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Policy Number: C17923-A

Beovu (brolucizumab)

PRODUCTS AFFECTED

Beovu (brolucizumab)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

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, patient 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.

DIAGNOSIS:
Neovascular (wet) age-related macular degeneration, Diabetic macular edema

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ALL INDICATIONS:
   1. Documentation of definitive diagnosis of Neovascular (Wet) Age-Related Macular Degeneration (AMD) or Diabetic Macular Edema (DME)
      AND

2. Documentation of baseline visual status with notation of eye(s) being treated [DOCUMENTATION REQUIRED]
   AND
3. Documentation of an inadequate response (defined as 1-2 injections with minimal to no improvement), clinically significant adverse effects, or contraindication to bevacizumab OR bevacizumab is indicated by the provider as unavailable and there is documentation of an inadequate response, serious side effects or contraindication to ranibizumab
   AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Beovu (brolucizumab) include: ocular or periocular infections, active intraocular inflammation, known hypersensitivity to brolucizumab or any of the excipients in Beovu (brolucizumab)]

CONTINUATION OF THERAPY:

A. ALL INDICATIONS:

1. Reauthorization request is for the same eye(s) as initial authorization
   NOTE: The continuation of therapy criteria is only for the same previously treated eye(s). If member has developed condition in an untreated eye, Prescriber must submit new request with Initial Coverage criteria.
   AND
2. Documentation of improvement or stabilization of disease state (e.g., reduction in rate of progression and frequency of retinopathy, hemorrhage, macular edema, etc.) and visual status [DOCUMENTATION REQUIRED]
   AND
3. Documentation of administration records showing dates and eye(s) administered, along with documentation of member compliance with treatment plan
   AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified ophthalmologist, ophthalmic surgeon or retinal specialist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

Neovascular (Wet) Age-Related Macular Degeneration:
Initial dosage: 6 mg (0.05 mL of 120 mg/mL solution) by intravitreal injection once per month (approximately every 25 to 31 days) for 3 months (3 doses)
Maintenance dosage: 6 mg by intravitreal injection once every 8 to 12 weeks

Diabetic Macular Edema:
Initial dosage: 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every six weeks (approximately every 39-45 days) for the first five doses
Maintenance dosage: 6 mg (0.05 mL) by intravitreal injection once every 8-12 weeks.

PLACE OF ADMINISTRATION:
The recommendation is that intravitreal medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravitreal Injection

DRUG CLASS:
Vascular Endothelial Growth Factor (VEGF) Antagonists

FDA-APPROVED USES:
Indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Beovu (brolucizumab-dbll)

Human vascular endothelial growth factor (VEGF) inhibitor

- Humanized monoclonal single-chain antibody fragment which binds to vascular endothelial growth factor A (VEGF-A); prevents the factor from stimulating the growth of fragile and permeable new blood vessels associated with wet AMD.
- A humanized single-chain antibody fragment differs from currently available full-length monoclonal antibodies VEGF inhibitors due to its small size, single-chain antibody fragments which can provide enhanced tissue penetration and rapid clearance from systemic circulation.
- The Beovu molecule is engineered to deliver the highest concentration of drug, providing more active binding agents than other anti-VEGFs. By inhibiting VEGF, Beovu suppresses the growth of abnormal blood vessels and the potential for fluid leakage into the retina (Dugel P, et al.).
- Indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)
- Wet age-related macular degeneration (wet AMD) includes activating the vascular endothelial growth factor A (VEGF-A) pathway which signals blood vessels to grow abnormally in the eye's retina, which may cause fluid leakage and vision loss.
- Wet AMD is a chronic, degenerative eye disease caused by an excess of VEGF, a protein that promotes the growth of abnormal blood vessels underneath the macula, the area of the retina responsible for sharp, central vision (National Eye Institute). Fluid that leaks out of these abnormal blood vessels disrupts the normal retinal structure and ultimately damages the macula (National Eye Institute; WHO; NHS Choices).

Brolucizumab provides an additional VEGF inhibitor treatment option for wet AMD. Other VEGF inhibitors indicated for wet AMD include Eylea and Lucentis. While brolucizumab did not demonstrate superiority for the primary endpoint, key secondary outcomes did favor brolucizumab over aflibercept (Eylea).

