

Ranibizumab

ACG: A-0450 (AC)
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Clinical Indications

- Ranibizumab may be indicated when **ALL** of the following are present(1)(2):
 - Age 18 years or older
 - Eye condition appropriate for ranibizumab treatment, as indicated by **1 or more** of the following:
 - Diabetic macular edema[A](23)(24)(25)(26)(27)(28)[N](#)
 - Diabetic retinopathy[B](25)(26)(36)(43)[N](#)
 - Macular edema following retinal vein occlusion[C](46)(47)(48)(49)(50)[N](#)
 - Myopic choroidal neovascularization[D](63)[N](#)
 - Neovascular (wet, or exudative) age-related macular degeneration[E](24)(69)(70)(71)(72)(73)(74)[N](#)
 - Ocular histoplasmosis[F] with choroidal neovascularization(90)[N](#)
 - Polypoidal choroidal vasculopathy[G] with active juxtafoveal or subfoveal lesions and **ALL** of the following(93):[N](#)
 - Diagnosis of polypoidal choroidal vasculopathy and **1 or more** of the following:
 - Fluorescein angiography results show leakage at retinal pigment epithelium.
 - Pigment epithelium detachment
 - Subretinal hemorrhage or sub-retinal pigment epithelium hemorrhage
 - Subretinal or intraretinal fluid
 - Vision loss attributable to polypoidal choroidal vasculopathy
 - Concurrent administration with verteporfin photodynamic therapy
 - No concurrent ocular or periocular infection

Evidence Summary

Background

Ranibizumab is a recombinant human monoclonal antibody that acts as an antagonist to vascular endothelial growth factor and inhibits angiogenesis and vascular permeability.(1)(3) (**EG 2**)

Criteria

The evidence for the clinical indications found in this guideline includes 76 published peer reviewed articles, 6 specialty society or other evidence-based guidelines, and 10 Cochrane systematic reviews.

For diabetic macular edema, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review and meta-analysis of 8 randomized trials (1067 eyes) comparing ranibizumab with aflibercept for the treatment of diabetic macular edema found, at 12-month follow-up, that there was no difference in either best-corrected visual acuity or reduction of central macular thickness between the 2 treatment groups.(29) **(EG 1)** A randomized study of 854 eyes in 691 patients with diabetic macular edema assigned patients to sham injection with prompt laser, ranibizumab injection with prompt laser, triamcinolone injection with prompt laser, or ranibizumab injection with laser deferred by at least 24 weeks. After 1 year of follow-up, ranibizumab with prompt or deferred laser appeared to be the most effective treatment.(30) **(EG 1)** Longer-term 3-year and 5-year follow-up studies of patients enrolled in this trial reported that continued ranibizumab therapy resulted in improved foveal thickness and best-corrected visual acuity, and that adding prompt laser is no better, and possibly worse, than deferring laser treatment for at least 24 weeks. However, the number of cumulative ranibizumab injections was fewer in the prompt laser group, which may have been responsible for some of the observed differences.(31)(32) **(EG 1)** A randomized controlled trial of 396 patients showed that ranibizumab monotherapy or ranibizumab combined with laser showed superior improvements in best-corrected visual acuity as compared with laser treatment alone.(33) **(EG 1)** Systematic and literature reviews of randomized controlled trials concluded that, in a proportion of patients with diabetic macular edema, vascular endothelial growth factor inhibitors such as ranibizumab result in better visual acuity than treatment with laser photocoagulation or sham therapy. However, the authors acknowledged that long-term efficacy and the number of ranibizumab injections required for long-term improvement of diabetic macular edema are unknown.(34)(35) **(EG 1)** Two parallel, phase III, multicenter, double-blind, sham injection-controlled, randomized studies of 377 and 382 patients with decreased vision due to diabetic macular edema studied the effect of monthly intravitreal injections of ranibizumab on best-corrected visual acuity at 24 months. Results showed that patients treated with monthly injections of 0.3 mg of ranibizumab were more likely to gain 15 or more letters on an eye chart, as compared with sham patients (34% to 45% vs 12% to 18%, respectively). In addition, improvement in macular edema was seen on optical coherence tomography.(36) **(EG 1)** A study of 759 patients from both trials reported that intravitreal ranibizumab significantly reduced the risk of progression of diabetic macular edema as compared with sham treatment at 3-year follow-up.(37) **(EG 1)** A randomized study focusing specifically on patient-reported visual outcomes in diabetic macular edema confirmed significant incremental benefit from ranibizumab, with reported subjective improvement reflecting objectively documented visual acuity improvement.(38) **(EG 1)** A randomized study of 660 adults with diabetic macular edema who received either intravitreal aflibercept, ranibizumab, or bevacizumab found, after 1 year, that visual acuity improvement was comparable among all 3 drugs in those with mild initial visual acuity loss.(39) **(EG 1)** A secondary analysis also found, at 2-year follow-up, that aflibercept, bevacizumab, and ranibizumab therapy for diabetic macular edema resulted in an improvement in diabetic retinopathy in 24.8%, 22.1%, and 31.0%, respectively, of eyes with nonproliferative diabetic retinopathy at baseline and 70.4%, 30.3%, and 37.5%, respectively, of eyes with proliferative diabetic retinopathy at baseline.(40) **(EG 1)** Randomized studies of patients with diabetic macular edema who received ranibizumab for 12 to 36 months have shown that diabetic retinopathy often improves or worsens to a lesser degree.(41) **(EG 1)** A systematic review and meta-analysis of 8 randomized controlled trials (817 eyes) evaluating the efficacy of intravitreal ranibizumab or bevacizumab combined with intravitreal steroids for the treatment of diabetic macular edema found no difference in both the mean change in visual acuity and central macular thickness at 6-month to 2-year follow-up compared with vascular endothelial growth factor inhibitor therapy alone. Additionally, combination therapy was associated with an increased rate of cataract development and raised intraocular pressure.(42) **(EG 1)**

