Neurokinin Receptor Antagonists Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
1/1/2024	1/1/2024

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
VEOZAH™ (fezolinetant) Tablet	Treatment of moderate to severe vasomotor symptoms due to menopause		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Vasomotor Symptoms	Menopause is the final stage of the ovarian physiology in patients and represents a time when reproductive function is lost due to complete depletion of finite ovarian follicle supply.(2) It is defined as 12 months of amenorrhea and occurs at a median age of 51.3 years in the United States.(1,3) While the fundamental process of menopause is related directly to ovarian aging, all aspects of the hypothalamic-pituitary-ovarian-uterine axis are altered with time.(2) Estrogen withdrawal during the menopause transition (MT) is associated with alterations in the hypothalamic thermoregulatory neutral zone, a group of neurons that regulate body temperature. Normally inhibited by estrogen, this group of hypothalamic neurons, known collectively as KNDy neurons for the co-expression of kisspeptin, neurokinin B (NKB), and dynorphin, are overstimulated during the MT and can lead to dysregulation of body temperature. These changes lead to an increased frequency of bodily reaction to both internal and environmental triggers that prevent heat loss. Vasomotor symptoms (VMS), also known as hot flashes, are known as the hallmark manifestations of the MT which include feelings of flushing, warmth sensation, skin reddening, and perspiration.(2,3) Symptoms of menopause are most prevalent and severe during the first 1 to 2 years after the final menstrual period (FMP). Some patients will experience bothersome symptoms for more than a decade. VMS affect as many as 80% of midlife patients. Moderate to severe VMS (i.e., 7 or more episodes per day or 50-60 episodes per week) affects 32% to 46% percent of patients undergoing menopause. Data show that patients who experience frequent VMS (greater than 6 days in the previous 2 weeks) also experience higher rates of anxiety, depression, difficulty sleeping and overall impaired quality of life.(1,2,3,5) Frequent VMS persisted on average 7.4 years in the Study of Women's Health Across the Nation and appear to be linked to cardiovascular, bone, and cognitive risks.(6)

	Hormone therapy (HT) remains the gold standard, most effective treatment for relief of VMS and has been shown to prevent bone loss and fracture.(3,6) Patients with significant sleep or mood disturbance during the MT may also benefit from HT. HT reduces symptom frequency by 75% and symptom severity by 90%, usually within one month of initiation.(3,6) In the Women's Health Initiative (WHI), patients with VMS experienced an 85% reduction in symptoms after treatment with estrogen plus progesterone.(2) For patients 60 years of age or younger who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is favorable for hormone treatment of bothersome VMS. HT are considered safe and effective in low-risk patients without underlying coronary heart disease or history of breast cancer. Generally well tolerated, the most common acute adverse effects of HT are breast pain and uterine bleeding. HT has been shown to improve glycemic control and insulin resistance in patients with and without type 2 diabetes, as well as other cardiovascular disease risk factors such as lipid profile. For patients more than 10 years /from menopause onset or 60 years or older who initiate hormone therapy, the benefit-risk ration appears less favorable because of greater absolute risks of CHD, stroke, VTE, and dementia.(2,3,6) Estrogen regimens are available as estrogen-only, combined with progestin, or combined with a serum estrogen receptor modulator (SERM).(2) Systemic estrogens can be prescribed as oral drugs; transdermal patches, sprays and gels; or as vaginal rings. Meta-analysis of estrogen preparations found no evidence of a significant difference between transdermal and oral preparations for alleviating VMS. Estrogen-alone therapy (ET) can be used for symptomatic patients without a uterus and estrogen plus progesterone therapy (EPT) or tissue-selective estrogen complex (TSEC) for patients with a uterus to protect against endometrial neoplasia.(6) Vaginal formulations do not require progestin as these have not been shown to induce endometrial proliferation.(2) Nonhormone options are important considerations for patients who are not good candidates for HT.(7) Paroxetine 7.5 mg was the first nonhormonal pharmaceutical FDA approved for the treatment of moderate to severe VMS, with improvements found in VMS severity and frequency for up to 24 months, along with improvements in sleep disruption, without weight gain or negative effects on libido. Other nonhormone medications that are recommended to reduce VMS include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, oxybutynin. Paroxetine, escitalopram, citalopram, venlafaxine, and desvenlafaxine have been shown to significantly reduce VMS in large, double-blind, randomized, controlled trials (RCTs) of symptomatic patients. Trends towards improvement have been seen with sertraline and fluoxetine but were statistically insignificant, therefore, not recommended. Duloxetine has been found to reduce VMS in smaller studies. Hot flash reductions vary from 25% to 69% with these treatments, with improvement in composite hot flash severity and frequency from 27 to 61%. A pooled analysis from three RCTs showed that 10 mg to 20 mg of escitalopram, 0.5 mg of oral 17-beta-estradiol, and 75 mg of venlafaxine daily resulted in comparable reductions of VMS frequency. Gabapentin, an antiepileptic drug, has shown that it has improved the frequency and severity of VMS in several trial studying the dose of 900 mg/day. Gabapentin at higher doses (titrated to 2,400 mg/d) has been shown to be as beneficial as estrogen (conjugated equine estrogens 0.625 mg/d) in reducing hot flash scores. Oxybutynin, an antimuscarinic, anticholinergic therapy, demonstrated in one prospective study and two randomized double-blind studies in postmenopausal patients, that doses ranging from 2.5 mg or 5 mg twice daily up to 15 mg extended-release daily, significantly improved moderate to severe VMS.(7)
Safety(1)	VEOZAH is a neurokinin 3 (NK3) receptor antagonist that blocked the neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center. Elevations in serum transaminase levels greater than three times the upper limit of normal (ULN) occurred in 2.3% of women receiving VEOZAH. Labeling recommends baseline bloodwork be evaluated for hepatic function and injury prior to VEOZAH initiation. If baseline hepatic transaminase evaluation is less than two times the ULN and the total bilirubin is normal, VEOZAH can be initiated. Follow up evaluations of hepatic transaminase concentrations are