Brolucizumab is administered every 12 weeks whereas the recommended dosing frequency for Eylea is

every 8 weeks. However, in the clinical trials about 50% of brolucizumab-treated patients required dosing every 8 weeks. While the dosing frequency for Eylea can be extended to every 12 weeks after one year of effective therapy, it may not be as effective as the recommended every 8-week dosing regimen for some patients. The recommended dosing frequency for Lucentis is once every month.

AMD is a leading cause of vision loss globally, with adults > 50 years old most often affected. AMD is a progressive chronic retinal disease affecting the aging eye(s), characterized by drusen (focal yellowish deposits of acellular, polymorphous debris), geographic atrophy of retinal pigment epithelium, and neovascularization that can lead to visual impairment.

There are 2 forms of AMD: wet and dry. The dry form is the most common form and is characterized by yellow deposits in the retina, called “drusen.” The dry form can progress to the wet form, which is more aggressive and severe. Wet or exudative AMD is caused by the growth of abnormal leaky blood vessels (choroidal neovascularization or CNV) that eventually damage the macula. The macula is the area of the eye responsible for central vision, which is essential for most visual activities, including reading, driving, and recognizing faces. CNV associated with wet AMD may include classic or occult neovascular leakage patterns. Classic CNV is distinct or well demarcated during fluorescein angiography whereas occult CNV is obscured or poorly demarcated on fluorescein angiography.

Clinical Efficacy

The efficacy of brolucizumab was evaluated in two double-masked, active-controlled, Phase III randomized multi-center studies (HAWK and HARRIER) in 1,817 untreated wet AMD patients. Both studies were designed to provide a head-to-head non-inferiority comparison of brolucizumab to aflibercept in the treatment of nAMD.

Patients were randomized to brolucizumab or aflibercept. The studies compared two different doses of brolucizumab, 6 mg and 3 mg, to a 2 mg dose of aflibercept. Brolucizumab was administered as a maintenance dose every 8 or 12 weeks (depending on disease activity) vs. every 8 weeks for Eylea.

- All patients received study drug injections at weeks 0, 4, and 8 during a loading phase. Brolucizumab was then injected every 12 weeks; if disease activity was identified, the dosing interval was permanently changed to every 8 weeks. Aflibercept was injected every 8 weeks after the loading phase.
- Brolucizumab was administered as an intravitreal injection. Patients received a loading dose of three-monthly injections, followed by injections every 12 weeks. The interval could be adjusted to every 8 weeks if disease activity was present. The dosing interval for aflibercept was bi-monthly.

Study Endpoints

HAWK and HARRIER met their pre-specified primary and secondary endpoints.

The primary endpoint was non-inferiority in change in best-corrected visual acuity (BCVA) from baseline to week 48. Key secondary endpoints included the following:

- number of patients on 12-week dosing interval at 48 and 96 weeks
- change in BCVA from baseline at each visit up to 96 weeks
- change in central sub-field thickness (CST) at each visit up to 96 weeks
- presence of intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) from baseline at each visit up to 96 weeks
- presence of sub-retinal epithelium (sub-RPE) fluid from baseline at each visit up to 96 weeks

Brolucizumab demonstrated non-inferiority to aflibercept for the primary endpoint of mean BCVA change from baseline ($p < 0.001$) at year 1 (week 48) in both studies

- Mean baseline BCVA was 60.6 in the HAWK study and 61.2 in the HARRIER study
- Mean BCVA change from baseline to week 48 was non-inferior with brolucizumab 6 mg compared with aflibercept 2 mg in the 2-year randomized HAWK (N=1082; +6.6 vs +6.8 letters) and HARRIER(N=743; +6.9 vs +7.6 letters) studies; the HAWK study also included a brolucizumab 3 mg arm
- The average change in BCVA from baseline to weeks 36 to 48 was 6.7 for both brolucizumab-dbll 6mg and aflibercept in the HAWK study and 6.5 versus 7.7, respectively, in the HARRIER study; a 15or more

letter gain was achieved by 33.6% versus 25.4% in HAWK and 29.3% versus 29.9% in HARRIER.

