Aflibercept

ACG: A-0680 (AC)
Link to Codes

MCG Health
Ambulatory Care
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Clinical Indications

- Aflibercept may be indicated for **1 or more** of the following(1)(2):
  - Intravitreal administration needed, as indicated by **ALL** of the following:
    - Eye condition appropriate for aflibercept treatment as indicated by **1 or more** of the following:
      - Diabetic macular edema[A](13)(14)(15)(16)(17)(18)N
      - Diabetic retinopathy[B](33)(34)N
      - Macular edema following central or branch retinal vein occlusion[C](39)(40)(41)(42)N
      - Neovascular (wet, or exudative) age-related macular degeneration[D](14)(42)(52)(53)(54)N
      - Ocular histoplasmosis[E] with choroidal neovascularization(66)N
      - Retinopathy of prematurity[F](69)N
    - No active intraocular inflammation(72)
    - No concurrent ocular or periocular infection(72)
  - Systemic administration needed, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Metastatic colorectal cancer with progression of disease on initial therapy(73)(74)(75)N

Evidence Summary

Background

Aflibercept acts as a decoy receptor that binds vascular endothelial growth factor, which inhibits its role in promoting neovascularization and vascular permeability.(1)(3)(4) **(EG 2)**

Criteria

The evidence for the clinical indications found in this guideline includes 67 published peer reviewed articles, 3 specialty society or other evidence-based guidelines, and 3 Cochrane systematic reviews.

For diabetic macular edema, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Meta-analyses and systematic reviews have demonstrated that all vascular endothelial growth factor inhibitors appear to have some activity against diabetic macular edema,(19)(20) with some clinical trial evidence suggesting that aflibercept may improve best-corrected visual

acuity (measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters) compared with bevacizumab, but not compared with ranibizumab.(21) **(EG 1)** A randomized trial of 270 patients (312 eyes) with diabetic macular edema involving the macular center compared treatment with either aflibercept monotherapy or step therapy (bevacizumab with a switch to aflibercept at 12 weeks in patients with persistent diabetic macular edema, no improvement in visual acuity or central subfield thickness, and suboptimal vision after at least 2 doses of bevacizumab) and found, at 2-year follow-up, no difference in change in visual acuity or retinal central subfield thickness between groups, with higher adverse event rates in the aflibercept group compared with the step therapy group.(22) **(EG 1)** A multicenter randomized double-masked study of 221 patients with diabetic macular edema reported significant improvement with aflibercept in mean best-corrected visual acuity after 24 weeks and 52 weeks.(23)(24) **(EG 1)** A randomized study of 872 eyes of patients with central involvement of diabetic macular edema found that intravitreal administration of aflibercept, as compared with laser photocoagulation, produced significantly greater improvement in both visual acuity and central retinal thickness after 52 weeks.(25) **(EG 1)** Follow-up studies showed that incremental visual acuity benefits were maintained at 100 weeks to 148 weeks.(26)(27) **(EG 1)** A randomized study of 660 adults with diabetic macular edema who received either intravitreal aflibercept, ranibizumab, or bevacizumab found that, after 1 year, visual acuity improvement was comparable among all 3 drugs in those with mild initial visual acuity loss; however, for those with worse initial levels of visual acuity, aflibercept was more effective at improving vision.(28) **(EG 1)** A follow-up study for up to 2 years found that all 3 groups showed continuing improvement in visual acuity, with similar improvement across all 3 drugs in eyes with better baseline acuity. However, among eyes with poorer baseline acuity, aflibercept had significantly better acuity improvement after 2 years as compared with bevacizumab.(29)(30) **(EG 1)** A secondary analysis also found, in eyes with proliferative diabetic retinopathy at baseline, that aflibercept therapy for diabetic macular edema was associated with a higher rate of diabetic retinopathy improvement compared with bevacizumab at both 1-year (75.9% vs 31.4%, respectively) and 2-year (70.4% vs 30.3%, respectively) follow-up; bevacizumab was also associated with a higher rate of improvement compared with ranibizumab at both 1-year (75.9% vs 55.2%, respectively) and 2-year (70.4% vs 37.5%, respectively) follow-up.(31) **(EG 1)** A randomized phase II/III noninferiority trial of 660 patients with diabetic macular edema compared treatment with aflibercept 2 mg every 8 weeks (current standard), aflibercept 8 mg every 12 weeks, and aflibercept 8 mg every 16 weeks; this treatment started after initial treatment with 3 (aflibercept 2 mg) to 5 (aflibercept 8 mg) doses. At week 44, patients treated with aflibercept 8 mg every 12 weeks or aflibercept 8 mg every 16 weeks had noninferior best-corrected visual acuity gains compared with those treated with aflibercept 2 mg every 8 weeks. No significant differences in adverse outcomes among the groups were noted.(32) **(EG 1)**