For diabetic retinopathy, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Two parallel, phase III, multicenter, double-blind, sham injection-controlled, randomized studies of 377 and 382 patients studied the effect of monthly intravitreal injections of ranibizumab on impaired vision due to diabetic macular edema. At 24 months, patients given ranibizumab as compared with sham treatment noted improved visual acuity and were less likely to develop proliferative diabetic retinopathy (3.6% vs 13.2%, respectively).(36) **(EG 1)** A randomized controlled study with 305 adults and 394 eyes with diabetic proliferative retinopathy assigned patients to treatment with either intravitreal ranibizumab or panretinal photocoagulation; 108 eyes (53%) treated with panretinal photocoagulation also received ranibizumab for diabetic macular edema, either at baseline or during the 2-year trial. At 2-year follow-up, 47% of eyes treated with ranibizumab improved 2 steps or greater in diabetic retinopathy severity as measured by fundus photography; additionally, visual acuity in patients given ranibizumab was noninferior to those treated with panretinal photocoagulation.(43) **(EG 1)** An extension of this study found, at 5-year follow-up, that visual acuity letter scores and mean visual acuity were similar between the ranibizumab and photocoagulation treatment groups. However, treatment with ranibizumab was associated with fewer patients developing vision-impairing diabetic macular edema compared with photocoagulation.(44) **(EG 1)** A phase II study of 106 patients with proliferative diabetic retinopathy compared treatment with ranibizumab, panretinal laser photocoagulation, or the combination of both and found, at 12-month follow-up, that ranibizumab monotherapy was associated with a decrease from baseline in the area of neovascularization and improved best-corrected visual acuity compared with laser photocoagulation monotherapy; no difference was seen between either monotherapy compared with combination therapy.(45) **(EG 1)** An international consensus guideline recommends ranibizumab for the treatment of proliferative diabetic retinopathy.(23) **(EG 2)**

For macular edema following retinal vein occlusion, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Meta-analyses and systematic reviews have confirmed the efficacy and safety of vascular endothelial growth factor inhibitors for treatment of central and branch retinal vein occlusion for up to 26 to 52 weeks.(51)(52)(53)(54) **(EG 1)** A network meta-analysis of 8 randomized controlled studies of various interventions for branch retinal vein occlusion found no statistically significant difference between aflibercept and ranibizumab in terms of efficacy.(55) **(EG 1)** A systematic review and meta-analysis of 5 studies including 678 patients with macular edema due to branch retinal vein occlusion compared treatment with ranibizumab or dexamethasone intravitreal implant and found, at 6-month follow-up, that ranibizumab was associated with improved best-corrected visual acuity from baseline compared with dexamethasone.(56) **(EG 1)** A randomized controlled trial of 98 patients with either central or branch retinal vein occlusion found that intravitreal bevacizumab and ranibizumab have similar efficacy in improving both macular thickness and visual acuity after 6 months.(57) **(EG 1)** A randomized noninferiority trial of 463 patients with macular edema due to central retinal vein

occlusion compared treatment with ranibizumab, aflibercept, or bevacizumab and found, at 100-week follow-up, mean gains in best-corrected visual acuity letter scores of 12.5, 15.1, and 9.8 in patients treated with ranibizumab, aflibercept, and bevacizumab, respectively. The authors found that aflibercept was noninferior compared with ranibizumab; however, bevacizumab was not noninferior compared with ranibizumab.(58) **(EG 1)** Specialty society guidelines state that several studies support ranibizumab for treatment of macular edema due to retinal vein occlusion.(59)(60)(61)(62) **(EG 2)**

For myopic choroidal neovascularization, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A meta-analysis and systematic review of 6 randomized studies of 594 patients with myopic choroidal neovascularization found low-certainty to moderate-certainty evidence that ranibizumab is effective in treating this condition for up to a period of 1 to 2 years.(64) **(EG 1)** A technology assessment and systematic reviews of randomized controlled trials report that ranibizumab may be an effective option for myopic choroidal neovascularization, although there is uncertainty about longer-term effectiveness.(65)(66)(67) **(EG 1)** A specialty society consensus statement supported by a literature review recommends that vascular endothelial growth factor inhibitor therapy should be the first-line treatment for patients with myopic choroidal neovascularization.(68) **(EG 2)**

For neovascular age-related macular degeneration, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A meta-analysis of 15 randomized controlled trials (8320 patients) evaluating the relative efficacy of vascular endothelial growth factor inhibitors for neovascular age-related macular degeneration found that ranibizumab and bevacizumab had comparable best-corrected visual acuity at 1 and 2 years of treatment, while ranibizumab had a greater reduction in central macular thickness from baseline at 2-year follow-up.(74) **(EG 1)** A systematic review and meta-analysis of randomized controlled trials reported that ranibizumab is effective in improving visual acuity.(75) **(EG 1)** A meta-analysis and systematic review identified 2 randomized trials with a total of 2457 patients with neovascular age-related macular degeneration who received either intravitreal aflibercept or ranibizumab and found that patients achieved comparable improvement in visual acuity with either drug up to 1 year after initiation of treatment.(76) **(EG 1)** However, other authors have found that intraocular pressure is higher in patients who receive ranibizumab as compared with aflibercept.(77) **(EG 1)** A randomized trial of 278 patients with neovascular age-related macular degeneration compared treatment with intravitreal ranibizumab or aflibercept and found, at 24-month follow-up, no difference in development or growth of macular atrophy or change in best-corrected visual acuity between the groups.(78) **(EG 1)** In a multicenter randomized single-blind trial, 1208 patients with neovascular age-related macular degeneration were assigned to receive intravitreal injections of either bevacizumab or ranibizumab, either monthly or as needed with monthly evaluation. After 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule.(79) **(EG 1)** These results were maintained at 2-year follow-up.(80)(81)(82) **(EG 1)** Four randomized trials, of 610, 501, 441, and 327 patients with neovascular age-related macular edema, reported equivalent outcomes with either ranibizumab or bevacizumab at 1-year follow-up.(83)(84)(85)(86) **(EG 1)** A long-term open-label extension study of patients from 3 prior randomized clinical trials reported that patients with neovascular age-related macular edema receiving ranibizumab maintained vision for over 4 years.(87) **(EG 2)** A meta-analysis of randomized studies totaling 2686 patients receiving either bevacizumab or ranibizumab for neovascular age-related macular edema confirmed that both drugs had comparable positive effects on visual acuity after 1 year but that bevacizumab was associated with a higher risk of serious systemic adverse events.(88) **(EG 1)** A specialty society guideline recommends ranibizumab as a management option for patients with age-related neovascular macular degeneration.(69) **(EG 2)**

