Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, icatibant (Firazyr), Kalbitor, Ruconest, Takhzyro, Andembry, Dawnzera	**MP-RX-FP-36-23**	☒ **MMM MA** ☒ **MMM MultiHealth**	**11/30/2023** **Last Review Date:** **7/1/2026**	**7/1/2026** **Frequently Revision:** **Annual**

Service Category:

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Other: Part B Drugs

Service Description:

This document addresses the use of drugs for the treatment or prevention of hereditary angioedema (HAE) attacks. The agents are listed in the following table:

C1 Esterase Inhibitor	Bradykinin B2 receptor antagonists	Plasma kallikrein inhibitor	Activated Factor XIIa inhibitor	Prekallikrein-directed antisense oligonucleotide
Haegarda (C1 Esterase Inhibitor, Human)	Firazyr (icatibant)	Kalbitor (ecallantide)	Andembry (garadacimab-gxii)	Dawnzera (donidalorsen)
Berinert (C1 Esterase Inhibitor, Human)	Sajazir (icatibant acetate)^	Takhzyro (lanadelumab-flyo)		
Cinryze (C1 Esterase Inhibitor, Human)		Orladeyo (berotralstat)*		
Ruconest (C1 Esterase Inhibitor, Recombinant)		Ekterly (sebetralstat)*		

* Orladeyo (berotralstat) and Ekterly (sebetralstat) are oral hereditary angioedema agents and are not addressed in this Part B medical policy. For clinical criteria, refer to the applicable pharmacy benefit/Part D clinical criteria, when available.

^ Sajazir (icatibant acetate) is a subcutaneous injection intended for self-administration; therefore, it is not addressed in this Part B medical policy because it is managed under the pharmacy benefit/Part D criteria, as applicable.

Background Information:

Hereditary Angioedema (HAE) is a chronic autosomal dominant disorder associated with recurrent, unpredictable, and potentially life-threatening acute attacks. There are three known types of HAE with types I and II being most common. Types I and II are associated with mutations to C1-INH. C1-INH deficiency results in an overproduction of bradykinin which is a vasodilator thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Mutations that cause type I HAE lead to reduced levels of C1-INH. A serum C4 level is a useful screening test for HAE-C1INH. A normal C4 during an angioedema episode excludes the diagnosis of HAE-C1INH. HAE with normal C1-INH (HAE-nl-C1INH), previously referred to as Type III HAE, is extremely rare and occurs primarily in women. Treatments for HAE-nl-C1INH are not well established (Busse P, et al 2020).

The signs and symptoms associated with acute HAE attacks include intense and painful swelling of the face, larynx, gastrointestinal (GI) tract, limbs, or genitalia. Episodic attacks of HAE produce edema in three primary

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areas: periphery, abdomen, and larynx. Peripheral attacks are associated with painful disfigurement and physical disability; abdominal attacks result in severe abdominal pain, nausea, and vomiting; and laryngeal attacks may result in death by asphyxiation. An individual with HAE may be sensitive to multiple triggers related to HAE attacks, and it is often difficult or impossible to identify all of the triggers for a particular individual with HAE.

In the United States, plasma-derived C1-INH is a first-line long-term prophylactic agent for HAE-C1-INH without the need to have failed or experienced side effects from other medications such as androgens or antifibrinolytics (Maurer M, et al 2018). In some other countries, plasma-derived C1-INH may be restricted to patients who have had adverse effects to androgens or antifibrinolytics, were not adequately controlled on these agents, or who do not wish to take these agents.

Takhzyro (lanadelumab) is approved as the first monoclonal antibody for the prevention of angioedema attacks in patients 2 years and older. Takhzyro is a fully human monoclonal antibody that binds and inhibits plasma kallikrein. The strength and dosing intervals are dependent on patient age. In those 6 years of age or older, a dosing interval of every 4 weeks can be effective and may be considered if the individual is well-controlled (e.g. attack free) for more than 6 months. The recommended dosage in those 2 years of age or older but less than 6 years old is 150 mg every 4 weeks.

Orladeyo (berotralstat) for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 2 years and older. This is the first FDA-approved, orally administered, non-steroidal treatment for HAE prophylaxis. Berotralstat is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. An increase in QT prolongation can occur at dosages higher than the recommended 150 mg once-daily dosage. Additional doses or doses of Orladeyo higher than 150 mg once daily are not recommended.