- With all treatments, gains in BCVA were achieved during the loading phase with slight increases to week 48
- In both trials, patients on brolucizumab achieved vision gains that were non-inferior to aflibercept at year one with longer treatment intervals in a majority of patients. In both clinical trials, approximately30% of patients gained at least 15 letters at year one.
- During the first 16 weeks of treatment when all patients had at least 8 weeks until the next treatment after loading doses, brolucizumab-dbll 6 mg compared with aflibercept had significantly fewer patients with disease activity (HAWK, 24% vs 34.5%; HARRIER, 22.7% vs 32.2%), greater mean reductions in central subfield thickness (HAWK, -161.4 vs -133.6 mcm; HARRIER, -174.4 vs -134.2 mcm), and fewer eyes with intraretinal/subretinal fluid (HAWK, 33.9% vs 52.2%; HARRIER, 29.4% vs 45.1%).

Beovu also demonstrated superiority to aflibercept in several secondary endpoints including improvements in disease activity and other anatomical retinal fluid outcomes:
At week 16, fewer brolucizumab patients had disease activity vs. aflibercept in HAWK (24.0% vs. 34.5%; p = 0.001) and HARRIER (22.7% vs. 32.2%; p = 0.002).

- Beovu showed greater reduction in central subfield thickness (CST) as early as week 16 and at year one, and fewer patients had intra-retinal (IRF) and/or sub-retinal fluid (SRF).
  A reduction of CST is an important measure of abnormal fluid accumulation and edema that may result in reduced vision
- Lower number of patients with retinal fluid (intraretinal and/or subretinal).
  Retinal fluid is a key marker of disease activity and key markers used by providers to determine injection frequency
- A reduction in disease activity

- Results at week 96 with the 6 mg dose of brolucizumab have been consistent with the 48- week results in both primary and secondary endpoints.
- In both trials eligible patients could be maintained on a three-month dosing interval immediately after the loading phase.
  - At year one, over half of patients were maintained on the three-month dosing interval (56% in HAWK and 51% in HARRIER). The remaining patients in the study were treated on a two- month dosing schedule.
- Adverse events with brolucizumab-dbll 6 mg compared with aflibercept included conjunctival hemorrhage (HAWK, 6.4% vs 5.6%; HARRIER, 1.9% vs 3.3%), reduced visual acuity (HAWK, 5.3% vs 6.7%; HARRIER, 5.4% vs 5.4%), uveitis (HAWK, 2.2% vs 0.3%; HARRIER, 0.8% vs 0%), and iritis (HAWK, 2.2% vs 0%; HARRIER, 0% vs 0.3%).
- According to *a report issued by a Safety Review Committee established by the manufacturer, the overall rate of vision loss in the study population was similar between the brolucizumab and aflibercept arms in HAWK & HARRIER despite the risk of vision loss associated with the adverse events of interest (Data on file. Safety Review Committee Report. Novartis; 2020).*
- Phase 3 data from the post-hoc analyses of the HAWK and HARRIER trials indicate that fewer Beovu (brolucizumab) patients were found with early persistent fluid (12.5% vs. 20.4% of aflibercept patients), defined as the presence of intra-retinal fluid and/or sub-retinal fluid through week 12 of treatment. Patients who had early persistent fluid and treated with Beovu achieved greater best- corrected visual acuity (BCVA) gains and greater reductions in central subfield thickness (CST) at week 96 versus those treated with aflibercept (6.4 vs. 3.7 letters, respectively). This data further supports Beovu as an efficacious treatment option for wet AMD (Lally D; Presented at: EURETINA 2020 congress. October 2020).
- The prescribing information updated to include characterization of adverse events, retinal vasculitis and retinal vascular occlusion. The update to the US label includes the addition of a sub-section dedicated to retinal vasculitis and/or retinal vascular occlusion under 'Warnings and Precautions' (in Section 5 of Prescribing Information). It also specifies that these adverse reactions are part of a spectrum of intraocular inflammation rates from the Phase III HAWK & HARRIER trials (Novartis PI, June 9, 2020).

