



Avastin™ (Bevacizumab) Injections: Risk Management Recommendations

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PURPOSE OF RISK MANAGEMENT RECOMMENDATIONS

OMIC regularly analyzes its claims experience to determine loss prevention measures that our insured ophthalmologists can take to reduce the likelihood of professional liability lawsuits. OMIC policyholders are not required to implement these risk management recommendations. Rather, physicians should use their professional judgment in determining the applicability of a given recommendation to their particular patients and practice situation. These loss prevention documents may refer to clinical care guidelines such as the American Academy of Ophthalmology's Preferred Practice Patterns, peer-reviewed articles, or to federal or state laws and regulations. However, our risk management recommendations do not constitute the standard of care nor do they provide legal advice. If legal advice is desired or needed, an attorney should be consulted. Information contained here is not intended to be a modification of the terms and conditions of the OMIC professional and limited office premises liability insurance policy. Please refer to the OMIC policy for these terms and conditions.

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Avastin™ (bevacizumab) is administered off-label for the treatment of a number of ophthalmic conditions. This document answers many questions ophthalmologists have about the patient safety and professional liability risks of this medication.

Patient selection

Now that Lucentis™ has been approved for the treatment of AMD, physicians who have been treating their patients with Avastin™ wonder if they are required to now switch to Lucentis™. Off-label use of an approved medication is a common and legal part of the practice of medicine. OMIC believes that the treating ophthalmologist is in the best position to determine what a particular patient needs, and leaves this decision up to the physician's judgment. The OMIC website has a sample consent form for Lucentis™.

- Consider first treating patients with AMD with FDA-approved medications such as Lucentis,™ Visudyne,™ and Macugen™.
- Conduct at least an initial fluorescein angiogram and OCT, and evaluate lesion type, location, and size, and presence of subretinal fluid to determine if patients may benefit from Avastin™.

Warnings Associated with Intravenous Avastin™

The prescribing information for intravenous systemic Avastin™ contains **warnings** about gastrointestinal perforations/wound healing complications, hemorrhage, arterial thromboembolic events, hypertension, proteinuria, and congestive heart failure.

- Screen patients for medical conditions that increase their risk for these complications.

- Consider obtaining medical clearance for patients with pertinent medical comorbidities.
- Monitor patients for adverse events before, during, and after administration.
- At the time of discharge, give patients written instructions about how to contact you and eye symptoms that should be immediately reported. Instruct them to call 911 or go to the Emergency Room if they experience symptoms of life-threatening conditions affecting other organs.
- Avastin™ should not be administered for at least 28 days following major surgery, and should be suspended prior to elective surgery. The appropriate interval is unknown; however, the half-life of Avastin™ is estimated to be 20 days, and the interval chosen should take into consideration the half-life of the drug.
- See the full prescribing information at <http://www.avastin.com/avastin/prescribingPIPro.m>

Stroke Risk of Intravitreal Anti-VEGF Drugs

The prescribing information for the related medication Lucentis™ contains a **warning** about arterial thromboembolic events: “Although there was a low rate (<4%) of arterial thromboembolic events observed in the LUCENTIS clinical trials, there is a theoretical risk of arterial thromboembolic events following intravitreal use of inhibitors of VEGF.”¹ A “Dear Healthcare Provider” letter of 24 January 2007 from Genentech advised ophthalmologists “of a higher incidence in one study of strokes in the 0.5-mg Lucentis dose group compared with the 0.3-mg dose group (1.2% versus 0.3%, respectively; $P=0.02$).”² Avastin and Lucentis are both anti-VEGF drugs with a similar mode of action. It would be prudent to assume that the stroke risk might be similar, but the actual risk of stroke with these drugs is currently unknown.

