-to- treat (ITT) population. An open-label, long-term safety and efficacy study is ongoing and expected to complete in November 2019. The HELP study also collected exploratory endpoints that included the percentage of members who were attack free for the entire 26-week treatment period. The percentage of attack-free members for the entire 26-week treatment period is listed in the chart above. The attack-free rate was used to determine whether and how members could step down in dosing frequency. For members on the 300 mg every 2 weeks, the attack-free rate increased to 77% when measured from days 70-182 on treatment. The lower attack-free rate seen in the first 6 months was likely due to the long half-life of Takhzyro and that members did not reach steady state until around 70 days. There have been no head-to-head comparisons among any of the products for HAE. According to the individual product prescribing information, the reduction in monthly attack rate versus placebo of all three products remain comparable

THERAPIES FOR HEREDITARY ANGIOEDEMA

	FDA INDICATION	DOSE	MECHANISM OF ACTION	AGE INDICATIONS
Berinert® C1 esterase inhibitor (human)	ACUTE TREATMENT	20 units/kg IV	C1-inhibitor [human]	5 AND OLDER
Ruconest® C1-inhibitor (recombinant)	ACUTE TREATMENT	50 units/kg IV (max. 4,200 units)	C1-inhibitor [recombinant]	13 AND OLDER
Kalbitor® ecallantide	ACUTE TREATMENT	30 mg SC (as three 10 mg/ml injections)	Plasma kallikrein inhibitor	12 AND OLDER
Firazyr® Icatibant acetate	ACUTE TREATMENT	30 mg SC	Bradykinin receptor antagonist	18 AND OLDER
Cinryze® C1 esterase inhibitor (human)	PROPHYLAXIS	1,000 units via IV route every 3-4 days	C1-inhibitor [human]	6 AND OLDER
Haegarda® C1 esterase inhibitor (human)	PROPHYLAXIS	60 units/kg SC every 3-4 days	C1-inhibitor [human]	12 AND OLDER
Takhzyro® lanadelumab	PROPHYLAXIS	300 mg SC every 2 weeks	Plasma kallikrein inhibitor	12 AND OLDER

BACKGROUND:

Hereditary Angioedema (HAE)

A rare genetic disorder of recurrent attacks of localized subcutaneous or mucosal swelling that affects 1 in 10,000 to 1 in 50,000 individuals in the United States. Attack frequency varies from a few days to decades between attacks and severity ranges from mild to more severe laryngeal edema causing airway obstruction and fatal asphyxiation. Formal diagnosis is often significantly delayed following onset of symptoms and misdiagnosis or medical mismanagement is not uncommon. The two most common forms of HAE (Types I and II) may be managed with prophylaxis or acute treatment depending on attack frequency, severity, and drug tolerability.

HAE-1/2 is a rare autosomal dominant condition affecting an estimated 1 in 50,000 individuals, although this may vary in different regions. HAE-1/2 is caused by one of more than 450 different mutations in the SERPING1 gene, which codes for C1-INH [40]. In approximately 20–25% of patients, a de novo mutation of SERPING1 is responsible for the disease. C1-INH is a serine protease inhibitor (SERPIN) and the major inhibitor of several complement proteases (C1r, C1s, and mannose-binding lectin–associated serine protease [MASP] 1 and 2) and contact-system proteases (plasma kallikrein and coagulation factor XIIa) as well as a relatively minor inhibitor of the fibrinolytic protease plasmin.

The primary mediator of swelling in HAE-1/2 is bradykinin [28]. Bradykinin is a low molecular weight nonapeptide, which is generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Bradykinin is rapidly metabolized by endogenous metalloproteases including

angiotensin-converting enzyme (ACE). Plasma kallikrein is activated from its inactive zymogen prekallikrein
by the protease factor XII, which can easily autoactivate upon contact with negatively charged surfaces. Both, plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability induced by the liberation of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor.

HAE with normal C1 inhibitor

HAE with normal C1-INH (HAE nC1-INH) is a very rare disease. Its clinical appearance largely resembles that of HAE-1/2. In a subgroup of patients, HAE nC1-INH is associated with mutations of the factor XII (FXII-HAE) gene. Recently, two new mutations in - (ANGPT1) and plasminogen (PLG) were reported in HAE nC1-INH. However, in most patients with HAE nC1-INH, no
gene mutation can be found, and the pathogenesis remains to be characterized in detail. However, there is clinical evidence that bradykinin may play a major role in some types of HAE nC1-INH, primarily in patients with a FXII-mutation [52–54]. Although HAE nC1-INH shares some clinical features and, possibly, therapeutic options with HAE-1/2, this guideline is for HAE-1/2.

C1-Inh Deficiency	Inherited	HAE-1 hereditary angioedema due to C1-Inhibitor deficiency, HAE-2 hereditary angioedema due to C1-Inhibitor dysfunction
	Acquired	AAE-C1-INH acquired angioedema due to C1-Inhibitor deficiency
C1 Inh- Normal	Inherited	HAE nC1-INH hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII, ANGPTI, PLG or unknown (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-UNK),
	Acquired	ACEI-AE angiotensin converting enzyme inhibitor-induced angioedema

APPENDIX:

None

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, member records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

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