For ocular histoplasmosis with choroidal neovascularization, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A retrospective chart review of 54 eyes with ocular histoplasmosis treated with either intravitreal ranibizumab or bevacizumab found, at 26.8-month follow-up, that treatment with either agent was associated with improved visual acuity.(91) **(EG 2)** A randomized controlled trial (9 patients) compared intravitreal ranibizumab with intravenous verteporfin phototherapy for treatment of ocular histoplasmosis and found, at 1-year follow-up, no difference in visual acuity measures between groups; notably, all patients in the phototherapy group received rescue ranibizumab due to symptom worsening on phototherapy alone. The authors recommended further, larger randomized trials.(92) **(EG 1)** A phase I randomized controlled trial (30 patients) compared scheduled monthly intravitreal ranibizumab with 3 monthly injections followed by as-needed dosing in patients with choroidal neovascularization (including 9 with ocular histoplasmosis) and found, at 12-month follow-up, that visual acuity improved similarly in both groups.(7) **(EG 1)** A narrative review notes that both verteporfin and anti-vascular endothelial growth factor injections are treatment options for patients with ocular histoplasmosis with choroidal neovascularization.(89) **(EG 2)**

For polypoidal choroidal vasculopathy, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A randomized controlled trial of 322 patients with symptomatic macular polypoidal choroidal vasculopathy who underwent photodynamic therapy with verteporfin in combination with ranibizumab found, at 12-month follow-up, a greater improvement in best-corrected visual acuity from baseline (8.3 letters) and a higher rate of complete polyp regression (69.3%) compared with ranibizumab treatment alone (5.1 letters improvement in best-corrected visual acuity from baseline and 34.7% complete polyp regression).(94) **(EG 1)** At 24-month follow-up, the adjusted mean best-corrected visual acuity gains were 9.6 letters and 5.5 letters in the combination therapy and ranibizumab groups, respectively, and rates of complete polypoidal regression were 56.6% and 26.7% in the combination therapy and ranibizumab groups, respectively.(95) **(EG 1)** A meta-analysis and systematic review found 2 randomized studies involving 68 patients and determined that photodynamic therapy was more effective than ranibizumab at improving central retinal thickness and polypoidal regression at 6 months; however, both therapies appeared to be comparable in significantly improving visual acuity for up to 24 months.(96) **(EG 1)** An evidence-based guideline recommends initial treatment of juxtafoveal and subfoveal polypoidal choroidal vasculopathy with photodynamic therapy with verteporfin, either alone or combined with antiangiogenic therapy with ranibizumab, as well as retreatment for incomplete regression of polyps.(93) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For central serous chorioretinopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A network meta-analysis of interventions for central serous chorioretinopathy found that treatment with anti-vascular endothelial growth factor agents did not consistently demonstrate improvement in visual acuity.(4) **(EG 1)** A consensus guideline notes that evidence does not support treatment with anti-vascular endothelial growth factor agents such as ranibizumab for patients with central serous chorioretinopathy; however, off-label treatment may be considered for patients who have evidence of macular neovascularization.(5) **(EG 2)**

For choroidal neovascularization due to angioid streaks, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A retrospective case series of 39 patients (52 eyes) with choroidal neovascularization secondary to angioid streaks treated as needed with ranibizumab (33 eyes), bevacizumab (13 eyes), or a combination (6 eyes) found, at a mean follow-up of 33.8 months, that treatment slowed the progression of choroidal neovascularization but did not prevent progressive visual loss. Further prospective randomized studies were recommended.(6) **(EG 2)** A phase I randomized controlled trial (30 patients) compared scheduled monthly intravitreal ranibizumab with 3 monthly injections followed by as-needed dosing in patients with choroidal neovascularization (including 3 with angioid streaks) and found, at 12-month follow-up, that visual acuity improved similarly in both groups. Due to the small number of patients, the authors recommended larger randomized studies to confirm the findings.(7) **(EG 1)**

For neovascular glaucoma, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis and systematic review studying the subconjunctival use of ranibizumab or bevacizumab to inhibit scar formation after trabeculectomy for glaucoma found 5 randomized controlled trials involving 177 eyes; however, the studies were heterogeneous and of low quality, and the authors stated that the evidence was insufficient to refute or support the use of ranibizumab or bevacizumab for this indication.(8) **(EG 1)** A systematic review evaluating intravitreal anti-vascular endothelial growth factors for treatment of neovascular glaucoma (including 2 studies of ranibizumab) found that, as an adjunct to panretinal photocoagulation, anti-vascular endothelial growth factors may help reduce intraocular pressure in the short term (4 to 6 weeks), but long-term effects are uncertain; further studies were recommended.(9) **(EG 1)**

For a port delivery system, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A phase III, open-label, randomized, noninferiority trial of 418 patients with neovascular age-related macular degeneration (all of whom had been treated with a least 3 prior anti-vascular endothelial growth factor injections) compared treatment with either monthly ranibizumab intravitreal injections or ranibizumab delivered via a port delivery system every 24 weeks and found, at 40-week follow-up, no difference in best-corrected visual acuity between groups. The ocular adverse event rate was higher among patients treated with the port delivery system compared with those treated with monthly intravitreal injections.(10) **(EG 1)**

For radiation retinopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** An industry-sponsored phase IIb randomized trial of 40 untreated patients with radiation-induced macular edema and decreased visual acuity (2.5 years after radiation therapy) compared 3 treatment regimens for 1 year (monthly ranibizumab alone, monthly ranibizumab plus targeted retinal photocoagulation, or as-needed ranibizumab plus targeted retinal photocoagulation after 3 monthly ranibizumab doses) followed by a treat-and-extend regimen for an additional year and found, at 48-week follow-up, improved central macular thickness and best-corrected visual acuity in all 3 arms; by 104-week follow-up, these improvements regressed to baseline and remained similar in all 3 arms. However, the authors noted that the small sample size and losses to follow-up limited the results, and further large randomized controlled trials were recommended.(11)(12) **(EG 1)** A retrospective review of 120 patients with radiation retinopathy treated with intravitreal ranibizumab or bevacizumab found, at a mean treatment interval of 38 months, that 80% of patients who received 3 or more injections remained within 2 lines of their initial visual acuity or better, with few acute or long-term side effects noted. However, due to the uncontrolled nature of the review, the authors noted that outcome assessments were limited.(13) **(EG 2)**

