Comment and Response Document

LCD Database ID Number
DL32013

LCD Title
Drugs and Biologics (Non-chemotherapy)

Contractor's Determination Number
INJ-041

Comment:
I would like to suggest the coverage for Macugen be extended to the treatment of diabetic macular edema. Macugen is a selective anti-VEGF drug which has been approved for the use in exudative ARMD. The injection of Macugen in the treatment of diabetic macular edema has been shown to be effective in improving the vision of patients with diabetic macular edema in the recently published article in Ophthalmology (June 2011). Diabetic patients are at higher risk of adverse side effects of nonselective anti-VEGF drugs such as Avastin. I would like to have the option of treating these higher risk patients with the lower risk, selective anti-VEGF drug, Macugen. My colleagues in most other states already have this option and I would appreciate having this option as well.

Comment:
I am corresponding with you today as a provider in your jurisdiction. I would like to submit comments concerning draft LCD DL32013, Drugs and Biologics (non-chemotherapy). I am requesting an additional diagnosis, Diabetic Macular Edema (DME) (code 362.07), be added for the drug Pegaptanib Sodium (MacugenTM) J2503.

I understand that you are aware of the various available treatments for DME. Although laser remains a primary treatment, less than 3% of patients in the Early Treatment of Diabetic Retinopathy Study (ETDRS) for laser treatment of DME experienced an improvement in visual acuity, based on a 15-letter gain at 3 years. 1

Recent prospective phase 3 studies with anti-VEGF agents, RIDE and RISE trials, have demonstrated significant visual gain in a much higher percentage of patients than with laser alone. This has led retina specialists to offer anti-VEGF therapy as a standard of care treatment option in daily clinical practice. Individual leaking aneurysms respond well to focal laser therapy, but diffuse vascular leakage appears to be controlled better with anti-VEGF therapy and/or steroid therapy. Steroid therapy risks the development of steroid induced glaucoma in approximately 1/3 of patients. 2

New evidence to justify this request was recently published in the peer-reviewed journal referenced below, and is attached. The article “A Phase 2/3, Multicenter, Randomized, Double-Masked Trial of Pegaptanib Sodium for the Treatment of Diabetic Macular Edema,”3 demonstrates that Macugen is safe and effective for up to 24 months in the treatment of DME.

Also attached are two peer-reviewed published papers using Macugen for DME.4,5 This data was from a randomized, controlled, prospective Phase II trial and was deemed appropriate for inclusion as a “non-FDA Labeled Indication” in the CMS-recognized Drug Dex and Clinical Pharmacology compendia.

Diabetic patients, in particular, have many systemic complications. I am grateful that Avastin anti-VEGF therapy was covered for the treatment of DME by WPS Medicare, but feel that there are very important reasons why a more selective, alternative anti-VEGF drug should be available. Avastin is a non-selective pan-VEGF inhibitor, as is Lucentis. In June 2010, the Lucentis package insert was amended, changing its description for the risk of thromboembolic events (defined as nonfatal stroke, nonfatal myocardial infarction or vascular deaths, including deaths of unknown cause) from theoretical to potential. It further added data that compared the risk of stroke of 0.5 mg Lucentis (2.7%) to control (1.1%), odds ratio 2.2, 95% confidence interval (0.8-7.1), in a pooled analysis of three randomized, controlled trials.

Illustrative of my concerns for using non-selective anti-VEGF therapies in diabetics who are inherently vascular compromised, is the recently presented adverse event rates in the phase 3 RIDE and RISE trials of ranibizumab for DME. In the 0.5 mg ranibizumab arm (n=252), 3.2% experienced a CVA and 4.4% died vs. 1.6% and 1.2%, respectively, in the sham arm (n=257). Though this was considered a non-significant outcome based on the number of patients in the trial, the doubling of CVA's is similar to previous studies using pan-VEGF therapies.

