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Drug Class Update with New Drug Evaluation: Vascular Endothelial Growth Factors

Date of Review: August 2020

Date of Last Review: March 2017
Dates of Literature Search: 01/01/2017 – 01/09/2020
Brand Name (Manufacturer): Beovu® (Novartis)
Dossier Received: yes

Generic Name: brolucizumab-dbll

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To evaluate new comparative evidence for vascular endothelial growth factors (VEGF) inhibitors for ocular conditions and place in therapy of brolucizumab, a new molecular entity approved by the Food and Drug Administration (FDA) in 2019 for neovascular age-related macular degeneration (AMD).

Research Questions:
1. What is the evidence for comparative efficacy of VEGF inhibitors for ocular conditions?
2. What is the evidence for comparative safety of VEGF inhibitors for ocular conditions?
3. Are there any subpopulations (based on patient or disease characteristics) for which a specific agent may be more effective or associated with less harm?

Conclusions:
- Current evidence indicates that there is no clinically meaningful difference in best corrected visual acuity (BCVA) between ranibizumab, bevacizumab, or aflibercept in patients treated for diabetic macular edema (DME), neovascular AMD, or macular edema associated with retinal vein occlusion (RVO) based on moderate to high quality evidence.[1-4]
- Evidence on the risk of serious adverse events between VEGF inhibitors is mixed. However, new literature did not identify any new safety signals for VEGF inhibitors and indicates the risk for serious thromboembolic or ocular adverse effects (including endophthalmitis, eye pain, macular hole, macular edema, retinal hemorrhage or reduced visual acuity) is likely comparable between agents (low to moderate quality evidence).[1-5]
- There is moderate quality evidence that brolucizumab is non-inferior to aflibercept at 48 weeks based on BCVA in patients with neovascular AMD.[6]
- There is insufficient evidence on long-term safety of brolucizumab beyond 2 years. Labeling for brolucizumab is consistent with other VEGF inhibitors and includes warnings for thromboembolic and serious ocular adverse events.[7]

Recommendations:
- No PDL changes recommended based on clinical evidence or after evaluation of costs in executive session.

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Summary of Prior Reviews and Current Policy

- There is high to moderate quality evidence of no difference in best corrected visual acuity between ranibizumab and bevacizumab or ranibizumab and aflibercept for neovascular AMD.
- There is moderate quality evidence of no clinical meaningful difference in efficacy (defined as a change of >15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) between anti-VEGF agents in patients treated for diabetic macular edema.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.
- There is no difference in serious ocular events between ranibizumab, bevacizumab or aflibercept (low quality evidence). Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed, though higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between agents. Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).
- Bevacizumab is the current preferred product. All other VEGF inhibitors are non-preferred.

Background:

Vascular endothelial growth factor (VEGF) inhibitors are indicated for a wide variety of ocular conditions. FDA-approved indications differ between agents, but commonly include macular edema associated with diabetic retinopathy or retinal vein occlusion, neovascular age-related macular degeneration (AMD), and myopic choroidal neovascularization. In these diseases, vascular damage can trigger inflammatory responses, expression of VEGF, and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.[8] Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.[8] Intraocular injections of VEGF inhibitors work to prevent vascular endothelial growth factor expression in late stage disease, thereby preventing further choroidal neovascularization and preserving vision in these populations.[8]

These ocular conditions are often categorized according to the type of retinal abnormalities present including presence or absence of neovascularization or macular edema. With presence of neovascularization or macular edema, VEGF inhibitors are typically indicated as a first-line treatment option. Guidelines from the American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first-line therapy for macular edema associated with branched or central retinal vein occlusion, neovascular AMD, and clinically significant diabetic macular edema associated with vision loss.[8] No recommendations are made for any specific agent. Similar guidelines are available from National Institute for Health and Care Excellence (NICE) which recommend VEGF inhibitors as first-line therapy for neovascular AMD and recommend use for myopic choroidal neovascularization and macular edema associated with retinal vein occlusion or diabetes.[1,9-11] Alternative treatment options vary by condition and disease characteristics, but can include intraocular steroids, laser photocoagulation, and pan-retinal photocoagulation. In patients with other associated complications of diabetic retinopathy, these non-pharmacological options may be preferred or used in combination with VEGF inhibitors.[12]

VEGF inhibitors used most commonly in practice in the United States (US) include bevacizumab, ranibizumab and aflibercept. See **Table 1** for a list of FDA-approved ocular indications. While bevacizumab is not FDA-approved for any ophthalmic indications, there is a substantial body of evidence supporting off-label use.