Haegarda carries the same warnings and precautions as Cinryze and Berinert related to severe hypersensitivity, thromboembolic events, and potential transmission of infectious agents.

Kalbitor has a black box warning for the risk of anaphylaxis and must be administered by a healthcare professional for management.

Ruconest is contraindicated in those with a known or suspected allergy to rabbits and rabbit-derived products. Ruconest also carries warning and precautions for severe hypersensitivity and thromboembolic events. Ruconest is an intravenous therapy for acute attacks in adults and adolescents with HAE but lacks established effectiveness to treat individuals with laryngeal attacks.

Andembry (garadacimab-gxii) is a human recombinant monoclonal antibody that inhibitors Factor XIIa, which in turn, acts on both the complement and kallikrein-kinin pathways. Blocking the activation of these pathways ultimately results in inhibiting bradykinin formation. Andembry is a subcutaneous injection that is intended for self-administration or administration by a caregiver. The recommended dosing is an initial loading dose of 400 mg (two injections of 200 mg) administered subcutaneously on the first day of treatment followed by a maintenance dosage of 200 mg monthly thereafter. Andembry can prolong coagulation tests (aPTT and PT). However, none of the increases in aPTT, PT and INR were associated with bleeding events during the VANGUARD trial.

Dawnzera (donidalorsen) is an antisense oligonucleotide which selectively binds to prekallikrein messenger RNA which leads to its degradation via ribonuclease H1. This mechanism reduces the production of protein that is the

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precursor to the kallikrein-kinin cascade. Dawnzera is a subcutaneous injection that was studied in individuals 12 years of age and older who had confirmed hereditary angioedema type I or type II in the OASIS-HAE trial. Dawnzera reduced the monthly HAE attack rate by 81% (mean difference of -1.82 attacks per month) in those administering Dawnzera every 4 weeks. Dawnzera was also studied using an 8 week dosing frequency, which can be considered for some individuals. However, the efficacy decreases when using this 8 week dosing frequency. Dawnzera is not recommended for individuals with moderate or severe hepatic impairment.

Firazyr (icatibant) is a bradykinin B2 receptor antagonist indicated for the treatment of acute attacks of HAE in adults 18 years of age and older. It is supplied as a single-dose, prefilled syringe for subcutaneous administration and may be self-administered after training by a healthcare professional. Sajazir (icatibant acetate) is also an icatibant subcutaneous injection indicated for the treatment of acute HAE attacks in adults 18 years of age and older; however, Sajazir is not addressed in this Part B medical policy because it is managed under the pharmacy benefit/Part D criteria, as applicable.

Approved Indications

The following table presents the FDA indication of commercially available C1 Esterase Inhibitor:

Agent	Prophylaxis or Treatment	Indication	Route of Administration	Safety
Cinryze (C1 Esterase Inhibitor, Human)	Prophylaxis	Routine prophylaxis against HAE attacks in adolescent (≥ 6 years) and adult pts	Intravenous infusion	- Risk of serious anaphylactic reactions -Serious arterial and venous Thromboembolic events -Made from human plasma and may contain infectious agents
Haegarda (C1 Esterase Inhibitor, Human)	Prophylaxis	Routine prophylaxis against HAE attacks (≥ 6 years)	Subcutaneous	
Berinert (C1 Esterase Inhibitor, Human)	Treatment	Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric pts (≥5 years)	Intravenous infusion	
Firazyr and Sajazir (icatibant)	Treatment	Treatment of acute attacks of HAE in adults pts (≥ 18 years)	Subcutaneous	-Laryngeal attacks
Kalbitor (ecallantide)	Treatment	Treatment of acute attacks of HAE in adult and pediatric pts (≥12 years)	Subcutaneous	-Black box warning: Risk of serious anaphylactic reactions
Ruconest (C1 Esterase Inhibitor, Recombinant)	Treatment	Treatment of acute attacks of HAE in adult and adolescent pts (≥13 years) Note: Effectiveness not established in pts with laryngeal attacks	Intravenous infusion	-Risk of serious Anaphylactic reactions -Serious arterial and venous thromboembolic events

