Select Vascular Endothelial Growth Factor (VEGF) Inhibitors and Combination Products

Policy # 00805
Original Effective Date: 10/10/2022
Current Effective Date: 03/11/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider select vascular endothelial growth factor (VEGF) inhibitors and combination products, including, but not limited to ranibizumab (Susvimo™)‡, faricimab-svoa (Vabysmo™)‡, ranibizumab-nuna (Byooviz™)‡, and ranibizumab-eqrn (Cimerli™)‡ for the treatment of various ocular conditions to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for select VEGF inhibitors and combination products, including, but not limited to ranibizumab (Susvimo), faricimab-svoa (Vabysmo), ranibizumab-nuna (Byooviz), and ranibizumab-eqrn (Cimerli) will be considered when the following criteria are met for the requested drug:

- For Susvimo requests:
    - Patient has a diagnosis of Neovascular (wet) age-related Macular Degeneration (nAMD); AND
    - Patient is 18 years of age or older; AND
    - Patient has tried and failed (e.g., intolerance or inadequate response) at least two doses of BOTH of the following unique ingredient VEGF Inhibitors (which are FDA approved for nAMD): ranibizumab (Lucentis®, Byooviz, Cimerli)‡ and aflibercept (Eylea®)‡; AND
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Susvimo is dosed 2 mg every 6 months via the Susvimo ocular implant.

- For Vabysmo requests:
  - Patient is 18 years of age or older; AND
  - Patient has a diagnosis of nAMD; AND
    - Patient has tried and failed (e.g., intolerance or inadequate response) BOTH of the following unique ingredient VEGF Inhibitors (which are FDA approved for nAMD): ranibizumab (Lucentis, Byooviz, Cimerli) and aflibercept (Eylea); AND
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Dose does not exceed 6 mg every 4 weeks for 4 doses, then one of the following: weeks 28 and 44; OR weeks 24, 36, and 48; OR weeks 20, 28, 36, and 44; OR
  - Patient has a diagnosis of diabetic macular edema (DME); AND
    - Patient has tried and failed (e.g., intolerance or inadequate response) BOTH of the following unique ingredient VEGF Inhibitors (which are FDA approved for DME): ranibizumab (Lucentis, Cimerli) and aflibercept (Eylea); AND
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Dose does not exceed 6 mg every 4 weeks for 4 doses, then either every 4 or 8 weeks thereafter OR 6 mg every 4 weeks for the first 6 doses, followed by 6 mg every 8 weeks over the next 28 weeks; OR
  - Patient has a diagnosis of macular edema following retinal vein occlusion (RVO); AND
    - Patient has tried and failed (e.g., intolerance or inadequate response) BOTH of the following unique ingredient VEGF inhibitors (which are FDA approved for RVO): ranibizumab (Lucentis, Byooviz, Cimerli) and aflibercept (Eylea); AND
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
    - Dose does not exceed 6 mg every 4 weeks.

- For Byooviz and Cimerli requests:
  - Patient has a diagnosis of nAMD; AND
    - Patient is 18 years of age or older; AND
    - The dose is 0.5 mg administered as an intravitreal injection once per month or 0.5 mg administered as an intravitreal injection less frequently than monthly; OR
  - Patient has a diagnosis of macular edema following retinal vein occlusion (RVO); AND
    - Patient is 18 years of age or older; AND
    - The dose is 0.5 mg administered as an intravitreal injection once per month; OR
  - Patient has a diagnosis of myopic choroidal neovascularization (mCNV); AND
    - Patient is 18 years of age or older; AND
    - The dose is 0.5 mg administered as an intravitreal injection once per month for up to 3 months (re-treatment is allowed).
- For Cimerli requests:
  - Patient has a diagnosis of DME or diabetic retinopathy (DR); AND
  - Patient is 18 years of age or older; AND
  - The dose is 0.3 mg administered as an intravitreal injection once per month.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of ranibizumab (Susvimo) and faricimab-svoa (Vabysmo) when the patient has not tried and failed the required pre-requisite medications to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of select VEGF inhibitors and combination products, including, but not limited to ranibizumab (Susvimo), faricimab-svoa (Vabysmo), ranibizumab-nuna (Byooviz), and ranibizumab-eqrn (Cimerli) when patient selection criteria are not met (except the criteria denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Vabysmo is a VEGF and angiopoietin inhibitor indicated for the treatment of patients with nAMD DME, or macular edema following retinal vein occlusion (RVO). It is available as 120 mg/ml solution in a single-dose vial and is initially dosed at 6 mg every 4 weeks and then adjusted according to indication and patient response per the package insert. Susvimo is a VEGF inhibitor indicated for the treatment of patients with nAMD who have previously responded to two intravitreal injections of a VEGF inhibitor. Susvimo contains the same ingredient as Lucentis, which is ranibizumab, but is delivered via an ocular implant as opposed to an intravitreal injection. Byooviz is a biosimilar to Lucentis, but it doesn't have all of the FDA approved indications that Lucentis has. Byooviz is indicated for the treatment of patients with nAMD, macular edema following RVO, and mCNV. Byooviz is initially dosed as 0.5 mg via intravitreal injection once per month, but may be adjusted according to indication, which can be found in the package insert. Cimerli, another biosimilar of Lucentis, is indicated for the treatment of patients with nAMD, macular edema following RVO, DME, DR, and mCNV. Cimerli is the first drug approved to be interchangeable with Lucentis. It is available as single-dose glass vials that provide either a 0.5 mg or 0.3 mg dose.