Table 1. FDA-approved ophthalmic indications for VEGF inhibitors

Generic Drug Name (Brand)	Neovascular AMD	Macular Edema Following RVO	Diabetic Retinopathy	Diabetic Macular Edema	Myopic Choroidal Neovascularization
Aflibercept (Eylea®)	**X**	**X**	**X**	**X**	
Bevacizumab (Avastin®)					
Brolucizumab (Beovu®)	**X**				
Pegaptanib sodium (Macugen®)	**X**				
Ranibizumab (Lucentis®)	**X**	**X**	**X**	**X**	**X**

Abbreviations:AMD = age related macular degeneration; RVO = retinal vein occlusion

In clinical trials, visual acuity changes are often evaluated using the ETDRS chart. The minimal clinically important difference referenced in the literature can vary, but a change of 5 letters (corresponding to 1 line on the chart) is typically considered to be the minimum clinically detectable change.[1] For many conditions, moderate visual gains or losses are defined as changes of at least 10 to 15 letters (corresponding to approximately 2-3 lines).[1]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), NICE, Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

CADTH evaluated the safety of VEGF inhibitors in 2 systematic reviews. The first review assessed risk factors for development of acute, sustained intraocular pressure increases following VEGF administration.[13] Overall there was insufficient evidence assessing risk factors for sustained intraocular pressure requiring medical or surgical intervention and insufficient comparative evidence between VEGF agents.[13] Evidence was limited by high heterogeneity between identified studies, lack of consistently reported outcomes, and variable follow-up periods.[13] A second CADTH report evaluated ocular and cardio-thromboembolic adverse events.[5] The report included a descriptive analysis of 5 systematic reviews (including over 30 RCTs), and multiple large, retrospective, observational studies which compared incidence of adverse events with bevacizumab, ranibizumab, and aflibercept.[5] One of the included systematic reviews, published in 2012, noted a slightly increased risk of serious ocular adverse events associated with bevacizumab compared to ranibizumab or aflibercept.[5] However, 3 subsequent systematic reviews have failed to identify an increased risk with bevacizumab upon incorporation of data from new RCTs.[5] Similarly, a single center retrospective cohort study identified a higher risk of endophthalmitis with bevacizumab compared to ranibizumab.[5] However, this study had high risk of selection bias from imbalances in baseline characteristics and was limited by inclusion of only one study site. Other observational studies with lower risk of bias have failed to identify differences in incidence between agents. Overall, incidence of endophthalmitis was low, ranging from 0% to 0.11% for all studies.[5] Of the observational studies assessing risk for thromboembolic events, none identified a difference in risk between VEGF inhibitors.[5] Data are limited by lack of large, well-designed

RCTs powered to detect differences in adverse events. However, this data does not identify any new safety signals for VEGF inhibitors and indicates risk is likely comparable between agents.

A 2019 systematic review evaluated the comparative efficacy and safety of VEGF inhibitors for treatment of neovascular AMD, DME and RVO.[2] The review included 24 publications of 17 RCTs. Most studies (n=11) evaluated patients with neovascular AMD.[2] In patients with AMD, there was no difference in mean BCVA or proportion of patients gaining 15 or more letters at 12 months or 18-24 months upon comparison of bevacizumab and ranibizumab.[2] Two trials compared aflibercept and ranibizumab with low quality evidence of no clinical difference between agents based on mean change in BCVA and proportion of patients gaining 15 or more letters.[2] Data for this comparison was limited by high heterogeneity between trials. There was no direct comparative evidence for aflibercept and bevacizumab in neovascular AMD.[2] Three trials compared bevacizumab to ranibizumab in patients with DME and found no difference in mean BCVA (MD 2.0 letters; 95% CI −0.4 to 4.4) or proportion of patients gaining 15 or more letters at 24 months.[2] One trial comparing bevacizumab to aflibercept in DME found statistical improvements in mean BCVA with aflibercept at 12 months (MD 3.5 letters; 95% CI 1.4 to 5.7) and 24 months (MD 2.7 letters; 95% CI 0.3 to 4.2) which did not meet the threshold for clinically important differences.[2] The proportion of patients with a gain of 15 or more letters was improved with aflibercept compared to bevacizumab at 12 months, but was not statistically significant at 24 months.[2] Subgroup analyses indicate that benefit of aflibercept may be improved particularly in patients with worse visual acuity at baseline (<69 letters) who appeared to have a statistical and slight clinical benefit with aflibercept versus bevacizumab at 12 months (MD 6.5 letters; 95% CI 2.9 to 10.1).[2] The difference observed at 24 months was smaller and did not meet the minimum difference for a clinically meaningful change (MD 4.7 letters; 95% CI 0.5 to 8.8; MCID of 5 letters).[2] Upon comparison of aflibercept to ranibizumab in one trial, there were small statistical differences in BCVA between the drugs at 12 months (MD 2.1 letters; 95% CI 0.1 to 4.2) which failed to meet the threshold for clinically important differences and were not sustained at 24 months.[2] Similar trends were noted for the subgroup with worse visual acuity at baseline with a small statistical benefit at 12 months (MD 4.7 letters; 95% CI 1.4 to 8.0) and no difference observed at 24 months (MD 2.3 letters; 95% CI −1.1 to 5.6).[2] One RCT compared aflibercept to bevacizumab in RVO with no differences based on mean BCVA and proportion of patients gaining 15 or more letters.[2] There was insufficient evidence from 2 RCTs comparing ranibizumab to bevacizumab. Evidence was limited by small sample size and imprecision. For the majority of trials included in this review, there was no difference in harms reported including serious ocular or systemic adverse events based on low to moderate evidence.[2] However, studies were not powered to detect differences in adverse events. For patients with neovascular AMD, only one in 5 trials identified a difference in systemic events with a higher rate with ranibizumab compared to bevacizumab at 12 months that was not observed at 24 months.[2] In this trial, evidence was limited by differences in baseline characteristics between groups. Bevacizumab was associated with more gastrointestinal events in 2 of 6 trials compared to ranibizumab.[2] In patients with DME, there was low quality evidence of no difference in serious ocular or systemic adverse events between agents. Upon analysis of individual adverse events, there was evidence from one trial that arterial thrombotic events may be higher with ranibizumab versus aflibercept (11.9% vs. 5.4%; p=0.047), but neither therapy was statistically different compared to bevacizumab (7.8%).[2] There was insufficient evidence on harms for patients with RVO.