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Takhzyro (lanadelumab-flyo)	Prophylaxis	Routine prophylaxis against HAE attacks in adult and pediatric patients (≥2 years)	Subcutaneous	-Adverse events were mild to moderate, mainly injection-site reactions
Orladeyo (berotralstat)	Prophylaxis	Routine prophylaxis against HAE attacks in adult and pediatric patients (≥12 years)	Oral	-QT prolongation can occur in those taking more than one capsule per day
Andembry (garadacimab-gxii)	Prophylaxis	Routine prophylaxis against HAE attacks in adult and pediatric patients (≥12 years)	Subcutaneous	-Adverse events were injectionsite reactions, nasopharyngitis, abdominal pain
Ekterly (sebetralstat)	Acute Treatment	Treatment of acute attacks of HAE in adult and pediatric patients (≥12 years)	Oral	-Avoid use in: Strong CYP3A4 inhibitors; moderate to strong CYP3A4 inducers; severe hepatic impairment.
Dawnzera (donidalorsen)	Prophylaxis	Routine prophylaxis against HAE attacks in adult and pediatric patients (≥12 years)	Subcutaneous	-Avoid use in those with moderate or severe hepatic impairment.

Other Uses

A. None.

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Medical Necessity Guidelines:

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

B vs D Criteria: *Takhzyro included in this PA is subject to B vs D evaluation. Medication must be furnished "incident to" physician service provided and usually not self-administered to be covered by Medicare and to be eligible to be evaluated through part B. If not, medication must be evaluated through part D.*

Hereditary Angioedema Agents for Prophylaxis of Acute Attacks: Cinryze, Haegarda, Takhzyro, Andembry, Dawnzera

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Initial requests for Cinryze or Haegarda (C1 esterase inhibitor [human]), Takhzyro (lanadelumab-flyo), Andembry (garadacimab-gxii), or Dawnzera (donidalorsen) may be approved if the following criteria are met:

i. Individual has a diagnosis of hereditary angioedema; **AND**

ii. Individual is using for prophylaxis against acute attacks of hereditary angioedema for either of the following:
   - A. Short-term prophylaxis prior to surgery, dental procedures or intubation; **OR**
   - B. Long-term prophylaxis to minimize the frequency and/or severity of recurrent attacks;

AND

iii. Individual is of appropriate age for the specific drug requested:
   - A. 6 years of age or older for Cinryze or Haegarda; **OR**
   - B. 2 years of age or older for Takhzyro; **OR**
   - C. 12 years of age or older for Andembry or Dawnzera;

AND

iv. Documentation is provided that diagnosis is confirmed by a C4 level below the lower limit of normal as defined by laboratory test AND any of the following:
   - A. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by lab test; **OR**
   - B. C1-INH functional level below the lower limit of normal as defined by lab test; **OR**
   - C. Presence of a known HAE-causing C1-INH mutation;

AND

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v. Individual has a history of moderate or severe attacks such as airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, or painful facial distortion.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of therapy with Cinryze, Haegarda, Takhzyro, Andembry, or Dawnzera when requested for an indication listed above (Section A) if the following criteria are met:

A. Documentation is provided confirming that the individual has had a positive clinical response, defined as a clinically significant reduction (e.g., 50% or more) in the number and/or frequency of HAE attacks, including a reduction in the use of medications to treat acute attacks since starting treatment; **AND**

B. If the patient has been well controlled on therapy, a less frequent administration is prescribed or has been considered.

C. Authorization Duration

i. Initial Approval Duration:
   A. Cinryze, Haegarda, Andembry, Dawnzera: 6 months
   B. Takhzyro: 8 months

ii. Reauthorization Approval Duration:
   A. Cinryze, Haegarda, Takhzyro, Andembry, Dawnzera: 1 year

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

Requests for Cinryze (C1 esterase inhibitor [human]), Haegarda (C1 esterase inhibitor [human]), Takhzyro (lanadelumab-flyo), or Andembry (garadacimab-gxii) may not be approved for the following:

i. In combination with other HAE agents for prophylaxis of acute attacks (including but not limited to Cinryze, Haegarda, Takhzyro, Andembry, or Dawnzera);
ii. When the above criteria are not met and for all other indications.