For retinal angiomatous proliferation, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A prospective case series of 31 patients treated over 13 months found that intravitreal ranibizumab resulted in improvements in both visual acuity and macular thickness. The authors concluded that longer-term randomized controlled studies are warranted.(14) **(EG 2)** Similar results were noted in a retrospective case series of 20 eyes in 15 patients, after up to 24 months, but the results for visual improvement were only statistically significant for the first 3 months.(15) **(EG 2)** A randomized study assigned 50 patients with early or moderate disease to either intravitreal bevacizumab or ranibizumab; each group demonstrated comparable significant improvement after 1 year. However, there was no untreated control group, and the authors indicated that large randomized studies are needed.(16) **(EG 1)**

For retinopathy of prematurity, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review evaluating the efficacy of anti-vascular endothelial growth factor drugs for the treatment of retinopathy of prematurity identified one randomized trial (50 infants) comparing ranibizumab with laser therapy and found no decrease in the risks of retinal detachment, disease recurrence, and corneal or lens opacities requiring treatment between groups. The authors concluded that further studies are needed to evaluate structural and functional outcomes in childhood and delayed systemic effects.(17) **(EG 1)** A randomized open-label trial that included 225 infants born at less than 1500 grams with bilateral retinopathy of prematurity compared treatment with either intravitreal ranibizumab (at 1 of 2 doses) or laser therapy and found, at 24-

week follow-up, that ranibizumab was not significantly more likely than laser therapy to lead to treatment success, as defined by survival without active retinopathy of prematurity, unfavorable structural outcomes, or treatment switch. The study was limited by slow enrollment requiring a change in total patients per treatment arm and potential for bias due to individualized retreatment decisions and other factors.(18) **(EG 1)** A network meta-analysis of retreatment rates following treatment with anti-vascular endothelial growth factor agents or laser found that laser treatment was associated with a reduction in treatment risk compared with ranibizumab.(19) **(EG 1)** A specialty society technology assessment found low-quality to moderate-quality evidence that vascular endothelial growth factor inhibitors are as effective as laser photocoagulation for achieving regression of acute type 1 retinopathy of prematurity; treatment with vascular endothelial growth factor inhibitors is associated with increased recurrence. The authors recommended further research to evaluate the long-term safety of these agents as well as the optimal choice of drug.(20) **(EG 2)**

For uveitis complications such as cytoid macular edema, choroidal neovascularization, and retinal neovascularization, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of vascular endothelial growth factor inhibitors found mainly small case series and concluded that prospective studies are needed to evaluate the use of these agents for these conditions.(21) **(EG 2)**

For vitreous hemorrhage secondary to diabetic retinopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A multicenter, randomized, double-masked, controlled trial of 261 eyes in 261 patients with vitreous hemorrhage found no significant clinical difference between treatment with ranibizumab vs saline injection on the cumulative probability of subsequent vitrectomy at 16 weeks.(22) **(EG 1)**

Rationale

Use of this MCG care guideline helps the clinician determine if a particular treatment, medication, or service might be appropriate for a specific patient, taking into account their unique health complexities.

Use of these evidence-based clinical criteria to support decision making benefits the patient by identifying patient-specific complex clinical factors and conditions, promoting personalized treatment. Utilizing evidence-based clinical criteria promotes patient safety by helping ensure that potential patient benefits outweigh the risks. In addition, the use of evidence-based guidelines can increase consistency in treatment thresholds, leading to less variation in care and promoting equitable treatment among patients.

Related CMS Coverage Guidance

This guideline supplements but does not replace, modify, or supersede existing Medicare regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs).

Code of Federal Regulations (CFR): 42 CFR 419.22(97); 42 CFR 422.101(98)

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(99); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(100); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(101)

Medicare Coverage Determinations: Medicare Coverage Database(102)

References

1. Lucentis (ranibizumab injection) for intravitreal injection. Physician Prescribing Information [Internet] Genentech, Inc. 2024 Feb Accessed at: <https://www.lucetis.com/>. [created 2006; accessed 2025 Nov 07] [Context Link 1, 2, 3, 4, 5, 6, 7]
2. Dedania VS, Bakri SJ. Current perspectives on ranibizumab. *Clinical Ophthalmology (Auckland, N.Z.)* 2015;9:533-42. DOI: 10.2147/OPHTH.S80049. [Context Link 1] View abstract...
3. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. *Nature Reviews. Drug Discovery* 2016;15(6):385-403. DOI: 10.1038/nrd.2015.17. [Context Link 1] View abstract...
4. Lange CA, Qureshi R, Pauleikhoff L. Interventions for central serous chorioretinopathy: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2025, Issue 6. Art. No.: CD011841. DOI: 10.1002/14651858.CD011841.pub3. [Context Link 1] View abstract...
5. Feenstra HMA, et al. Central serous chorioretinopathy: An evidence-based treatment guideline. *Progress in Retinal and Eye Research* 2024;101:101236. DOI: 10.1016/j.preteyeres.2024.101236. [Context Link 1] View abstract...
6. Giacomelli G, et al. Long-term follow-up of choroidal neovascularization due to angioid streaks with pro re nata intravitreal anti-VEGF treatment. *Ophthalmologica* 2017;238(1-2):44-51. DOI: 10.1159/000477498. [Context Link 1] View abstract...
7. Heier JS, et al. Ranibizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration: a phase I clinical trial. *Ophthalmology* 2011;118(1):111-8. DOI: 10.1016/j.ophtha.2010.04.016. [Context Link 1, 2] View abstract...
8. Cheng JW, Cheng SW, Wei RL, Lu GC. Anti-vascular endothelial growth factor for control of wound healing in glaucoma surgery. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD009782. DOI: 10.1002/14651858.CD009782.pub2. [Context Link 1] View abstract...
9. Rittiphairoj T, Roberti G, Michelessi M. Anti-vascular endothelial growth factor for neovascular glaucoma. *Cochrane Database of Systematic Reviews* 2023, Issue 4. Art. No.: CD007920. DOI: 10.1002/14651858.CD007920.pub4. [Context Link 1] View abstract...