	recommended at 3, 6, and 9 months after initiation or when symptoms suggest liver injury.(1) VEOZAH is contraindicated in women with any of the following indications: • Known cirrhosis • Severe renal impairment or end-stage renal disease • Concomitant use with CYP1A2 inhibitors

REFERENCES

Number	Reference
1	VEOZAH prescribing information. Astellas Pharma US LLC. May 2023.
2	Santoro N, et al. The Menopause Transition: Signs, Symptoms, and Management Options. *The Journal of Clinical Endocrinology & Metabolism*, Jan 2021; 106(1): 1-15. https://doi.org/10.1210/clinem/dgaa764
3	Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. *Int J Womens Health*. 2023 Feb 14;15:273-287. doi:10.2147/IJWH.S365808.
4	Avis NE, Crawford SL, Greendale G, et al. Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. *JAMA Intern Med*. 2015;175(4):531–539. doi:10.1001/jamainternmed.2014.8063.
5	Beaudoin FL, et al. Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Effectiveness and Value; Final Evidence Report. Institute for Clinical and Economic Review, January 23, 2023. https://icer.org/assessment/vasomotor-symptoms-menopause-2022/#overview
6	The 2022 hormone therapy position statement of The North American Menopause Society. (2022). *Menopause,* 29(7), 767–794. DOI: 10.1097/GME.0000000000002028.
7	The 2023 nonhormone therapy position statement of The North American Menopause Society. (2023). *Menopause*, 30(6), 573-590. DOI: 10.1097/GME.0000000000002200.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Veozah	fezolinetant tab	45 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Veozah	fezolinetant tab	45 MG	30	Tablet	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Veozah	fezolinetant tab	45 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Target Agent(s) will be approved when BOTH of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

   1. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
   2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

   B. The patient has a diagnosis of vasomotor symptoms AND ALL of the following:
      1. The patient is menopausal **AND**
      2. The patient's symptoms are moderate to severe (i.e., 7 or more episodes per day or 50-60 episodes per week) **AND**
      3. Baseline (prior to starting the requested agent) hepatic function (i.e., ALT, AST, serum bilirubin [total and direct]) has been evaluated **AND**
      4. Hepatic transaminases are less than two times the upper limit of normal (ULN) and the total bilirubin is normal **AND**
      5. ONE of the following:
         A. The patient's medication history includes the use of ONE menopausal hormone therapy (i.e., estrogen therapy [ET] or estrogen plus progesterone therapy [EPT] including oral, transdermal patches, sprays and gels, and vaginal ring agents) as indicated by:
            1. Evidence of a paid claim(s) **OR**
            2. The prescriber has stated that the patient has tried ONE menopausal hormone therapy (i.e., estrogen therapy [ET] or estrogen plus progesterone therapy [EPT] including oral, transdermal patches, sprays and gels, and vaginal ring agents) AND the menopausal hormone therapy was discontinued due to lack of effectiveness or an adverse event **OR**

Module	Clinical Criteria for Approval
	B. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** C. The prescriber has provided documentation that ALL menopausal hormone therapies (i.e., estrogen therapy [ET] or estrogen plus progesterone therapy [EPT] including oral, transdermal patches, sprays and gels, and vaginal ring agents) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **OR** D. The patient is over 60 years of age or onset of menopause was greater than or equal to 10 years prior **AND** 6. ONE of the following: A. The patient's medication history includes the use of ONE nonhormonal therapy used to treat vasomotor symptoms of menopause (i.e., paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, duloxetine, gabapentin, oxybutynin) as indicated by: 1. Evidence of a paid claim(s) **OR** 2. The prescriber has stated that the patient has tried ONE nonhormonal therapy used to treat vasomotor symptoms of menopause (i.e., paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, duloxetine, gabapentin, oxybutynin) AND the nonhormonal therapy was discontinued due to lack of effectiveness or an adverse event **OR** B. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** C. The prescriber has provided documentation that ALL nonhormonal therapies used to treat vasomotor symptoms of menopause (i.e., paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, duloxetine, gabapentin, oxybutynin) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **OR** C. The patient has another FDA approved indication for the requested agent and route of administration **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit (e.g., reduction in vasomotor symptoms and/or severity) with the requested agent **AND** 3. BOTH of the following: A. Hepatic function (i.e., ALT, AST, serum bilirubin [total and direct]) has been evaluated since starting the requested agent **AND** B. Hepatic transaminases are less than two times the upper limit of normal (ULN) and the total bilirubin is normal **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of approval:** 3 months for Initial; 12 months for Renewal