Having provided published authoritative evidence from peer-reviewed journals and the safety concerns identified with other VEGF inhibitors used to treat DME, I believe the level of evidence is appropriate to add DME as a diagnosis for treatment with Macugen.

Comment:
There are a limited number of treatment options for patients with diabetic macular edema. Laser surgery is destructive and only modestly effective at improving vision. Furthermore, not all macular edema is responsive to laser. Injectable pharmaceuticals are a very necessary part of our armamentarium in the management of these patients. The vast majority of states do have Medicare coverage of Pegatanib for diabetic macular edema. I used to practice in a state where it was covered and have used it in selected patients with good success. Having this treatment option available to my patients in Minnesota would significantly improve their standard of care.

I appreciate that Bevacizumab is covered and I have also had very good success with this treatment. However this treatment does raise some safety concerns for high-risk patients due to its pan-VEGF blockade. I feel Pegatanib fills a needed void for those high-risk patients since it has selective blockade of VEGF165. There is good, peer-reviewed phase 2/3 data supporting the safety and efficacy of PegatanIb in the treatment of diabetic macular edema. Please refer to Ophthalmology Vol 118, Number 6, 2011, "A phase 2/3, Multicenter, Randomized, Double-Masked, 2-Year Trial of Pegatanib Sodium for the Treatment of Diabetic Macular Edema".

Comment: I am a retina specialist treating the disease of retina.
We have been using Macugen for Diabetic Macular Edema. Of course, Avastin has been also used. However, there are diabetic patients with severe circulatory systemic issues and only Macugen can be administered safely. Recently, I came across the interesting article about the efficacy of Macugen for Diabetic Macular Edema. Hopefully this will give the support for Macugen use of Diabetic Macular Edema.

A Phase 2/3, Multicenter, Randomized, Doulble-Masked, 2-year Trial of Pegaptamib Sodium for the Treatment of Diabetic Macular Edema. Ophthalmology, 118:6, 1107-1118, 2011.

For the safety issues, we should continue to have the Macugen as the therapeutic option for Diabetic Macular Edema.

In addition, Anti-VEGF agent has been great asset for treating Retinal Vein Occlusion patients. Macugen should be added for these patients as well.
Here is the another references for Macugen for Branch and Central Retinal Vein Occlusion.
Pegaptanib Sodium for Macular Edema Secondary to Branch Retinal Vein Occlusion. American Journal of Ophthalmology. 149:147-154, 2010.

Pegaptanib Sodium for Macular Edema Secondary to Central Retinal Vein Occlusion. Archives of Ophthalmology. 127:374-380, 2009.

Comment:
Macugen is a selective vascular endothelial growth factor (VEGF) blocker that has been shown to be effective and safe in the treatment of neovascular age related macular degeneration (wet AMD), diabetic macular edema (DME) and vein occlusions. Lucentis (ranibizumab) and Avastin (bevacizumab) are non-selective VEGF blockers that have been shown to have a systemic risk of cerebral vascular accidents (CVA). Both Lucentis and Avastin are effective treatments for wet AMD and DME but do place the patient at risk for a stroke, especially if they have a prior history of a CVA. Because of this I think that Macugen offers a safer and effective treatment for at risk patients with retinal vascular diseases such as wet AMD, diabetic retinopathy and retinal vein occlusions. I am requesting that WPS continue current coverage of DME and consider expanding coverage to include proliferative diabetic retinopathy, retinal vein occlusion and central retinal vein occlusions. I have sent via FedEx a hard copy of this letter and supporting Journal articles showing that Macugen is an effective and proven treatment for these diseases. Included in this set of articles is the most recent publication showing two year data using Macugen for the treatment of DME.

The current treatment modalities for DME and edema associated with retinal vein occlusions (CVO and BVO) include thermal laser, intravitreal and subtenons injection of steroids, Avastin and Lucentis. Most retinal specialists have developed different treatment regimens and criteria for use of these therapies. We all have had success and failure with these varied treatment options. I believe that Macugen should be an option to have available for our patients who have these chronic conditions. The prospective efficacy and safety data for Macugen demonstrates that this is a reasonable treatment option for patients with DME, PDR and retinal vein occlusions.