Other products, which are not targeted by this policy, are available for the treatment of these conditions. These include Eylea, Lucentis, and Beovu®‡. Eylea is a VEGF inhibitor indicated for the treatment of patients with nAMD, macular edema following RVO, DME, and DR. Lucentis is a VEGF inhibitor indicated for nAMD, macular edema following RVO, DME, DR, and mCNV. Beovu is a VEGF inhibitor indicated for the treatment of nAMD and DME.

It should be noted that the medications targeted in this policy have not shown superiority to any of the pre-requisite products that are required for trial and failure. This class of medications will be soon expanding precipitously with the continued introduction of biosimilars.

Neovascular (wet) Age Related Macular Degeneration (AMD)
Age related macular degeneration is a common eye condition that is a leading cause of vision loss among people 60 years of age and older. Neovascular AMD is defined by CNV that causes bleeding, fluid accumulation, and fibrosis of the macula. The macula is a small spot near the center of the retina responsible for sharp, central vision and allows the eye to see objects that are straight ahead. Wet AMD, although less common than dry AMD, is associated with more of a sudden loss of central vision. Intravitreal VEGF agents are the standard of care for nAMD.

Macular Edema Following Retinal Vein Occlusion (RVO)
Retinal vein occlusion occurs when the veins of the retina become blocked. It can be classified into branch RVO, central RVO, and hemiretinal RVO. Branch RVO is in one of the branches of the central vein whereas central RVO is located in the central vein and affects most of the retina. RVO can be further classified as ischemic or non-ischemic, with ischemic RVO associated with a significant loss in visual acuity at presentation and a poor prognosis, often with substantial and irreversible damage. Patients with RVO will typically present with painless loss of vision. Vision loss or blurry vision can also occur due to macular edema when blood and fluids leak into the macula and cause swelling.

Diabetic Macular Edema (DME)
Diabetic macular edema is a vision-threatening complication of diabetes. It is defined as retinal thickening or the presence of hard exudates within 1 disk diameter from the center of the macula and is the most frequent retinal vascular disorder. Visual impairment occurs when edema affects the central retina or the macula. This condition can occur at any stage or severity of diabetic retinopathy. Because VEGF has a role in increasing the extracellular accumulation of fluid in DME, VEGF inhibitors are used in the treatment of DME.

Diabetic Retinopathy (DR)
Diabetic retinopathy is a common cause of vision loss and is the principal cause of vision impairment in patients between 25 and 74 years old. It can be classified as two major forms: nonproliferative

and proliferative. Visual loss resulting from this condition may occur due to macular edema, hemorrhage from new vessels, retinal detachment, and neovascular glaucoma.