Requests for Dawnzera (donidalorsen) may not be approved for the following:

i. Individual has moderate or severe hepatic impairment (defined by NCI-ODWG Criteria: total bilirubin greater than 1.5 times the upper limit of normal regardless of AST level); **OR**
ii. In combination with other HAE agents for prophylaxis of acute attacks (including but not limited to Cinryze, Haegarda, Orladeyo, Takhzyro, or Andembry); **OR**
iii. When the above criteria are not met and for all other indications.

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Hereditary Angioedema (HAE) Agents for Treatment of Acute Attacks: Berinert (C1 esterase inhibitor [human]), Icatibant (Firazyr), Ruconest (C1 esterase inhibitor [recombinant]), or Kalbitor (ecallantide)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Requests for Berinert (C1 esterase inhibitor [human]), Icatibant (Firazyr), Ruconest (C1 esterase inhibitor [recombinant]), or Kalbitor (ecallantide), may be approved if the following criteria are met:

i. Individual has a diagnosis hereditary angioedema; **AND**
ii. Individual is using for the treatment of acute attacks (not prophylaxis); **AND**
iii. Individual is of appropriate age for the specific drug requested:
   A. 5 years and older for Berinert; **OR**
   B. 13 years and older for Ruconest; **OR**
   C. 18 years and older for Icatibant (Firazyr); **OR**
   D. 12 years and older for Kalbitor;

AND

iv. Documentation is provided that diagnosis is confirmed by a C4 level below the lower limit of normal as defined by laboratory testing AND one of the following:
   A. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by laboratory testing; **OR**
   B. C1-INH functional level below the lower limit of normal as defined by the laboratory testing;

AND

v. Individual has a history of moderate or severe attacks such as airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, or painful facial distortion.

B. Criteria for Continuation of Therapy

i. MMM considers continuation of therapy in patients requesting the medication for an indication listed above when all criteria for initial approval are met; **AND**
ii. Documentation is provided confirming that the patient had positive clinical response to therapy.

C. Authorization Duration

i. Initial Authorization: 3 months
ii. Re-authorization: 6 months

D. Criteria for Continuation of Therapy

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Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Ruconest may not be approved for the following:

A. Individuals using to treat laryngeal attacks; **OR**
B. In combination with other HAE agents for acute attacks (including but not limited to Berinert, Icatibant (Firazyr, Sajazir), Kalbitor, or Ekterly); **OR**
C. Individual has a known or suspected allergy to rabbits or rabbit-derived products.
D. When the above criteria are not met and for all other indications.

ii. Requests for Berinert, Icatibant (Firazyr, Sajazir), or Kalbitor may not be approved for the following:

A. In combination with other HAE agents for acute attacks (including but not limited to Berinert, Icatibant (Firazyr, Sajazir, Kalbitor, Ruconest, or Ekterly).
B. When the above criteria are not met and for all other indications.

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Limits or Restrictions:

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Hereditary Angioedema (HAE) Acute Attack Agents

Drug	Limit
Ruconest (C1 esterase inhibitor [recombinant]) 2100 unit vial	• Up to two 50 units/kg doses [max of 4200 units (2 vials) per dose] per attack (Max: 16 vials/30 days)
Icatibant (Firazyr) 30 mg prefilled syringe	• Up to 3 syringes (90 mg) per attack (Max: 18 syringes/30 days)
Kalbitor (ecallantide) 10 mg vial	• Up to 6 vials (60 mg) per attack (Max: 36 vials/30 days)
Berinert (C1 esterase inhibitor [human]) 500 IU kit	• Up to 20 IU/kg once per attack (Max: 24 kits/30 days)
Exceptions	
N/A	