10. Holekamp NM, et al. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology* 2022;129(3):295-307. DOI: 10.1016/j.ophtha.2021.09.016. [Context Link 1] View abstract...
11. Yu HJ, et al. Two-year results for ranibizumab for radiation retinopathy (RRR): a randomized, prospective trial. *Graefes Archive for Clinical and Experimental Ophthalmology* 2022;260(1):47-54. DOI: 10.1007/s00417-021-05281-2. [Context Link 1] View abstract...
12. Scheffler AC, et al. Randomized trial of monthly versus as-needed intravitreal ranibizumab for radiation retinopathy-related macular edema: 1-year outcomes. *American Journal of Ophthalmology* 2020;216:165-173. DOI: 10.1016/j.ajo.2020.03.045. [Context Link 1] View abstract...
13. Finger PT, Chin KJ, Semenova EA. Intravitreal anti-VEGF therapy for macular radiation retinopathy: a 10-year study. *European Journal of Ophthalmology* 2015;26(1):60-66. DOI: 10.5301/ejo.5000670. [Context Link 1] View abstract...
14. Konstantinidis L, Mameletzi E, Mantel I, Pournaras JA, Zografos L, Ambresin A. Intravitreal ranibizumab (Lucentis) in the treatment of retinal angiomatous proliferation (RAP). *Graefes Archive for Clinical and Experimental Ophthalmology* 2009;247(9):1165-71. DOI: 10.1007/s00417-009-1089-3. [Context Link 1] View abstract...
15. Hemeida TS, Keane PA, Dustin L, Sadda SR, Fawzi AA. Long-term visual and anatomical outcomes following anti-VEGF monotherapy for retinal angiomatous proliferation. *British Journal of Ophthalmology* 2010;94(6):701-5. DOI: 10.1136/bjo.2009.167627. [Context Link 1] View abstract...
16. Parodi MB, et al. Intravitreal bevacizumab versus ranibizumab for the treatment of retinal angiomatous proliferation. *Acta Ophthalmologica* 2013;91(3):267-273. DOI: 10.1111/j.1755-3768.2011.02265.x. [Context Link 1] View abstract...
17. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD009734. DOI: 10.1002/14651858.CD009734.pub3. [Context Link 1] View abstract...
18. Stahl A, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet* 2019;394(10208):1551-1559. DOI: 10.1016/S0140-6736(19)31344-3. [Context Link 1] View abstract...
19. Chang E, Josan AS, Purohit R, Patel CK, Xue K. A network meta-analysis of retreatment rates following bevacizumab, ranibizumab, aflibercept, and laser for retinopathy of prematurity. *Ophthalmology* 2022;129(12):1389-1401. DOI: 10.1016/j.ophtha.2022.06.042. [Context Link 1] View abstract...
20. VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-vascular endothelial growth factor therapy for primary treatment of type 1 retinopathy of prematurity: a report by the American Academy of Ophthalmology. *Ophthalmology* 2017;124(5):619-633. DOI: 10.1016/j.ophtha.2016.12.025. [Context Link 1] View abstract...
21. Gulati N, Forooghian F, Lieberman R, Jabs DA. Vascular endothelial growth factor inhibition in uveitis: a systematic review. *British Journal of Ophthalmology* 2011;95(2):162-5. DOI: 10.1136/bjo.2009.177279. [Context Link 1] View abstract...
22. Diabetic Retinopathy Clinical Research Network*. Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. *JAMA Ophthalmology* 2013;131(3):283-93. DOI: 10.1001/jamaophthalmol.2013.2015. [Context Link 1] View abstract...
23. Diabetic retinopathy: management and monitoring. NICE guideline NG242 [Internet] National Institute for Health and Care Excellence. 2024 Aug 13 Accessed at: <http://guidance.nice.org.uk>. [accessed 2025 Jan 21] [Context Link 1, 2]
24. VEGF inhibitors for AMD and diabetic macular edema. *Medical Letter on Drugs and Therapeutics* 2015;57(1464):41-42. [Context Link 1, 2] View abstract...
25. Chatziralli I. Ranibizumab for the treatment of diabetic retinopathy. *Expert Opinion on Biological Therapy* 2021;21(8):991-997. DOI: 10.1080/14712598.2021.1928629. [Context Link 1, 2] View abstract...
26. Stewart MW. A review of ranibizumab for the treatment of diabetic retinopathy. *Ophthalmology and Therapy* 2017;6(1):33-47. DOI: 10.1007/s40123-017-0083-9. [Context Link 1, 2] View abstract...
27. Stefanini FR, Badaro E, Falabella P, Koss M, Farah ME, Maia M. Anti-VEGF for the management of diabetic macular edema. *Journal of Immunology Research* 2014;2014:632307. DOI: 10.1155/2014/632307. [Context Link 1] View abstract...
28. Ehlers JP, et al. Intravitreal pharmacotherapies for diabetic macular edema: a report by the American Academy of Ophthalmology. *Ophthalmology* 2022;129(1):88-99. DOI: 10.1016/j.ophtha.2021.07.009. [Context Link 1] View abstract...
29. Chen H, Shi X, Zhang W, Han Q. Aflibercept versus ranibizumab for diabetic macular edema: A meta-analysis. *European Journal of Ophthalmology* 2024;34(3):615-623. DOI: 10.1177/11206721231178658. [Context Link 1] View abstract...
30. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117(6):1064-1077.e35. DOI: 10.1016/j.ophtha.2010.02.031. [Context Link 1] View abstract...
31. Diabetic Retinopathy Clinical Research Network, et al. Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology* 2012;119(11):2312-8. DOI: 10.1016/j.ophtha.2012.08.022. [Context Link 1] View abstract...
32. Elman MJ, et al. Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology* 2015;122(2):375-81. DOI: 10.1016/j.ophtha.2014.08.047. [Context Link 1] View abstract...
33. Ishibashi T, et al. The REVEAL study: Ranibizumab monotherapy or combined with laser versus laser monotherapy in Asian patients with diabetic macular edema. *Ophthalmology* 2015;122(7):1402-15. DOI: 10.1016/j.ophtha.2015.02.006. [Context Link 1] View abstract...
34. Zechmeister-Koss I, Huic M. Vascular endothelial growth factor inhibitors (anti-VEGF) in the management of diabetic macular oedema: a systematic review. *British Journal of Ophthalmology* 2012;96(2):167-78. DOI: 10.1136/bjophthalmol-2011-300674. [Context Link 1] View abstract...
35. Mitchell P, Wong TY, Diabetic Macular Edema Treatment Guideline Working Group. Management paradigms for diabetic macular edema. *American Journal of Ophthalmology* 2014;157(3):505-513.e1-e8. DOI: 10.1016/j.ajo.2013.11.012. [Context Link 1] View abstract...