Myopic Choroidal Neovascularization (mCNV)
The pathogenesis of mCNV is not fully understood, and there is no standard definition of mCNV or of its relationship to axial length or other myopic degenerative changes.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Vabysmo is a VEGF and angiopoietin-2 inhibitor indicated for the treatment of patients with nAMD, DME, or macular edema following RVO. Susvimo is a VEGF inhibitor indicated for the treatment of patients with nAMD who have previously responded to two intravitreal injections of a VEGF inhibitor. Byooviz is indicated for the treatment of patients with nAMD, patients with macular edema following RVO, and patients with mCNV. Cimerli is indicated for the treatment of patients with any of the following ocular conditions: nAMD, macular edema following RVO, DME, DR, and mCNV.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

It should be noted that the medications targeted in this policy have not shown superiority to any of the pre-requisite products that are required for trial and failure. The intent of this policy is to ensure appropriate use and to encourage use of the most economical and equally effective products on the market.

It should also be noted that clinical studies for Byooviz and Cimerli are not included in this section of the policy. Studies for these two medications were derived from the reference product, Lucentis, which is not targeted in this policy.

Susvimo-nAMD
The clinical efficacy and safety of Susvimo (ranibizumab injection) was assessed in a randomized, visual assessor-masked, active treatment-controlled study in patients with AMD. A total of 415 patients (248 in the Susvimo arm and 167 in the intravitreal ranibizumab arm) were enrolled and treated in this study. Patients were diagnosed with nAMD within the 9 months prior to screening and received ≥ 3 doses of anti-VEGF intravitreal agents in the study eye within the last 6 months prior to screening. Each patient was required to have demonstrated a response to an anti-VEGF intravitreal agent prior to randomization. Patients were randomized in a 3:2 ratio to receive continuous delivery of Susvimo (ranibizumab injection) via the Susvimo implant every 24 weeks or 0.5 mg intravitreal ranibizumab injections every 4 weeks. For patients randomized to the Susvimo arm, supplemental treatment with 0.5 mg intravitreal ranibizumab injections was available at Weeks 16, 20, 40, 44, 64, 68, 88, and 92, if needed. In the first 24 weeks, 1.6% of patients assessed for supplemental treatment received 1 or more supplemental treatment(s) and in the following 24 weeks, 5.4% of patients assessed for supplemental treatment received 1 or more supplemental treatment(s).

The primary efficacy endpoint of change from baseline in distance Best Corrected Visual Acuity (BCVA) score averaged over Week 36 and Week 40 demonstrated that Susvimo was equivalent to intravitreal ranibizumab injections administered every 4 weeks. Averaged between Week 36 and Week 40, the mean change from baseline BCVA was +0.2 letters with Susvimo vs. +0.5 letters with ranibizumab, meeting the threshold for non-inferiority and equivalence between Susvimo and ranibizumab.

Vabysmo-nAMD
The safety and efficacy of Vabysmo were assessed in two randomized, multi-center, double-masked, active comparator-controlled, 2-year studies in patients with nAMD. A total of 1,329 newly diagnosed, treatment-naive patients were enrolled in these studies, and 664 patients received at least one dose of Vabysmo. Patient ages ranged from 50 to 99 with a mean of 75.9 years. The studies were identically designed two year studies. Patients were randomized in a 1:1 ratio to one of two treatment arms: 1) aflibercept 2 mg administered fixed every 8 weeks (Q8W) after three initial monthly doses; and Vabysmo 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to determine whether to give a 6 mg (0.05 mL of 120 mg/mL solution) dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; (also referred to as Q16W dosing); 2) Weeks 24,

36 and 48 (also referred to as Q12W dosing); or 3) Weeks 20, 28, 36 and 44 (also referred to as Q8W dosing). At week 48, after 4 initial monthly doses in the Vabysmo arm, 45% of patients received the Weeks 28 and 44 dosing, 33% of patients received the Weeks 24, 36 and 48 dosing, and the remaining 22% of patients received dosing every 8 weeks.

Both studies demonstrated non-inferiority to the comparator control, aflibercept, at the primary endpoint, defined as the mean change from baseline in Best Corrected Visual Acuity (BCVA) when averaged over the week 40, 44, and 48 visits and measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart. The mean increase in BCVA was +5.8 letters vs. +5.1 letters (Study 1) and +6.6 letters vs. +6.6 letters (Study 2) for the Vabysmo groups compared with the aflibercept groups, respectively.

Vabysmo-DME
The safety and efficacy of Vabysmo were assessed in two randomized, multi-center, double-masked, active comparator-controlled 2-year studies in patients with DME.