Another high quality systematic review evaluating comparative effectiveness of VEGF inhibitors in patients with DME, neovascular AMD, RVO or myopic CNV reached similar conclusions.[3] The primary outcomes examined included vision gain of 15 or more letters, vision loss of 15 or more letters, mean change in BCVA, and progression to legal blindness (20/200).[3] Overall, they found no statistical differences in efficacy outcomes or serious harms between treatments for patients with neovascular AMD, DME, RVO or myopic CNV.[3] In a subgroup of patients with DME and with worse visual acuity at baseline (BCVA <69 letters), aflibercept had improved vision gain of 15 or more letters at 12 months (67%) compared to ranibizumab (50%) or bevacizumab (41%).[3] However, results were no longer statistically significant at 24 months (52%, 55%, and 58% for bevacizumab, ranibizumab, and aflibercept, respectively).[3]

A Cochrane systematic review of RCTs evaluated efficacy of pegaptanib, ranibizumab or bevacizumab for treatment of patients with neovascular AMD.[4] Outcomes pertaining to direct comparative evidence will be the focus of this discussion. There was no evidence comparing pegaptanib to other treatments. Ten trials were identified comparing bevacizumab to ranibizumab. The majority of trials had low risk of bias and reported no difference in mean BCVA (MD -0.5 letters 95% CI -1.5 to 0.4; n=3190 patients). Similarly, there was no difference in prevention of blindness in the study eye defined as BCVA > 20/200, gain of 15 or more letters, or loss of 15 or more letters at 1 or 2 years of treatment based on high quality evidence.[4] Only one trial evaluated quality of life or functional visual outcomes and had no difference observed between treatments (moderate quality evidence).[4] Patients treated with bevacizumab had less reduction in central retinal thickness at 12 months, though differences were small, within the range of measurement error, and not considered clinically significant (MD -11.6 µm, 95% CI -21.6 to -1.7; n=2693 patients; high quality evidence).[4] Similar results were seen after 2 years of treatment. There were no differences observed in serious systemic or ocular adverse events between treatments at 12 months, though studies were not powered to detect differences between groups.[4] Rate of serious adverse events at 2 years was slightly more common with bevacizumab compared to ranibizumab (36% vs. 30%; RR 1.20, 95% CI 1.05 to 1.37).[4] Upon analysis of individual adverse events at 2 years, gastrointestinal disorders were slightly more common with bevacizumab compared to ranibizumab (RR 2.74, 95% CI 1.49 to 5.02), and there was a trend toward more cardiac disorders with bevacizumab, though differences did not achieve statistical significance (RR 1.25, 95% CI 0.92 to 1.71).[4] Less than 2% of patients experienced a serious cardiovascular event after 2 years of therapy and serious ocular events occurred in less than 1% of patients receiving VEGF inhibitors.[4]

A 2018 systematic review from NICE was used to inform guidelines for the management of age-related macular degeneration.[1] Pharmacologic therapies evaluated as part of this guidance included aflibercept, ranibizumab, and bevacizumab. There was high quality evidence from 8 RCTs (n=3101) of no difference in visual acuity between bevacizumab and ranibizumab after 1 year of treatment based on outcomes of mean change in BCVA (MD -0.48 ETDRS letters, 95% CI -1.47 to 0.51), gain of 15 or more letters (RR 0.96; 95% CI 0.85 to 1.08) and loss of less than 15 letters (RR 1.00; 95% CI 0.98 to 1.02).[1] Similarly, there was high quality evidence from 2 RCTs (n=2412) of no difference in visual acuity between aflibercept and ranibizumab after 1 year of treatment based on mean change (MD -0.15 ETDRS letters; 95% CI -1.47 to 1.17) and gain of 15 or more ETDRS letters (RR 0.97; 95% CI 0.85 to 1.11).[1] No difference was observed in vision-related or health-related quality-of-life between treatments (moderate to high quality evidence).[1] There was moderate quality evidence that patients treated with bevacizumab received more injections over the course of a year compared to patients treated with ranibizumab (MD 0.60; 95% CI 0.33 to 0.87). No difference in serious systemic adverse events (including myocardial infarction, stroke, venous thrombotic events) or serious ocular adverse events (e.g., severe uveitis, retinal pigment epithelial tear, cataract, endophthalmitis, retinal tear) was observed between bevacizumab and ranibizumab (low quality evidence) or between ranibizumab and aflibercept (moderate quality evidence) with one year of treatment.[1] Compared to ranibizumab, patients treated with bevacizumab were more likely to have gastrointestinal disorders (RR 1.85; 95% CI 1.01 to 3.40; 5 RCTs, n=3038 people).[1]