36. Nguyen QD, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119(4):789-801. DOI: 10.1016/j.ophtha.2011.12.039. [Context Link 1, 2, 3] View abstract...
37. Brown DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;120(10):2013-22. DOI: 10.1016/j.ophtha.2013.02.034. [Context Link 1] View abstract...
38. Mitchell P, et al. Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema: randomized clinical trial. *JAMA Ophthalmology* 2013;131(10):1339-47. DOI: 10.1001/jamaophthalmol.2013.4592. [Context Link 1] View abstract...
39. The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *New England Journal of Medicine* 2015;372(13):1193-1203. DOI: 10.1056/NEJMoa1414264. [Context Link 1] View abstract...
40. Bressler SB, et al. Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmology* 2017;135(6):558-568. DOI: 10.1001/jamaophthalmol.2017.0821. [Context Link 1] View abstract...
41. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology* 2015;122(2):367-74. DOI: 10.1016/j.ophtha.2014.08.048. [Context Link 1] View abstract...
42. Mehta H, Hennings C, Gillies MC, Nguyen V, Campain A, Fraser-Bell S. Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD011599. DOI: 10.1002/14651858.CD011599.pub2. [Context Link 1] View abstract...
43. Writing Committee for the Diabetic Retinopathy Clinical Research Network, et al. Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: A randomized clinical trial. *Journal of the American Medical Association* 2015;314(20):2137-2146. DOI: 10.1001/jama.2015.15217. [Context Link 1, 2] View abstract...
44. Gross JG, et al. Five-year outcomes of panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmology* 2018;136(10):1138-1148. DOI: 10.1001/jamaophthalmol.2018.3255. [Context Link 1] View abstract...
45. Lang GE, et al. Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy - the PRIDE study. *Acta Ophthalmologica* 2019;Online. DOI: 10.1111/aos.14312. [Context Link 1] View abstract...
46. Ranibizumab (Lucentis - Novartis Pharmaceuticals Canada Inc.) New Indication: Macular Edema Secondary to Retinal Vein Occlusion. CDC Final Recommendation [Internet] Canadian Agency for Drugs and Technologies in Health. 2012 Oct Accessed at: <https://www.cadth.ca/>. [accessed 2025 Sep 08] [Context Link 1]
47. Gerding H, Mones J, Tadayoni R, Boscia F, Pearce I, Priglinger S. Ranibizumab in retinal vein occlusion: treatment recommendations by an expert panel. *British Journal of Ophthalmology* 2015;99(3):297-304. DOI: 10.1136/bjophthalmol-2014-305041. [Context Link 1] View abstract...
48. Song WT, Xia XB. Ranibizumab for macular edema secondary to retinal vein occlusion: a meta-analysis of dose effects and comparison with no anti-VEGF treatment. *BMC Ophthalmology* 2015;15(1):31. DOI: 10.1186/s12886-015-0017-z. [Context Link 1] View abstract...
49. Yeh S, et al. Therapies for macular edema associated with central retinal vein occlusion: A report by the American Academy of Ophthalmology. *Ophthalmology* 2015;122(4):769-778. DOI: 10.1016/j.ophtha.2014.10.013. (Reaffirmed 2025 Jun) [Context Link 1] View abstract...
50. Ehlers JP, et al. Therapies for macular edema associated with branch retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology* 2017;124(9):1412-23. DOI: 10.1016/j.ophtha.2017.03.060. [Context Link 1] View abstract...
51. Braithwaite T, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD007325. DOI: 10.1002/14651858.CD007325.pub3. [Context Link 1] View abstract...
52. Shalchi Z, Mahroo O, Bunce C, Mitry D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No.: CD009510. DOI: 10.1002/14651858.CD009510.pub3. [Context Link 1] View abstract...
53. Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. NICE Technology Appraisal Guidance TA283 [Internet] National Institute for Health and Care Excellence. 2024 May 22 Accessed at: <https://www.nice.org.uk/guidance/>. [accessed 2024 Jun] [Context Link 1]
54. Ho M, Liu DT, Lam DS, Jonas JB. Retinal vein occlusions, from basics to the latest treatments. *Retina* 2016;36(3):432-448. DOI: 10.1097/IAE.0000000000000843. [Context Link 1] View abstract...
55. Regnier SA, Larsen M, Bezlyak V, Allen F. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis. *BMJ Open* 2015;5(6):e007527. DOI: 10.1136/bmjopen-2014-007527. [Context Link 1] View abstract...
56. Pranata R, Vania A, Vania R, Victor AA. Intravitreal ranibizumab versus dexamethasone implant in macular edema due to branch retinal vein occlusion: Systematic review and meta-analysis. *European Journal of Ophthalmology* 2021;31(4):1907-1914. DOI: 10.1177/1120672120947595. [Context Link 1] View abstract...
57. Rajagopal R, et al. Bevacizumab versus ranibizumab in the treatment of macular edema due to retinal vein occlusion: 6-month results of the CRAVE study. *Ophthalmic Surgery, Lasers & Imaging Retina* 2015;46(8):844-850. DOI: 10.3928/23258160-20150909-09. [Context Link 1] View abstract...
58. Hykin P, et al. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmology* 2019;137(11):1256-1264. DOI: 10.1001/jamaophthalmol.2019.3305. [Context Link 1] View abstract...