For diabetic retinopathy, 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 randomized trial of 328 patients (399 eyes) with moderate to severe nonproliferative diabetic retinopathy compared treatment with either intravitreal aflibercept or sham injection and found, at 2-year and 4-year follow-up, that aflibercept was associated with reduced progression to proliferative diabetic retinopathy and center-involved macular edema, with no difference in visual acuity seen between groups.(35)(36) **(EG 1)** A multicenter phase III randomized trial of 402 adult patients with severe nonproliferative diabetic retinopathy without macular edema compared treatment with either intravitreal aflibercept (at 1 of 2 dosing regimens) or sham injection and found, at 52-week and 100-week follow-up, that aflibercept at either dose was associated with more patients achieving a 2-step or greater improvement in Diabetic Retinopathy Severity Scale (DRSS) scores, fewer vision-threatening complications, and a lower rate of development of center-involved diabetic macular edema compared with sham injection.(37) **(EG 1)** A phase II noninferiority trial of 221 patients with active proliferative diabetic retinopathy compared treatment with aflibercept or panretinal laser photocoagulation and found, at 52-week follow-up, that aflibercept was noninferior to laser photocoagulation for best-corrected visual acuity change from baseline.(33) **(EG 1)** A review article notes that patients with diabetic retinopathy who are treated with vascular endothelial growth factor inhibitors may have less visual field loss, less development of diabetic macular edema, and less need for vitrectomy surgery compared with patients treated with panretinal photocoagulation.(34) **(EG 2)**

For macular edema following central or branch 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 occlusions for up to 26 to 52 weeks.(43)(44)(45)(46) **(EG 1)** The gains in visual acuity with aflibercept were maintained at 52-week and 76-week follow-up and remained improved from baseline at 60-month follow-up.(47)(48) **(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.(49) **(EG 1)** Specialty society guidelines state that aflibercept is an effective treatment for macular edema due to retinal vein occlusion.(50)(51) **(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 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.(55) **(EG 1)** However, other authors have found that intraocular pressure is higher in patients who receive ranibizumab as compared with aflibercept.(56) **(EG 1)** Follow-up studies of patients treated with either ranibizumab or aflibercept for neovascular age-related macular degeneration indicate continued comparable effectiveness in improving visual acuity and preventing further vision loss for up to 96 weeks.(57)(58) **(EG 1)** A randomized double-masked noninferiority study of 1009 treatment-naive patients with neovascular age-related macular degeneration compared treatment with aflibercept 2 mg every 8 weeks (current standard), aflibercept 8 mg every 12 weeks, and aflibercept 8 mg every 16 weeks and found, at 48-week follow-up, that patients treated with aflibercept 8 mg with longer dosing intervals had noninferior best-corrected visual acuity compared with patients who received the standard regimen of aflibercept 2 mg every 8 weeks.(59) **(EG 1)** A randomized trial of

278 patients with neovascular age-related macular degeneration compared treatment with intravitreal aflibercept or ranibizumab 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.(60) **(EG 1)** A randomized trial of 127 patients with intermediate nonexudative age-related macular degeneration compared prophylactic treatment with either intravitreal aflibercept or sham injection and found, at 24-month follow-up, no difference in rates of conversion to exudative macular degeneration between groups.(61) **(EG 1)** Critical reviews of studies have found some evidence that switching from either ranibizumab or bevacizumab to aflibercept in refractory patients may further improve visual acuity outcomes. However, the authors caution that additional confirmatory randomized controlled trials are necessary.(62)(63) **(EG 2)** A specialty society guideline recommends aflibercept as a management option for patients with neovascular age-related macular degeneration.(64) **(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)** An open-label randomized trial of 39 patients with ocular histoplasmosis compared treatment with either scheduled aflibercept (ie, monthly injections for 3 months, followed by injections every other month for 12 months) or as-needed aflibercept (ie, injection at randomization then monthly as needed for 12 months) and found, after 12 months of follow-up, that patients demonstrated similar improvements in visual acuity with both regimens but that patients received fewer injections with the as-needed dosing regimen.(67) **(EG 1)** A retrospective study that included 82 eyes with ocular histoplasmosis and subfoveal or juxtafoveal choroidal neovascularization compared the effectiveness of anti-vascular endothelial growth factor injections alone or in combination with verteporfin photodynamic therapy and found, after 10 years of follow-up, that both treatment strategies were associated with improvement in visual acuity but that combination therapy was associated with fewer injections and longer treatment-free intervals.(68) **(EG 2)** 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.(65) **(EG 2)**

For retinopathy of prematurity, evidence demonstrates an incomplete assessment of net benefit vs harm; the drug is currently approved by a federal regulatory agency. **(RG A3)** A phase III randomized noninferiority study of 118 infants with retinopathy of prematurity compared treatment with either intravitreal aflibercept or laser photocoagulation and found, at 24-week follow-up, that aflibercept injections did not meet criteria for noninferiority for efficacy (defined as remission of retinopathy without unfavorable structural outcomes) compared with laser photocoagulation.(69) **(EG 1)** A 2-year exploratory follow-up study found that efficacy outcomes (ie, rates of remission of retinopathy without unfavorable structural outcomes) remained similar between treatment groups.(70) **(EG 1)** A systematic review and meta-analysis of 6 studies (all cohort studies or case series) including 218 eyes in patients with retinopathy of prematurity evaluated intravitreal aflibercept injection at half the adult dose as initial therapy for prethreshold type 1 retinopathy of prematurity, threshold retinopathy of prematurity, and aggressive posterior retinopathy of prematurity and found that aflibercept therapy resulted in a 97% average regression rate and a 16% average recurrence rate. However, the authors noted that randomized controlled trials are needed to compare outcomes for the various anti-vascular endothelial growth factor agents and evaluate safety in this population.(71) **(EG 1)**