In a subgroup analysis comparing patients varying levels of visual acuity, patients with BCVA better than 20/40 at baseline (approximately 70 ETDRS letters) had better visual acuity with VEGF inhibitor treatment at 1 year compared to patients with BCVA of 20/40 to 20/320 (MD 16.52 letters; 95% CI 13.41 to 19.64; low quality evidence).[1] However, compared to patients presenting with worse visual acuity at baseline, this subgroup also was more likely to have more visual acuity loss at 1 year (MD -6.34; 95%CI -7.33 to -5.36) and 5 years (MD -11.75; 95%CI -18.98 to -4.92) and less likely to have a gain in 15 or more ETDRS letters after 1 year of VEGF inhibitor treatment (RR 0.16; 95% CI 0.12 to 0.22).[1] Patients with baseline visual acuity worse than 6/96 were more likely to continue to have worse visual acuity after 1 year of treatment compared to patients with BCVA between 20/40 and 20/320 (MD -17.23 letters; 95% CI -22.36 to -12.10).[1] However, they were also more likely to gain more letters after 1 year of VEGF inhibitor treatment compared to those with better baseline BCVA (MD 13.99 letters; 95% CI 10.39 to 17.59).[1]

There was high quality evidence that BCVA was not improved at 6-12 months with use of combination VEGF inhibitor and photodynamic therapy compared to monotherapy with a VEGF inhibitor (MD −0.54; 95% CI −1.29 to 0.21).[1] More patients given monotherapy gained 15 or more letters compared to combination therapy at 6 to 12 months (RR 0.76; 95% CI 0.63 to 0.92; moderate quality evidence).[1] Patients given combination therapy received fewer VEGF inhibitor doses over 6 to 12 months (MD −0.94; 95% CI: −1.76 to −0.12).[1] No difference was seen in ocular or systemic adverse events. Similarly, there was no difference observed in BCVA, adverse events and number of injections for patients given combination VEGF inhibitors and steroids compared to VEGF inhibitor monotherapy. Evidence supporting switching therapies was all of low or very low quality and identified no clinical difference in BCVA upon switching between VEGF inhibitors.[1]

An analysis of different treatment regimens (e.g., PRN vs. routine injections vs. treat-and-extend) was also conducted. A treat-and-extend strategy involves progressive extension of routine treatment intervals for up to 12 weeks based on clinical findings, whereas a PRN regimen involves injections only if there is active progressive disease. Upon comparison of a PRN strategy to routine injections, there was moderate quality evidence that use of PRN regimens have worse visual acuity compared to routine injections (MD -1.45; 95% CI -2.45 to -0.45).[1] However, differences were not considered clinically significant (> 5 ETDRS letters), and there was no difference in the proportion of patients who had substantial visual changes (gain or loss of 15+ EDTRS letters) based on low and moderate quality evidence, respectively.[1] Patients treated with PRN regimens were less likely to have serious ocular adverse events compared with routine injections based on low quality evidence (RR 0.31; 95% CI 0.13 to 0.78).[1] No difference was observed in serious systemic adverse events (very low quality evidence). On average, patients using a PRN regimen had on average 4.22 fewer injections over the year (95% CI −4.72 to −3.73).[1] There is moderate quality evidence that visual acuity or adverse events did not differ between treat-and-extend compared to monthly regimens. Patients on the treat-and-extend regimens received on average 2.4 fewer injections per year (95% CI -2.8 to -2.0).[1] Compared to patients with longer time between injections, patients with routine injections at least every 6 weeks had better visual improvement (gain of 15+ ETDRS letters RR 1.28; 95%CI 1.08 to 1.52), but no clinical difference in visual loss (loss of fewer than 15 EDTRS letters) or average visual acuity.[1]

After review, 25 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
NICE guidelines for diagnosis and management of AMD were published in 2018.[1] This guideline included evidence for aflibercept, ranibizumab, and bevacizumab. No specific recommendations are made for any of these agents as no clinically significant differences in effectiveness or safety were observed for VEGF inhibitors. While switches in therapy can be considered for practical reasons, there is not expected to be any clinical benefit from switching therapy.[1] While there are no direct comparisons of these agents to pegaptanib, current NICE guidance does not recommend pegaptanib for neovascular AMD based on a previous review evaluating indirect comparisons to ranibizumab which indicate it may have less efficacy and higher cost.

The following recommendations guide use of VEGF inhibitors for the management of neovascular AMD:[1]

- VEGF inhibitors are recommended for patients with BCVA between 6/12 and 6/96 with evidence of recent disease progression (e.g., visual acuity changes or blood vessel growth). Evidence demonstrates that treatment is effective for patients with visual acuity better than 6/12 and may be cost effective depending on the agent used. For patients with visual acuity of less than 6/96, consider administration only if a benefit to the overall visual function is expected.
- Consider observation only in patients with stable disease and without recent disease progression.

- VEGF inhibitors (ranibizumab, aflibercept) are not recommended if there is permanent structural damage to the central fovea or if lesion size is 12 disc areas or greater.
- Treatment with VEGF inhibitors should only be continued for patients who demonstrate a response to therapy. Discontinue treatment if there is persistent deterioration in visual acuity, or identification of anatomical changes in the retina which indicate inadequate response to therapy or that functional improvement is unlikely.
- Photodynamic therapy and intravitreal corticosteroids are not recommended in combination with VEGF inhibitors.