The safety and efficacy of BEOVU for Diabetic Macular Edema (DME) were assessed in two randomized, multi-center, double-masked, active controlled studies (KESTREL – NCT03481634 and KITE -

NCT03481660) in patients with DME. A total of 926 patients were treated in these studies for 1 year (558 on brolucizumab and 368 on aflibercept 2 mg). Patient ages ranged from 23 to 87 years with a mean of 63 years. The primary efficacy endpoint for both studies was the change from baseline to Week 52 in Best Corrected Visual Acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score with the primary objective being to demonstrate non-inferiority of BEOVU vs. aflibercept 2 mg. In both studies, BEOVU was non-inferior to aflibercept 2 mg for the change in BCVA from baseline to Week 52 and the change from baseline over the period Week 40 through Week 52. Through Week 52, 55% (KESTREL) and 50% (KITE) of patients remained on BEOVU every 12 weeks. The probability of remaining on every 12-week dosing from Week 36 to Week 52 was 88% and 95% in KESTREL and KITE, respectively.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Beovu (brolucizumab-dbll) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Beovu (brolucizumab-dbll) include: Hypersensitivity (e.g., rash, pruritus, urticaria, erythema, severe intraocular inflammation) to brolucizumab or any component of the formulation, ocular or periocular infections; active intraocular inflammation.

Exclusions/Discontinuation:

Do not use Beovu (brolucizumab-dbll) with other ophthalmic VEGF inhibitors (i.e., aflibercept, bevacizumab, faricimab, ranibizumab, etc.).

OTHER SPECIAL CONSIDERATIONS:

Avastin (bevacizumab) is the preferred agent for the treatment of AMD and documentation of the failure of Avastin is required prior to authorization of Beovu (brolucizumab).

There is no evidence to support the use of one VEGF-Inhibitor over another as the clinical trials provided data that showed comparability, none showed superiority. Results from the CATT research group indicate that bevacizumab and ranibizumab have equivalent effects on visual acuity for the treatment of ARMD when administered according to the same schedule.

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). VEGF is the major angiogenic stimulus responsible for the formation of choroidal neovascularization and so represents a new paradigm in the treatment of retinovascular disease. Bevacizumab is FDA-approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer.

Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab. [Michels S, et al. 2005; Avery RL, etal. 2006; AAO Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. Age-Related Macular Degeneration.]

Based on published reports and compelling evidence of bevacizumab's safety and efficacy for use in a number of ophthalmic conditions, intravitreal bevacizumab is increasingly being administered as an off-label treatment in the United States and has been used in the treatment of the following off-label conditions that have not responded to other accepted therapies, including:

- Neovascular (wet) age-related macular degeneration
- Diabetic macular edema
- Central retinal vein occlusion
- Venous tributary (branch) occlusion
- Proliferative diabetic retinopathy
- Neovascular glaucoma; Adjunct

Comparative trials and uncontrolled case series reported improvements in visual acuity and decreased

retinal thickness by OCT (Optical Coherence Tomography) following intravitreal bevacizumab treatment.

Intravitreal injection of bevacizumab has been used for the treatment of neovascular age-related macular degeneration (AHFS 2019). Results of several randomized controlled studies suggest that intravitreal bevacizumab has similar efficacy as ranibizumab in improving visual acuity. In one study, the incidence of serious systemic adverse effects (primarily hospitalizations) appeared to be higher with bevacizumab compared with ranibizumab; however, other studies, including a systematic review of 9 randomized controlled studies, directly comparing intravitreal injections of bevacizumab and ranibizumab in patients with neovascular age-related macular degeneration have found no such difference.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J0179	Injection, brolucizumab-dbll, 1mg

AVAILABLE DOSAGE FORMS:
Beovu SOLN 6MG/0.05ML single-dose vial kit
Beovu SOSY 6MG/0.05ML prefilled syringe

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation References	Q4 2025
REVISION- Notable revisions: Required Medical Information	Q1 2025
REVISION- Notable revisions: Coding/Billing Information Template Update References	Q4 2024

REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Drug Class References	Q4 2023
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Quantity FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file