Retina specialists have varying opinions with respect to the safety of the treatments currently available to us for treatment of diabetic retinopathy. Almost 50 percent of patients with type II diabetes will develop vision loss due to macular edema. Until recently, the only randomized controlled clinical trial (RCT) validated treatment was focal/grid laser photocoagulation. This is a destructive laser procedure that slows down the rate of vision loss, but does not improve visual acuity in the majority of patients. The other common treatment is intraocular injection of triamcinolone acetonide. Recent RCT data have demonstrated that triamcinolone is not superior to laser, but did indicate up to 50 percent of patients who receive multiple injections of triamcinolone develop glaucoma, a complication that has severe morbidity and expense. Recently, the results of an RCT for the use of intravitreal Macugen have demonstrated a statistically significant and clinically significant response in patients with macular edema. The Macugen treated patients' demonstrated increased proportion of eyes gaining two and three lines of vision. The acuity benefit was maintained (compared to control group) even after discontinuation of the drug. These results are detailed in a publication entitled "A Phase 2/3 Multicenter, Randomized Double-Masked, 2-Year Trial of Pegaptanib Sodium for the Treatment of Diabetic Macular Edema." This demonstrates the ability of Macugen to improve and maintain visual gains in patients with clinically significant macular edema.

Long term safety of an agent used to treat diabetic retinopathy is of key importance due to the chronicity of the disease and the potential for onset early in life. The use of intravitreal injection of steroids can initially appear to be a cost effective treatment for diabetic macular edema. As mentioned above m any of these patients eventually develop steroid induced glaucoma and cataracts that increase the cost of this therapy and may have long term effects on the vision despite an initial positive response. Avastin has been used with varying success in the treatment of diabetic macular edema and proliferative diabetic retinopathy but the risk of systemic and intraocular complications is unknown. It is reasonable to be concerned about the risk of strokes with the use of Avastin, a non-selective anti-VEGF agent, in this patient population based on the data from the SAILOR trial using Lucentis, another non-selective anti-VEGF agent. Long-term use of Macugen has not demonstrated an increase in strokes or other vascular complications. A thorough review of the data available on Macugen shows that the safety and efficacy data suggests that it is a safe and effective treatment for diabetic retinopathy with minimal potential for long term complications as may be seen with steroids and Avastin.

Proliferative diabetic retinopathy is caused by the growth of abnormal new vessels on the surface of the retina that can bleed into the vitreous cavity causing severe loss of vision. Untreated, these vessels form scars, which upon contraction, lead to retinal detachment. Two RCTs from the 1970's and 1980's have confirmed the effectiveness of scatter laser photocoagulation in limiting the progression of retinopathy. Vitreous hemorrhage can prevent the retina specialist from being able to visualize the retina through the vitreous blood in order to perform laser. These patients usually are referred for an expensive surgical procedure, pars plana vitrectomy. Macugen has been shown to be effective and safe in causing regression of proliferative retinopathy in a study called "Intravitreal Injection of Pegaptanib Sodium for Proliferative Diabetic Retinopathy" published in the British Journal of Ophthalmology in 2009. Two of the patients in the laser only group, but none in the Macugen group, required vitrectomy. The ability to offer patients with proliferative retinopathy and vitreous hemorrhage one or two doses of Macugen, in order to facilitate laser treatment, would be sight-saving as well as a cost effective alternative to vitrectomy.

Retinal vein occlusion is another common cause of vision loss, also due to macular edema. Recent RCT have demonstrated that intravitreal injections of triamcinolone (up to three per year), of Lucentis (six to 10 per year), or of Ozurdex (two per year) are all effective therapies. A RCT of Macugen also demonstrated that three to five doses of Macugen significantly improved mean visual acuity. These findings were published in "Pegaptanib Sodium for Macular Edema Secondary to Central Retinal Vein Occlusion" in Archives of Ophthalmology in 2009.