After review, 4 guidelines were excluded due to poor quality.[12,14-16]

New Formulations or Indications:
In 2017, ranibizumab received an expanded indication for use in diabetic retinopathy for patients with or without diabetic macular edema.[17] Approval was based on 2 RCTs which evaluated ranibizumab to sham injection and one RCT comparing ranibizumab to panretinal photocoagulation. Two of the studies were used for FDA-approval in patients with diabetic macular edema and have been evaluated previously. The majority of patients enrolled in these studies had non-proliferative diabetic retinopathy (62%) and 20% of patients had a prior panretinal photocoagulation treatment.[17] The proportion of patients with a 3-step improvement in the ETDRS-Diabetic Retinopathy Severity Scale (DRSS) was evaluated at 24 months. The ETDRS-DRRS evaluates disease severity based on location of microaneurysms, venous beading, hemorrhage, neovascularization, and other intraretinal abnormalities. Patients are categorized into 13 disease severity levels with scores ranging from no retinopathy (score of 10) to severe non-proliferative diabetic retinopathy (score of 53) to advanced proliferative diabetic retinopathy (score of 85).[18] While the scale is non-linear, evidence demonstrates an increased risk of progression to proliferative retinopathy with higher levels of disease.[18] In patients with concomitant diabetic macular edema, more patients treated with ranibizumab had a 3-step improvement from baseline compared to sham injection at 24 months (estimated treatment differences of 15% (95% CI 7 to 22%) and 9% (95% CI 4 to 14%) for each trial).[17] Subgroup analyses based on age, baseline BCVA, disease severity, or prior treatments were consistent with the overall population.[17] One study (n=394) compared ranibizumab to panretinal photocoagulation in patients with or without macular edema.[17] The majority of patients enrolled had proliferative diabetic retinopathy (50% with mild-moderate; 37% with high-risk).[17] Approximately 78% of enrolled patients did not have concomitant macular edema present at baseline.[17] Baseline ETDRS-DRSS severity ranged from 20 to 85.[17] The primary outcome for this trial was mean change in BCVA at 2 years. Results of this study at 2 years indicate ranibizumab was noninferior to panretinal photocoagulation (difference 2.2 letters; 95% CI, -0.5 to 5.0).[19] FDA-approval was based on a secondary subgroup analyses indicating there was no difference in ETDRS-DRSS severity upon comparison of patients with or without macular edema. At 24 months, the proportion of patients with a 3-step improvement from baseline in ETDRS-DRSS was 32% (95% CI 17% to 46%) for patients with baseline macular edema compared to 28% (95% CI 21% to 36%) in patients without macular edema.[17]

In 2019, aflibercept received and expanded indication in a similar population of patients with diabetic retinopathy. Approval was based on data from the same trials used for FDA approval in diabetic macular edema and was supported by additional data from the PANORAMA trial. The PANORAMA trial enrolled patients with non-proliferative diabetic retinopathy and compared aflibercept (dosed every 8 or 16 weeks) to sham injection. The proportion of patients who had a 2 or more step improvement in the ETDRS-DRSS was evaluated at 24 and 52 weeks. At 24 weeks, both treatment groups had a greater proportion of patients with a 2-step improvement from baseline compared to placebo (adjusted difference of 52%; 95% CI 45% to 60%).[20] Significantly more patients at 52 weeks had a 2-step improvement when administered aflibercept every 8 weeks (80%) compared to placebo (15%; adjusted difference of 65%; 95% CI 56 to 74).[20]

New FDA Safety Alerts:
No new FDA safety alerts identified.

Randomized Controlled Trials:
A total of 258 citations were manually reviewed from the initial literature search. After further review, all other citations were excluded because of wrong study design (e.g., observational or post-hoc analyses), comparator (e.g., no control, placebo-controlled, or non-pharmacologic control), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
FDA approval for brolucizumab was primarily based on results from 2 phase 3 studies (HAWK and HARRIER) with supporting clinical evidence from a phase 2B study.[6,21] HAWK and HARRIER were multicenter, randomized non-inferiority trials evaluating efficacy of brolucizumab compared to aflibercept.

Loading doses of brolucizumab were administered through week 16 with subsequent maintenance doses administered every 8 or 12 weeks based on the disease activity of the patient. Disease activity was assessed based on changes in BCVA and/or new or worsening intraretinal fluid or intraretinal cysts.[6] However, it is unclear whether the criteria used to evaluate disease activity would accurately identify patients needing more frequent treatment. Other clinical trials using similar measures have failed to differentiate between patients needing additional treatment based on final visual acuity tests. Overall, the trial was well designed with only small differences in baseline characteristics. While use of sham injection techniques may increase risk of performance and detection bias, it is less likely to impact objective measures of visual function. Attrition was overall similar between groups. Patients were on average 76 years of age and had a mean BCVA of 60 letters (approximately 20/63 on the Snellen chart).[6] Other disease characteristics are listed in **Table 2**.

