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| Bevacizumab (Avastin®) | |
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Purpose

This bevacizumab medical guideline addresses use of bevacizumab for intravitreal route only. Coverage of bevacizumab for all other indications is reviewed through Milliman Care Guidelines.

Based on available evidence, CHP considers intravitreal administration of bevacizumab to be medically indicated for the treatment of exudative (wet) macular degeneration. While not FDA-approved for this indication and previously considered experimental/investigational, the available body of scientific evidence supports this use of bevacizumab and it has become the standard of care for many ophthalmologists.

Background

Age-related macular degeneration (ARMD), a progressive degenerative disease of the macula, is the leading cause of blindness in developed countries afflicting about 15 million people in the United States. The risk of ARMD increases with age, and usually affects people 60 years of age and older. Heavy alcohol consumption (more than 3 standard drinks per day) is associated with an increased risk of early ARMD (Chong, et al., 2008). Early ARMD is characterized by the presence of a few (less than 20) medium-size drusen or retinal pigmentary abnormalities. Intermediate ARMD is characterized by at least one large druse, numerous medium-size drusen, or geographic atrophy that does not extend to the center of the macula. Late or advanced ARMD can be either neovascular (wet or exudative) or non-neovascular (dry, atrophic, or non-exudative). The neovascular form includes serous or hemorrhagic detachment of retinal pigment epithelium and choroidal neovascularization (CNV), which lead to leakage and scarring. It is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, resulting in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of vascular endothelial growth factor (VEGF), which induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular form of ARMD. The non-neovascular form leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. It does not involve leakage of blood or serum, and is characterized by drusen and geographic atrophy extending to the center of the macula. Patients with non-exudative ARMD can progress to the exudative form of ARMD, in which pathologic CNV membranes develop under the retina, leak fluid and blood, and ultimately cause a blinding disciform scar in a relatively short time. Approximately 10 to 20% of patients with non-exudative ARMD eventually progress to the exudative form, which is responsible for most of the cases of advanced ARMD in the United States (AAO, 2006; Comer, 2006; Jager, et al., 2008).

Various therapeutic approaches have been employed in the treatment of patients with ARMD. High-dose antioxidants are thought to be able to limit the damage caused by oxidative stress in the macula. However, this treatment only slows progression in some patients and does not reverse damage already present. After ARMD becomes exudative, laser photocoagulation, photodynamic therapy (PDT) with verteporfin (Visudyne), and intravitreal injections of pegaptanib sodium (Macugen), bevacizumab (Avastin) and ranibizumab (Lucentis) have been used to control CNV.

Currently, the most common treatments for wet ARMD are intravitreal bevacizumab and ranibizumab. Bevacizumab, a monoclonal antibody to VEGF is being used off-label for wet ARMD. Although data from long-term studies are not yet available, several short-term studies of intravitreal bevacizumab have shown improvement in VA that is similar to the improvement with ranibizumab. Intravitreal bevacizumab appears to have systemic adverse events similar to those of ranibizumab, which is designed to block new blood vessel growth and leakiness, and is the first treatment which, when given monthly, can maintain the vision of more than 90% of patients with wet ARMD. In contrast to pegaptanib, ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF. Ranibizumab exhibits high affinity for human VEGF and exerts its neutralizing effects by inhibiting the VEGF-receptor interaction. Unlike the larger whole antibody, ranibizumab can penetrate the internal limiting membrane and reach the subretinal space following intravitreal injection (van Wijngaarden, et al., 2005).

In an editorial on the use of intravitreal bevacizumab as the low cost alternative to ranibizumab published in the American Journal of Ophthalmology, Rosenfeld (2006) stated that "[c]urrently, there appears to be a global consensus that the treatment strategy using intravitreal Avastin is logical, the potential risks to our patients are minimal, and the cost-effectiveness is so obvious that the treatment should not be withheld." On March 20, 2006, a survey by the American Society of Retinal Specialists of its membership was completed. It found that 92% of 289 respondents felt intravitreal bevacizumab was "somewhat better" or "much better" than other FDA-approved or covered therapies. Only 4% of respondents had seen any thromboembolic complications thought to be related to the intravitreal bevacizumab, and 96% thought intravitreal bevacizumab was the same or better in terms of overall safety compared to other FDA-approved or covered therapies.

On April 20, 2006, the American Academy of Ophthalmology (AAO) wrote to the Centers for Medicare and Medicaid Services supporting the reimbursement for treating ARMD with intravitreal injections of bevacizumab to meet the medical needs of patients who have not responded to Visudyne PDT or intravitreal pegaptanib. The AAO's support for reimbursement is limited to "such patients who are deemed by their treating physician to have failed FDA-approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intravitreal bevacizumab."

Indications/Criteria

Intravitreal bevacizumab is considered medically necessary for neovascular (wet or exudative) age-related macular degeneration once ALL of the following criteria are met:

- Age 18 years or older
- Baseline visual acuity in affected eye between 20/40 and 20/320
- No concurrent ocular or periocular infection
- Administration planned for single eye only

Intravitreal bevacizumab is considered experimental and investigational for the following conditions:

- Central retinal vein occlusion
- Choroidal neovascularization associated with Stargardt Disease
- Choroidal neovascularization secondary to multifocal choroiditis
- Choroidal neovascularization secondary to severe myopia
- Diabetic macular edema
- Diabetic retinopathy
- Retinopathy of prematurity
- **All other ocular diseases**

Limitations/Exclusions

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| Healthy Options: | None; pre-authorization required. |
| Basic Health Plan: | None; pre-authorization required. |
| GAU: | None; pre-authorization required. |
| Medicare Advantage: | None; pre-authorization required. |

Required Review and Approvals

Intravitreal bevacizumab requires prior authorization by the CHP Medical Director or his/her designee. Each authorization period will be for one year.

References

1. Rosenfeld PJ. Intravitreal Avastin: The Low Cost Alternative to Lucentis? *Am J Ophthalmol* 2006;142:141-143.
2. Steinbrook, R. The Price of Sight – Ranibizumab, Bevacizumab, and the Treatment of Macular Degeneration. *NEJM* 2006; 355:1409-1412.

3. Aetna Clinical Policy Bulletin:
Age-Related Macular Degeneration: Treatments. Number 0765. Last update:
01/08/2010. Accessed February 12, 2010.
4. [Iturralde D](#), et al. Intravitreal bevacizumab (Avastin) treatment of macular edema in
central retinal vein occlusion: a short-term study. [Retina](#). 2006 Mar;26(3):279-84.