A total of 1,891 diabetic patients were enrolled in the two studies with a total of 1,262 patients treated with at least one dose of Vabysmo. Patient ages ranged from 24 to 91 with a mean of 62.2 years. The overall population included both anti-VEGF naive patients (78%) and patients who had been previously treated with a VEGF inhibitor prior to study participation (22%). The studies were identically designed 2 year studies. Patients were randomized in a 1:1:1 ratio to one of three treatment regimens: 1) aflibercept 2 mg administered every 8 weeks (Q8W) after the first five monthly doses; 2) fixed Vabysmo 6 mg administered Q8W after the first six monthly doses; and 3) Vabysmo 6 mg administered every 4 weeks for at least 4 doses and until the central subfield thickness (CST) of the macula measured by optical coherence tomography was less than approximately 325 microns, then the interval of dosing was modified by up to 4 week interval extensions or reductions in up to 8 week interval increments based on CST and visual acuity disease activity criteria at study drug dosing visits.

Both studies demonstrated non-inferiority to the comparator control, aflibercept, at the primary endpoint, defined as the mean change from baseline in BCVA at year 1 (average of the week 48, 52, and 56 visits), measured by the ETDRS Letter Score. For the first study, the mean increase in BCVA was +10.7 letters and +11.6 letters vs. +10.9 letters for the Vabysmo Q8W and Vabysmo individualized treatment interval groups vs. the aflibercept Q8W group, respectively. Similar results

were reported for the second study; the mean increase in BCVA was +11.8 letters and +10.8 letters vs. +10.3 letters for the Vabysmo Q8W and Vabysmo individualized treatment interval groups vs. for the aflibercept Q8W group, respectively.

Vabysmo- RVO
The safety and efficacy of Vabysmo were assessed in two randomized, multicenter, double-masked studies (BALATON in patients with macular edema following branch retinal vein occlusion, and COMINO in patients with macular edema following central retinal vein occlusion/hemiretinal vein occlusion). A total of 1,282 newly diagnosed, treatment-naïve patients were enrolled in these studies, of which 641 patients received at least one dose of Vabysmo through 6 months.

In both studies, patients were randomized in a 1:1 ratio to either 6 mg Vabysmo administered every 4 weeks, or the control arm receiving aflibercept 2 mg injections every 4 weeks for a total of 6 injections. The primary endpoint was defined as the change from baseline in BCVA at week 24, measured by the ETDRS Letter Score. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and Vabysmo arms where the lower bound of the 95% confidence interval for the mean change in BCVA could not be lower than minus 4 letters to declare non-inferiority. In both studies, the Vabysmo 6 mg Q4W arm demonstrated non-inferiority to the comparator control arm.

References

1. Susvimo [package insert]. Genentech, Inc. South San Francisco, California. Updated April 2022.
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3. Byooviz [package insert]. Biogen and Samsung. Cambridge, Massachusetts and Yeonsu-gu, Incheon, Republic of Korea. Updated April 2022.
4. Cimerli [package insert]. Coherus BioSciences, Inc. Redwood City, California. Updated August 2022.
5. Diabetic retinopathy: Classification and clinical features. UpToDate. Accessed August 2022.
6. Retinal vein occlusion: Epidemiology, clinical manifestations, and diagnosis. UpToDate. Accessed August 2022.
7. Cheung C, Arnold J, Holz, F, et al. Myopic Choroidal Neovascularization. American Academy of Ophthalmology. 2017;124:1690-1711.

8. Ophthalmology-Vascular Endothelia Growth Factor Inhibitors Therapy Class Summary. Express Scripts. Updated March 2022.

Policy History

Original Effective Date: 10/10/2022
Current Effective Date: 03/11/2024

09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. New policy.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Removed Beovu as a prerequisite item for Susvimo and Vabysmo due to safety concerns with the drug.
03/19/2023	Coding update
07/24/2023	Coding update
08/09/2023	Coding update
09/07/2023	Coding update
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Updated criteria and background information to include new indication for Vabysmo for macular edema following retinal vein occlusion.

Next Scheduled Review Date: 02/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	67027, 67028
HCPCS	C1889, C9399, J2777, J2779, J3490, J3590, Q5124, Q5128
ICD-10 Diagnosis	H35.3210-H35.3293, All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.