In both HAWK and HARRIER, brolucizumab 6 mg was non-inferior to aflibercept for the primary outcome of mean change in BCVA at 48 weeks.[6] The mean difference between treatments was -0.2 letters (95% CI -2.1 to 1.8) for HAWK and -0.7 letters (95% CI -2.1 to 1.0) for HARRIER.[6] The pre-specified non-inferiority margin was defined as a lower limit of -4 letters for BCVA corresponding to a difference of less than one line on the ETDRS chart.[6] Secondary clinical outcomes including mean change in BCVA at 36-48 weeks, and proportion of patients gaining 15 or more letters supported these findings. Subgroup analyses were conducted based on age and baseline BCVA. Results were overall consistent for all subgroups. Only one subgroup (patients with a BCVA of 55 letters or less on the ETDRS chart) failed to meet the prespecified non-inferiority margin.[6]

Secondary anatomic outcomes of disease activity included assessment of CST, presence of subretinal or intraretinal fluid and disease activity at week 16 were tested for superiority based upon a pre-specified analysis.[6] Disease activity was defined as 1) decrease in BCVA of 5 or more letters 2) new or worsening intraretinal cysts or fluid or 3) decrease in BCVA of 3 or more letters and CST increase of at least 75 µm.[6] Often anatomic changes precede visual acuity changes and may serve as an early marker for worsening disease. Brolucizumab 6 mg had improved CST at week 16 (MD of -27.8 µm; 95% CI -45.1 to -10.5 and -40.2 µm; 95% CI -58.9 to -21.6) and presence of subretinal or intraretinal fluid at week 48 (-13.5%; 95% CI -20.7 to -6.1% and 18.1%; 95% CI -24.9 to -11.8%) compared to aflibercept in both trials.[6] Similarly, more patients had reduced disease activity at 16 weeks upon comparison of brolucizumab 6 mg and aflibercept 2 mg every 8 weeks (24% vs. 34%; MD -14.5%; 95% CI -17.1% to -3.5% for HAWK and 23% vs. 32% MD -9.5%; 95% CI -15.8% to -3.1% for HARRIER, respectively).[6] The clinical

significance of these anatomic findings is unclear as there is no consensus on whether CST correlates with functional outcomes. However, these results provide supporting evidence for brolucizumab for treatment of neovascular AMD.

At this time, long-term efficacy, comparison to other treatments for neovascular AMD, and efficacy for other ocular indications remain unknown. There are ongoing clinical trials to assess efficacy of brolucizumab in patients with DME and RVO as well as trials to assess other alternative dosing regimens.

Clinical Safety:

A total of 1088 patients were included in the safety analysis conducted by the FDA.[7] Of these patients, 730 had received the FDA-approved dose of 6 mg.[7] Common adverse events occurring in more than 5% of patients treated with brolucizumab included blurred vision, cataracts, conjunctival hemorrhage, vitreous floaters and eye pain.[7] Overall, occurrence of adverse events was similar to aflibercept, though incidence of cataracts was numerically higher in patients treated with aflibercept (11%) compared to brolucizumab (7%).[7] Labeling is consistent with other VEGF inhibitors and includes contraindications for patients active intraocular inflammation or periocular infection.[7] Warnings which are consistent with other VEGF inhibitors include endophthalmitis, retinal detachment, increased intraocular pressure, and thrombotic events.[7] Additionally brolucizumab had warnings for retinal vasculitis and retinal vascular occlusion which have been reported and typically occur in the presence of intraocular inflammation. In phase 3 trials, incidence of serious ocular adverse events were infrequent (1-3%) and similar between groups.[6] Similarly, there were no statistical differences in rates of serious systemic adverse events compared to aflibercept and events were numerically higher with aflibercept treatment in both trials.[6] Only 1-3% of patients discontinued treatment due to adverse events. Thrombotic events documented over 96 weeks of treatment were 4.5% with brolucizumab compared to 4.7% of patients treated with aflibercept.[7] Thrombotic events thought to be associated with VEGF inhibitor administration can include nonfatal stroke, nonfatal myocardial infarction, or vascular death.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual symptom improvement
2) Visual Function or Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Best corrected visual acuity (BCVA)

Table 1. Pharmacology and Pharmacokinetic Properties.[7]

Parameter	
Mechanism of Action	Brolucizumab is a VEGF inhibitor which binds to VEGF-A isoforms preventing interaction with VEGF receptors and limiting endothelial cell proliferation, neovascularization and vascular permeability.
Oral Bioavailability	NA
Distribution and Protein Binding	Mean Cmax of 49 ng/mL (range 4 to 548 ng/mL) at 24 hours post-dose; no accumulation was observed in most patients after repeated dose administration at 4 weeks
Elimination	Exact excretion is unknown, but it is expected to undergo target-mediated disposition at VEGF receptors or passive renal excretion
Half-Life	Mean 4.4 days (SD 2.0) after a single dose
Metabolism	Exact metabolism is uncharacterized; free antibody is expected to undergo proteolysis

Abbreviations: Cmax = maximum serum concentration; NA = not applicable; ng/mL = nanograms per milliliter; SD = standard deviation; VEGF = vascular endothelial growth factor