59. Schmidt-Erfurth U, et al. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). *Ophthalmologica* 2019;242(3):123-162. DOI: 10.1159/000502041. [Context Link 1] View abstract...
60. Kovach JL, et al. Retinal Vein Occlusions. Preferred Practice Pattern [Internet] American Academy of Ophthalmology. 2025 Feb Accessed at: <https://www.aao.org/>. [accessed 2025 Sep 04] DOI: 10.1016/j.ophtha.2024.12.025. [Context Link 1] View abstract...
61. Nicholson L, Talks SJ, Amoaku W, Talks K, Sivaprasad S. Retinal vein occlusion (RVO) guideline: executive summary. *Eye (London, England)* 2022;36(5):909-912. DOI: 10.1038/s41433-022-02007-4. [Context Link 1] View abstract...
62. Retinal Vein Occlusion (RVO) Guidelines. [Internet] Royal College of Ophthalmologists. 2022 Jan Accessed at: <https://www.rcophth.ac.uk/>. [accessed 2025 Sep 16] [Context Link 1]
63. Ng DSC, Fung NSK, Yip FLT, Lai TYY. Ranibizumab for myopic choroidal neovascularization. *Expert Opinion on Biological Therapy* 2020;20(12):1385-1393. DOI: 10.1080/14712598.2021.1830969. [Context Link 1] View abstract...
64. Zhu Y, Zhang T, Xu G, Peng L. Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathological myopia. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD011160. DOI: 10.1002/14651858.CD011160.pub2. [Context Link 1] View abstract...
65. Ranibizumab for Treating Choroidal Neovascularisation Associated with Pathological Myopia. NICE Technology Appraisal Guidance TA298 [Internet] National Institute for Health and Care Excellence. 2024 May Accessed at: <https://www.nice.org.uk/guidance/>. [created 2013 Nov; accessed 2024 May 28] [Context Link 1]
66. Wang E, Chen Y. Intravitreal anti-vascular endothelial growth factor for choroidal neovascularization secondary to pathologic myopia: systematic review and meta-analysis. *Retina* 2013;33(7):1375-92. DOI: 10.1097/IAE.0b013e31827d260a. [Context Link 1] View abstract...
67. Deeks ED. Ranibizumab: a review of its use in myopic choroidal neovascularization. *BioDrugs* 2014;28(4):403-10. DOI: 10.1007/s40259-014-0102-5. [Context Link 1] View abstract...
68. Cheung CMG, et al. Myopic choroidal neovascularization: review, guidance, and consensus statement on management. *Ophthalmology* 2017;124(11):1690-1711. DOI: 10.1016/j.ophtha.2017.04.028. [Context Link 1] View abstract...
69. Vemulakonda GA, et al. Age-Related Macular Degeneration. Preferred Practice Pattern [Internet] American Academy of Ophthalmology. 2025 Feb Accessed at: <https://www.aao.org/>. [accessed 2025 Sep 04] DOI: 10.1016/j.ophtha.2024.12.018. [Context Link 1, 2] View abstract...
70. Age-Related Macular Degeneration: Diagnosis and Management. NICE Guidance NG82 [Internet] National Institute for Health and Care Excellence. 2018 Jan Accessed at: <https://www.nice.org.uk/guidance/>. [accessed 2024 Sep 19] [Context Link 1] View abstract...
71. Schmidt-Erfurth U, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *British Journal of Ophthalmology* 2014;98(9):1144-1167. DOI: 10.1136/bjophthalmol-2014-305702. [Context Link 1] View abstract...
72. Santarelli M, Diplotti L, Samassa F, Veritti D, Kuppermann BD, Lanzetta P. Advances in pharmacotherapy for wet age-related macular degeneration. *Expert Opinion on Pharmacotherapy* 2015;16(12):1769-1781. DOI: 10.1517/14656566.2015.1067679. [Context Link 1] View abstract...
73. Kim LN, Mehta H, Barthelmes D, Nguyen V, Gillies MC. Metaanalysis of real- world outcomes of intravitreal Ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina* 2016;36(8):1418-31. DOI: 10.1097/IAE.0000000000001142. [Context Link 1] View abstract...
74. Nguyen CL, Oh LJ, Wong E, Wei J, Chilov M. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. *BMC Ophthalmology* 2018;18(1):130. DOI: 10.1186/s12886-018-0785-3. [Context Link 1, 2] View abstract...
75. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No.: CD005139. DOI: 10.1002/14651858.CD005139.pub4. [Context Link 1] View abstract...
76. Sarwar S, et al. Aflibercept for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD011346. DOI: 10.1002/14651858.CD011346.pub2. [Context Link 1] View abstract...
77. Freund KB, Hoang QV, Saroj N, Thompson D. Intraocular pressure in patients with neovascular age-related macular degeneration receiving intravitreal aflibercept or ranibizumab. *Ophthalmology* 2015;122(9):1802-10. DOI: 10.1016/j.ophtha.2015.04.018. [Context Link 1] View abstract...
78. Gillies MC, et al. Macular atrophy in neovascular age-related macular degeneration: a randomized clinical trial comparing ranibizumab and aflibercept (RIVAL study). *Ophthalmology* 2020;127(2):198-210. DOI: 10.1016/j.ophtha.2019.08.023. [Context Link 1] View abstract...
79. The CATT Research Group. Ranibizumab and Bevacizumab for neovascular age-related macular degeneration. *New England Journal of Medicine* 2011;364(20):1897-1908. DOI: 10.1056/NEJMoa1102673. [Context Link 1] View abstract...
80. Schmidt-Erfurth U, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121(1):193-201. DOI: 10.1016/j.ophtha.2013.08.011. [Context Link 1] View abstract...
81. Scott AW, Bressler SB. Long-term follow-up of vascular endothelial growth factor inhibitor therapy for neovascular age-related macular degeneration. *Current Opinion in Ophthalmology* 2013;24(3):190-196. DOI: 10.1097/ICU.0b013e32835fefe. [Context Link 1] View abstract...
82. Ho AC, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2014;121(11):2181-92. DOI: 10.1016/j.ophtha.2014.05.009. [Context Link 1] View abstract...
83. IVAN Study Investigators, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119(7):1399-1411. DOI: 10.1016/j.ophtha.2012.04.015. [Context Link 1] View abstract...
84. Kodjikian L, et al. Ranibizumab versus Bevacizumab for neovascular age-related macular degeneration: Results from the GEFAL noninferiority randomized trial. *Ophthalmology* 2013;120(11):2300-2309. DOI: 10.1016/j.ophtha.2013.06.020. [Context Link 1] View abstract...

85. Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology* 2015;122(1):146-152. DOI: 10.1016/j.ophtha.2014.07.041. [Context Link 1] View abstract...
86. Schauwvlieghe AM, et al. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. *PLoS ONE* 2016;11(5):e0153052. DOI: 10.1371/journal.pone.0153052. [Context Link 1] View abstract...
87. Singer MA, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2012;119(6):1175-83. DOI: 10.1016/j.ophtha.2011.12.016. [Context Link 1] View abstract...
88. Kodjikian L, et al. Bevacizumab and ranibizumab for neovascular age-related macular degeneration: an updated meta-analysis of randomised clinical trials. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2014;252(10):1529-1537. DOI: 10.1007/s00417-014-2764-6. [Context Link 1] View abstract...
89. Garg SJ, Hadziahmetovic M. Verteporfin photodynamic therapy for the treatment of chorioretinal conditions: a narrative review. *Clinical Ophthalmology (Auckland, N.Z.)* 2024;18:1701-1716. DOI: 10.2147/OPTH.S464371. [Context Link 1, 2] View abstract...
90. Rosenfeld PJ, et al. Photodynamic therapy with verteporfin in ocular histoplasmosis: uncontrolled, open-label 2-year study. *Ophthalmology* 2004;111(9):1725-33. DOI: 10.1016/j.ophtha.2004.02.014. [Context Link 1] View abstract...
91. Nielsen JS, Fick TA, Saggau DD, Barnes CH. Intravitreal anti-vascular endothelial growth factor therapy for choroidal neovascularization secondary to ocular histoplasmosis syndrome. *Retina* 2012;32(3):468-472. DOI: 10.1097/IAE.0b013e318229b220. [Context Link 1] View abstract...
92. Ramaiya KJ, Blinder KJ, Ciulla T, Cooper B, Shah GK. Ranibizumab versus photodynamic therapy for presumed ocular histoplasmosis syndrome. *Ophthalmic Surgery, Lasers & Imaging Retina* 2013;44(1):17-21. DOI: 10.3928/23258160-20121221-07. [Context Link 1] View abstract...
93. Koh AH, et al. Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. *Retina* 2013;33(4):686-716. DOI: 10.1097/IAE.0b013e3182852446. [Context Link 1, 2, 3, 4] View abstract...
94. Koh A, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmology* 2017;135(11):1206-1213. DOI: 10.1001/jamaophthalmol.2017.4030. [Context Link 1] View abstract...
95. Lim TH, et al. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II randomized clinical trial. *JAMA Ophthalmology* 2020;138(9):935-942. DOI: 10.1001/jamaophthalmol.2020.2443. [Context Link 1] View abstract...
96. Yong M, Zhou M, Deng G. Photodynamic therapy versus anti-vascular endothelial growth factor agents for polypoidal choroidal vasculopathy: a meta-analysis. *BMC Ophthalmology* 2015;15:82. DOI: 10.1186/s12886-015-0064-5. [Context Link 1] View abstract...
97. Centers for Medicare and Medicaid Services. "Hospital services excluded from payment under the hospital outpatient prospective payment system." 42 CFR 419.22 Washington, DC 2023 Jul [accessed 2025 Jul 22] Accessed at: <https://www.ecfr.gov/>. [Context Link 1]
98. Centers for Medicare and Medicaid Services. "Requirements relating to basic benefits." 42 CFR 422.101 Washington, DC 2025 Jun 03 [accessed 2025 Jul 23] Accessed at: <https://www.ecfr.gov/>. [Context Link 1]
99. Centers for Medicare and Medicaid Services. Medicare Benefit Policy Manual. Chapter 14 - Medical Devices Rev. 198 [Internet] Centers for Medicare and Medicaid Services. 2014 Nov 06 Accessed at: <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/>. [accessed 2025 Sep 09] [Context Link 1]
100. Centers for Medicare and Medicaid Services. Medicare Benefit Policy Manual. Chapter 15 - Covered Medical and Other Health Services Rev. 13108 [Internet] Centers for Medicare and Medicaid Services. 2025 Apr 11 Accessed at: <https://www.cms.gov/manuals/>. [accessed 2025 Sep 09] [Context Link 1]
101. Centers for Medicare and Medicaid Services. Medicare Benefit Policy Manual. Chapter 16 - General Exclusions From Coverage Rev. 198 [Internet] Centers for Medicare and Medicaid Services. 2014 Nov 06 Accessed at: <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/>. [accessed 2025 Sep 09] [Context Link 1]
102. Medicare Coverage Database. [Internet] Centers for Medicare and Medicaid Services. Accessed at: <https://www.cms.gov/medicare-coverage-database/search.aspx?> Updated 2025 [accessed 2025 Oct 23] [Context Link 1]

Footnotes

[A] For diabetic macular edema, ranibizumab is administered by intravitreal injection, followed by careful monitoring for signs of increased ocular pressure or endophthalmitis. Retinal vasculitis with or without occlusion, typically in the presence of pre-existing intraocular inflammation or post treatment with other intravitreal agents, has been reported.(1) [A in Context Link 1]

[B] For diabetic retinopathy, ranibizumab is administered by intravitreal injection, followed by careful monitoring for signs of increased ocular pressure or endophthalmitis. Retinal vasculitis with or without occlusion, typically in the presence of pre-existing intraocular inflammation or post treatment with other intravitreal agents, has been reported.(1) [B in Context Link 1]

[C] For macular edema following retinal vein occlusion, ranibizumab is administered by intravitreal injection, followed by careful monitoring for signs of increased ocular pressure or endophthalmitis. Retinal vasculitis with or without occlusion, typically in the presence of pre-existing intraocular inflammation or post treatment with other intravitreal agents, has been reported.(1) [C in Context Link 1]

[D] For myopic choroidal neovascularization, ranibizumab is administered by intravitreal injection, followed by careful monitoring for signs of increased ocular pressure or endophthalmitis. Retinal vasculitis with or without occlusion, typically in the presence of pre-

existing intraocular inflammation or post treatment with other intravitreal agents, has been reported.(1) [D in Context Link 1]

[E] For neovascular age-related macular degeneration, ranibizumab is administered by intravitreal injection, followed by careful monitoring for signs of increased ocular pressure or endophthalmitis. Retinal vasculitis with or without occlusion, typically in the presence of pre-existing intraocular inflammation or post treatment with other intravitreal agents, has been reported.(1) [E in Context Link 1]

[F] Ocular histoplasmosis is a fungal infection of the chorioretinal region that is thought to be caused by *Histoplasma capsulatum*. The clinical diagnosis is defined as the absence of anterior or vitreous segment inflammation and 2 out of 3 of the following: multifocal chorioretinal scarring of the macular and midperiphery, chorioretinal peripapillary atrophy, or choroidal neovascularization.(89) [F in Context Link 1]

[G] Polypoidal choroidal vasculopathy is characterized by polypoidal dilatations along a branching network of choroidal neovascularization, in which fragile blood vessels may leak or hemorrhage into the macula, resulting in vision loss and chorioretinal atrophy.(93) For active juxtafoveal or subfoveal polypoidal choroidal vasculopathy, ranibizumab is administered by intravitreal injection during verteporfin photodynamic therapy.(93) [G in Context Link 1]

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