For metastatic colorectal cancer with progression of disease on initial therapy, 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 randomized phase III trial of 1226 patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen reported that the addition of aflibercept to standard fluoropyrimidine-based chemotherapy resulted in an improved mean overall survival of 13.5 months, as compared with 12.1 months in the group receiving standard chemotherapy.(76) **(EG 1)** Longer-term follow-up analysis of safety and efficacy of this phase III study indicated the following probabilities of survival for those receiving aflibercept vs placebo: 38.5% vs 30.9% at 18 months, 28% vs 18.7% at 24 months, and 22.3% vs 12% at 30 months; the majority of the most severe adverse events occurred within earlier cycles of treatment.(77) **(EG 1)** A post hoc analysis of this study suggested that inclusion of some patients who had rapidly relapsed within 6 months of oxaliplatin-containing adjuvant chemotherapy may have resulted in understating the treatment benefit of aflibercept in patients who did not belong to this poor prognosis subgroup.(78) **(EG 2)** A technology assessment stated that the impact of aflibercept on overall survival of patients with metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy was statistically significant but clinically small.(79) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)** A meta-analysis stated that the incidence of severe infections in patients with solid tumors who were treated with aflibercept was 7.3%, and the mortality rate was 2.2%.(80) **(EG 1)** Expert consensus guidelines state that aflibercept, when given in conjunction with other chemotherapeutics (such as irinotecan or the folinic acid, fluorouracil, and irinotecan (FOLFIRI) regimen), may be appropriate for patients with metastatic colorectal cancer who have progressed on initial therapy. Aflibercept plus FOLFIRI is only appropriate for those patients who have not yet been exposed to any other treatment regimen containing FOLFIRI.(73)(74) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For non-small cell lung cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A multicenter double-blind placebo-controlled trial of 913 patients with advanced or metastatic nonsquamous non-small cell lung cancer reported that the addition of aflibercept to standard docetaxel therapy did not improve overall survival and was associated with increased toxicities.(5)(6) **(EG 1)** Several cases of reversible posterior leukoencephalopathy syndrome have been observed in a phase II study of non-small cell lung cancer patients receiving a combination of aflibercept, pemetrexed, and cisplatin.(7) **(EG 2)**

For ovarian cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized phase II study of 84 patients with platinum-resistant advanced ovarian cancer found that, while the drug was well tolerated, the desired efficacy endpoints were not achieved.(8) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)**

For pancreatic cancer, 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 randomized study assigned 546 patients with metastatic pancreatic cancer to gemcitabine with or without aflibercept. The study was terminated when it was noted that the addition of aflibercept failed to significantly improve overall survival.(10) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(EG 1)**

For prostate cancer, 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 randomized study of 1224 patients with metastatic castration-resistant prostate cancer found that adding aflibercept to docetaxel and prednisone as first-line therapy resulted in no improvement in overall survival and incurred additional adverse effects. The authors indicated that docetaxel plus prednisone remains the standard treatment.(11) **(EG 1)** A meta-analysis of the use of aflibercept for treating various solid tumors found a significantly higher rate of fatal drug-related adverse events in treated patients as compared with controls, with an overall incidence of fatal events of 5.1%.(9) **(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(81); 42 CFR 422.101(82)

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(83); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(84); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(85)

Medicare Coverage Determinations: Medicare Coverage Database(86)

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Footnotes

[A] For diabetic macular edema, aflibercept is administered by intravitreal injection. Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, retinal detachment, and more rarely, retinal vasculitis with or without occlusion.(1)(12) [A in Context Link 1]

[B] For diabetic retinopathy, aflibercept is administered by intravitreal injection. Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, retinal detachment, and more rarely, retinal vasculitis with or without occlusion.(1)(12) [B in Context Link 1]

[C] For macular edema following central or branch retinal vein occlusion, aflibercept is administered by intravitreal injection. Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, retinal detachment, and more rarely, retinal vasculitis with or without occlusion.(1)(38) [C in Context Link 1]

[D] For neovascular (wet, or exudative) age-related macular degeneration, aflibercept is administered by intravitreal injection. Patients should be monitored for postinjection complications, including increased intraocular pressure, endophthalmitis, retinal detachment, and more rarely, retinal vasculitis with or without occlusion.(1)(12) [D in Context Link 1]

[E] 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.(65) [E in Context Link 1]

[F] For retinopathy of prematurity, aflibercept is administered as an intravitreal injection. In infants with retinopathy of prematurity, treatment with aflibercept will necessitate extended periods of monitoring, and additional injections and/or laser treatments may be necessary.(1) [F in Context Link 1]

Codes

HCPCS: J0177, J0178, J9400

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