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dugel, et al.[6] HAWK DB, MC, AC, phase 3, RCT Duration: 2 years	1. brolucizumab 3 mg 2. brolucizumab 6 mg 3. aflibercept 2 mg Aflibercept administered at weeks 0, 4, 8 and every 8 weeks thereafter Brolucizumab administered at weeks 0, 4, 8 and every 12 weeks thereafter. If disease activity was identified after loading period (week 16), dose was increased to every 8 weeks. About 50% of patients maintained dose every 12 weeks throughout the study.	Demographics: - Mean BCVA: 60.6 letters - BCVA ≥71 letters 1. 31% 2. 28% 3. 25% - Mean age: 76.5 - Female: 56% - White: 81%; Asian: 15% - Occult CNV: 58% - Predominately classic CNV: 32% - Mean CST: 462 mm - CST ≥400 mm 1. 56% 2. 56% 3. 59% - Subretinal fluid present: 69% - Subretinal hemorrhage present: 1. 11.5% 2. 15% 3. 14.5% Key Inclusion Criteria: - Age ≥ 50 years - Untreated neovascular AMD - CNV lesions in the central subfield (1mm from the foveal center) - CNV lesions for >50% of total lesion area - Intraretinal or subretinal fluid affecting the central subfield - BCVA of 78 to 23 ETDRS letters (Snellen chart of ~20/32 to 20/400) Key Exclusion Criteria: - Fibrosis, subretinal blood, or geographic atrophy in the central subfield or for ≥50% of the total lesion area - Other current eye conditions (retinal tears, vitreous hemorrhage, IOP ≥ 25 mmHg, infection or inflammation) - Prior therapy for AMD including recent use of VEGF inhibitors, surgery or laser treatment - History of intraocular surgery within prior 90 days, prior vitrectomy,	ITT: 1. 360 2. 361 3. 361 PP: 1. 325 2. 328 3. 312 Attrition: 1. 31 (9%) 2. 37 (10%) 3. 46 (13%)	Primary Endpoint: Change in mean BCVA (week 48) 1. 6.1 (SE 0.69) 2. 6.6 (SE 0.71) 3. 6.8 (SE 0.71) 1 vs. 3: -0.6 (95% CI -2.5 to 1.3); p<0.001 for NI 2 vs. 3: -0.2 (95% CI -2.1 to 1.8); p<0.001 for NI Secondary Endpoints: Change in averaged BCVA (week 36-48) 1. 6.2 (SE 0.67) 2. 6.7 (SE 0.68) 3. 6.7 (SE 0.68) 1 vs. 3: -0.5 (95% CI -2.4 to 1.3); p<0.001 for NI 2 vs. 3: 0 (95% CI -1.9 to 1.9); p<0.001 for NI BCVA gain of ≥ 15 letters 1. 25.2% 2. 33.6% 3. 25.4% p-value NR BCVA loss of ≥ 15 letters 1. 5.9% 2. 6.4% 3. 5.5% p-value NR	NA for all	DC due to AE 1. 8 (2%) 2. 11 (3%) 3. 8 (2%) Ocular AE 1. 175 (49%) 2. 179 (50%) 3. 170 (47%) Ocular SAE 1. 5 (1.4%) 2. 11 (3.1%) 3. 3 (0.8%) Non-ocular SAE 1. 47 (13.1%) 2. 47 (13.1%) 3. 68 (18.9%) Arterial thrombo-embolic event 1. 11 (3.1%) 2. 6 (1.7%) 3. 10 (2.8%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Adequate randomization and allocation concealment via interactive response technology. Average BVCA and CST was similar between groups, but BVCA≥71 letters was less frequent in aflibercept group which may bias results in favor of treatment and CST≥400 mm was slightly more frequent in aflibercept group which may provide a more conservative treatment effect. Performance Bias: LOW. Use of similar dosing regimen up to 16 weeks only. After week 16, sham placebo injections were administered to maintain blinding. Patient, sponsor, central reading centers and providers involved in monitoring, reviewing, or obtaining clinical evaluations were masked to treatment. Administering providers were not masked to treatment. Detection Bias: LOW. Providers involved in monitoring, reviewing, or obtaining clinical evaluations were masked to treatment. Masked investigator assessed disease activity. Attrition Bias: LOW. Overall attrition was low and slightly more frequent with aflibercept. Analysis performed with both PP and ITT using LOCF or observed data based on mixed-model repeated measures analysis for missing data. Reporting Bias: LOW. Pre-specified hierarchical testing method used to evaluate non-inferiority then superiority. Other Bias: UNCLEAR. Sponsor involved in writing draft. All except one author had financial disclosures related to industry. **Applicability**: Patient: Baseline characteristics consistent with expected AMD population. Intervention: FDA-approved dose of brolucizumab is 6 mg monthly for 3 doses then 6 mg every 8-12 weeks. Comparator: FDA-approved regimen of aflibercept every 8 weeks was used. While brolucizumab maintenance dose was adjusted based on disease activity, aflibercept dose was not. In general, there

		penetrating keratoplasty, panretinal photocoagulation - Corticosteroid eye drops in the prior 6 months - ≥30 days of systemic corticosteroids within the prior 90 days (low stable doses permitted) - Stroke or MI in the prior 90 days or blood pressure > 160/100 mmHg						were no differences in efficacy of monthly vs. every 8 week injections of aflibercept in trials. However, labeling for aflibercept indicates that some patients may benefit from more frequent monthly dosing. Outcomes: Changes of BCVA appropriate to evaluate visual changes in AMD. Setting: New Zealand, Israel, Australia, Japan, North, Central, and South America from December 2014 to May 2016. Proportion of patients from the United States was not reported.