In summary, anti-VEGF agents, including Macugen, have been demonstrated to be effective in treating diabetic macular edema, proliferative diabetic retinopathy, branch retinal vein occlusion and central retinal vein occlusion. Only for Macugen, however, have peer-reviewed results of RCTs for all four indications been published. I believe that there is compelling evidence that macugen should be covered as a treatment option for these diseases.

Response:
We have included the treatment of Diabetic macular edema (362.07) and Central vein occlusion (362.35) to our coverage of Macugen.

Comment:
Under the diagnoses for Avastin and Lucentis should be added "proliferative diabetic retinopathy, 362.02". These anti-VEGF agents are sometimes used immediately prior to surgical intervention in diabetics with very severe, active, proliferative disease who are about to undergo vitrectomy.

The injections will diminish the neovascular load and make the surgery much safer. Using these drugs has been the standard of care for several years among retina specialists.

Secondly, Avastin and Lucentis are also used for radiation retinopathy, most commonly in patients who have received plaque radiation therapy for melanoma. There is no specific code for radiation retinopathy, so the code used would be 362.10 which is background retinopathy, unspecified.

Thirdly, Avastin and Lucentis are widely used to treat choroidal neovascularization in the macula secondary to myopic degeneration. I cannot find and ICD code for myopic degeneration.

Response:
We have added proliferative diabetic retinopathy (362.02) to our coverage of Avastin and Lucentis. No literature was submitted to support the other conditions that were requested.

Comment: We received a request and literature to add the treatment of Ocular Histoplasmosis and Polypoidal Choroidopathy to our coverage of Bevacizumab.

Response:
We have added the treatment of ocular histoplasmosis (115.02, 115.12, and 115.92) to our coverage of Avastin. The literature submitted did not support the addition of polypoidal choroidopathy at this time. One study concluded that the combined treatment consisting of photodynamic therapy with verteporfin and intravitreal bevacizumab for polypoidal choroidal vasculopathy seemed to be effective for improving visual acuity and reducing retreatment rates and complications. Further study is needed to determine the long-term clinical results.

Comment:
We received a request and literature to expand our coverage of Bevacizumab and Ranibizumab for the treatment of choroidal neovascularization.

Response:
We added coverage of Retinal neovascularization (362.16) to our coverage of Lucentis and Avastin.

Comment:
Because we are focused on consistent and accurate coding and compliant billing practices, we are submitting the following comment on the Wisconsin Physician's Service Draft Local Coverage Determination (LCD) DL32013 related to Drugs and Biologics (Non-chemotherapy).
We are concerned with reporting an unclassified biological HCPCS code, J3590, for bevacizumab when used for ophthalmological conditions. There is currently an active HCPCS code of C9257 for "Injection, bevacizumab, 0.25 mg". This code is appropriate for reporting the low doses of bevacizumab used for intravitreal injections (1-3 mg). Medical coding guidelines require the most specific code available be used to report the service provided.

Response:
The omission of code C9257 Injection, bevacizumab, 0.25 mg was an oversight. This code is for use in the outpatient hospital and ASC settings. We have added C9257 to the LCD. Physician's administering Avastin intravitreally in their office/clinic should continue to use J3590.

Comment:

The policy lists the use of hcpcs code J2001 – drug Lidocaine HCL 10 mg as only being covered for 6 cardiac related diagnoses. However, Lidocaine is widely used as a local anesthetic as well as an anti-arrhythmic. A) Will the uses of Lidocaine as an anesthetic be denied as non-covered? B) Why is WPS creating a coverage policy for Lidocaine when there is zero reimbursement for J2001?

Response:
Lidocaine is not separately payable when it is used as an anesthetic. The reason we included Lidocaine with the cardiovascular conditions was to allow the claims processing system to pay for the drug when it is used to treat cardiac conditions and to deny when it is used as an anesthetic.