Hereditary Angioedema (HAE) for Prophylaxis of Acute Attacks Agents

Drug	Limit
Takhzyro (lanadelumab-flyo) 300 mg prefilled syringe/single-dose vial	1 syringe/vial per 28 days*
Takhzyro (lanadelumab-flyo) 150 mg prefilled syringe	1 syringe per 28 days*
Cinryze 500 units/vial	20 vials per 30 days
Haegarda 2,000IU/vial	24 vials per 28 days
Haegarda 3,000 IU/vial	16 vials per 28 days*
Andembry (garadacimab-gxii) 200 mg/1.2 mL prefilled autoinjector/prefilled syringe with needle safety device	1 prefilled autoinjector/syringe per 28 days^
Dawnzera (donidalorsen) 80 mg/0.8 mL autoinjector	1 autoinjector per 28 days
Exceptions	
*Initial authorization period for those 6 years of age or older: Requests for an additional Takhzyro syringe for a total of 2 syringes per 28 days may be approved for the initial 8 months as part of the titration period. For Takhzyro maintenance therapy for those 6 years of age or older: if an individual is well-controlled (attack free) for the last 6 months, continue authorization for one year with 1 syringe per 28 days. Two syringes per 28 days may be approved for one year if a provider submits documentation providing rationale for the 2 syringes per 28 days	

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dosing (i.e. patient has an attack in the last 6 months or history of very severe attacks i.e. laryngeal attack) or if the provider submits supporting documentation that the member has tried and failed 1 syringe per 28 days dosing (i.e. experiences an attack).

^Initiation of therapy of Andembry (garadacimab-gxii): May approve 2 prefilled autoinjectors/syringes per 28 days in the first month (28 days) of treatment.

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Codes Information:

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

ICD-10 Diagnostic Codes:

Codes	Description
D84.1	Defects in the complement system

HCPCS Codes:

Codes	Description
J0593	Inj., lanadelumab-flyo, 1 mg [Takhzyro] (code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered)
J0596	Injection, C-1 esterase inhibitor (recombinant), Ruconest, 10 units
J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units
J0599	Injection, c-1 esterase inhibitor (human), Haegarda, 10 units
J1290	Injection, ecallantide, 1 mg [Kalbitor]
J1744	Injection, icatibant, 1 mg [Firazyr] [Sajazir]
C9399	Unclassified drugs or biologicals [when specified as Andembry (garadacimab-gxii) or Dawnzera (donidalorsen)]
J3490	Unclassified drugs [when specified as Dawnzera (donidalorsen)]
J3590	Unclassified biologics [when specified as Andembry (garadacimab-gxii)]

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Reference Information:

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, icatibant (Firazyr), Kalbitor, Ruconest, Takhzyro, Andembry, Dawnzera	**MP-RX-FP-36-23**	☒ MMM MA ☒ MMM MultiHealth	**11/30/2023** **Last Review Date:** **7/1/2026**	**7/1/2026** **Frequently Revision:** **Annual**

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Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, icatibant (Firazyr), Kalbitor, Ruconest, Takhzyro, Andembry, Dawnzera	**MP-RX-FP-36-23**	☒ MMM MA ☒ MMM MultiHealth	**11/30/2023** **Last Review Date:** **7/1/2026**	**7/1/2026** **Frequently Revision:** **Annual**

Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Added new agents Andembry and Dawnzera to the background information, clinical criteria and quantity limits. Added agents Sajazir, Orladeyo, and Ekterly to the products and indications tables for reference, a with a note clarifying that these agents are evaluated under the pharmacy benefit/Part D criteria, as applicable. Coding Reviewed: Updated description for HCPCS J0593. Added HCPCS NOC C9399 and J3590 for Andembry. Added HCPCS NOC J3490 for Dawnzera and added Dawnzera to HCPCS NOC C9399. Updated references list. Performed an administrative update to add documentation requirements and incorporate the new policy template.	6/19/2026	7/1/2026
Annual Review	Minimal changes; Word formatting. Coding reviewed: No changes.	8/28/2025	9/8/2025
Annual Review	Clarified Criteria for Continuation of Therapy to state that a positive clinical response is defined as a clinically significant reduction (e.g., 50% or more) in the number and/or frequency of HAE attacks and including a reduction in the use of medications to treat acute attacks since starting treatment, and that if the patient has been well controlled on therapy, a less frequent administration (according to FDA labeling) is prescribed or has been considered; Changed initial authorization of Takhyzro to 6 months; Added Continuation Criteria and authorization duration for agents used for treatment of acute attacks; Removed Orladeyo information; Added the following statement to the Initial Authorization Criteria: (Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.; Wording and formatting changes	2/18/2025	3/6/2025
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023