2. Dugel, et al.[6]
 	
HARRIER
 	
DB, MC, AC, phase 3, RCT
 	
Duration: 2 years
	1. brolucizumab 6 mg
	2. aflibercept 2 mg
	
	See HAWK for dosing regimens
		Demographics:
		- Mean BCVA: 61.2 letters
		- Mean age: 75 years
		- Female: 57%
		- White: 92%
		- Type of CNV
		  - Occult: 50%
		  - Predominately classic: 40%
		- Mean CST: 469.5 mm
		- CST ≥400 mm
		  1. 60%
		  2. 65%
		- Subretinal fluid present:
		  1. 68%
		  2. 73%
		- Intraretinal hemorrhage present:
		  1. 28%
		  2. 18%
		
		Key Inclusion Criteria:
		See HAWK
		
		Key Exclusion Criteria:
		See HAWK
			ITT:
			1. 372
			2. 371
			
			PP:
			1. 351
			2. 341
			
			Attrition:
			1. 25 (7%)
			2. 24 (6%)
				Primary Endpoint:
				Change in mean BCVA (week 48)
				1. 6.9 (SE 0.61)
				2. 7.6 (SE 0.61)
				-0.7 (95% CI -2.1 to 1.0); p<0.001
				
				Secondary Endpoints:
				Change in averaged BCVA at weeks 36-48
				1. 6.5 (SE 0.58)
				2. 7.7 (SE 0.58)
				-1.2 (95% CI -2.8 to 0.5); p<0.001 for NI
				
				BCVA gain of ≥ 15 letters
				1. 29.3%
				2. 29.9%
				p-value NR
				
				BCVA loss ≥ 15 letters
				1. 3.8%
				2. 4.8%
				p-value NR
					NA for all	DC due to AE
						1. 12 (3%)
						2. 4 (1%)
						
						Ocular AE
						1. 122 (33%)
						2. 119 (32%)
						
						Ocular SAE
						1. 9 (2.4%)
						2. 4 (1.1%)
						
						Non-ocular SAE
						1. 35 (9.5%)
						2. 43 (11.7%)
						
						Arterial thrombo-embolic event
						1. 6 (1.6%)
						2. 8 (2.2%)
							NA for all	**Risk of Bias (low/high/unclear)**:
								Selection Bias: UNCLEAR. See HAWK. Baseline characteristics mostly balanced. There were slight differences between groups in patients with CST ≥400 mm, intraretinal hemorrhage, and subretinal fluid.
								Performance Bias: LOW. See HAWK
								Detection Bias: LOW. See HAWK
								Attrition Bias: LOW. See HAWK. Overall attrition was low and similar between groups.
								Reporting Bias: LOW. See HAWK.
								Other Bias: UNCLEAR. See HAWK
								
								Applicability:
								Patient: See HAWK.
								Intervention: See HAWK.
								Comparator: See HAWK.
								Outcomes: See HAWK.
								Setting: Europe, Middle East, Asia, and Russia. Enrollment dates between June 2105 and April 2016.

Abbreviations [alphabetical order]: AC = active controlled; AE = adverse event; AMD = age-related macular degeneration; ARR = absolute risk reduction; BCVA = best corrected visual acuity; CI = confidence interval; CNV = choroidal neovascular; CST = central subfield thickness; DB = double blind; DC = discontinuation; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; ITT = intention to treat; LOCF = last observation carried forward; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NI = noninferiority; NNT = number needed to treat; NR = not reported; PP = per protocol; RCT = randomized controlled trial; SE = standard error; SAE = severe adverse event.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
bevacizumab	AVASTIN	VIAL	intravenous	Y
aflibercept	EYLEA	SYRINGE	intraocular	N
aflibercept	EYLEA	VIAL	intraocular	N
pegaptanib sodium	MACUGEN	SYRINGE	intraocular	N
ranibizumab	LUCENTIS	SYRINGE	intraocular	N
ranibizumab	LUCENTIS	VIAL	intraocular	N

Appendix 2: Abstracts of Comparative Clinical Trials

None

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 09, 2020

1	exp bevacizumab/ or exp ranibizumab/	13307
2	aflibercept.mp.	2032
3	brolucizumab.mp.	20
4	pegaptanib.mp.	628
5	exp vascular endothelial growth factors/	53160
6	1 or 2 or 3 or 4 or 5	62378
7	exp Retinal Degeneration/	41253
8	exp Retinal Diseases/	127979
9	7 or 8	127979
10	6 and 9	8152
11	limit 10 to (english language and humans)	6819
12	limit 11 to yr="2017 -Current"	1497
14	limit 12 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	258

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEOVU safely and effectively. See full prescribing information for BEOVU.

BEOVU® (brolucizumab-dbll) injection, for intravitreal injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
BEOVU is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1).

----------DOSAGE AND ADMINISTRATION----------
BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks (2).

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 6 mg/0.05 mL solution for intravitreal injection in a single-dose vial (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Active intraocular inflammation (4.2).
- Hypersensitivity (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).
- Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2019

Appendix 5: Key Inclusion Criteria

Population	Patients with macular edema
Intervention	Drugs in **Appendix 1**
Comparator	Drugs in **Appendix 1**
Outcomes	Improvement in symptoms (e.g., visual acuity), function, quality of life, mortality, serious adverse events, or withdrawals due to adverse events
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes**: Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve for 12 months, or for length of the prescription, whichever is less
4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve for 12 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *8/20; 3/17 (SS)*
Implementation: *TBD*