- Consider medical conditions that increase the risk for thromboembolic events.
- Ask patients specifically if they have had a prior stroke.
- Consider providing or obtaining medical clearance for patients with pertinent medical comorbidities, such as a history of stroke.
- Consider whether a change in dosage is warranted in the setting of prior stroke history.
- Consider providing patients with a history of stroke the information on stroke symptoms and response from the American Heart Association.³ The AHA’s symptoms of stroke include sudden changes in vision; since such visual changes may not be reliable indicators of stroke in patients on Lucentis, these are not included here:
 - PATIENT STROKE EDUCATION
 - Call 911 or go the emergency room if you experience any of the following signs of a stroke:
 - sudden numbness or weakness of the face, arm, or leg, especially on one side of the body;
 - sudden confusion, trouble speaking or understanding;
 - sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe headache with no known cause.

Preparation of the medication

The medication comes in preservative-free vials intended for use at a much higher

¹ See the full prescribing information at <http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf>.

² “Dear Healthcare Provider,” Barron, Hal MD, Senior Vice President, Development, Chief Medical Officer, Genentech, Inc., 27 January 2007.

³ Stroke Warning Signs. American Heart Association. Patients are encouraged to note the time of the onset of symptoms and to seek care as soon as possible, as the most common type of stroke can be treated with a clot-dissolving medication. <http://www.americanheart.org/presenter.jhtml?identifier=3053#Stroke>

concentration on a single cancer patient. Many practices use a compounding pharmacy to prepare the medication. Compounding pharmacies must comply with USP (United States Pharmacopeia) Chapter 797, which sets standards for the compounding, transportation, and storage of compounded sterile products (CSP). There is now a Pharmacy Compounding Accreditation Board, which can verify that the pharmacy is adhering to these standards.

- Use proper aseptic technique during the preparation and administration of the injection.
- “Credential” the compounding pharmacy to which you send the prescription for intravitreal Avastin™.
 - Ask the compounding pharmacy for assurance that it is licensed/registered in the state in which it is dispensing.
 - Ask the pharmacy how it compounds Avastin (it should state that it complies with USP 797).
 - Ask the pharmacy if it is an accredited compounding pharmacy.
- Ask the compounding pharmacy to prepare the medication for ophthalmic use, confirm the dose and sterility, identify a syringe suitable for this protein, provide storage and “beyond-use” instructions, and the lot number of the vial.

Preventing and managing complications from intravitreal injections

Intravitreal injections have caused endophthalmitis, retinal detachment, and increased intraocular pressure.

- Be familiar with the latest guidelines on care before, during, and after administration. One such source is the article by Flynn, Harry W. and Scott, Ingrid U., Evolving Guidelines For Intravitreal Injections. *Retina* 24: S3-S19, 2004.
- Educate the patient about the warning signs of complications and how to contact you. Consider giving these instructions in writing.

Informed consent discussion and documentation

- Warnings and complications associated with intravenous systemic use in patients with colorectal cancer (see above)
 - Patients should be warned of these potential complications, but told that patients who experienced them had metastatic colon and lung cancer, and were given 400 times the dose at more frequent intervals in a way that spread the drug throughout their bodies. While the significantly lower dose and intravitreal administration is believed to reduce the risk of these complications, there is no FDA-approved study proving this reduced risk.
 - Patients should also be told that whenever a medication is used in a large number of patients, a small number of coincidental life-threatening problems may occur that have no relationship to the treatment.
- Systemic complications noted in ophthalmic use
 - The systemic risks of Avastin™ are not well known (see Stroke Risk, above). Patients should be told that preliminary studies of similar drugs show a possible increased risk of a repeat stroke in patients with a prior stroke.
 - One study of ophthalmic use of IV Avastin™ excluded patients with a history of myocardial infarction, stroke, or uncontrolled hypertension, and reported that patients developed only a mild elevation in blood pressure. See Michels S, Rosenfeld JR et al. Systemic Bevacizumab (Avastin) Therapy for Neovascular Age-Related Macular Degeneration: Twelve-Week Results of an Uncontrolled Open-Label Clinical Study. *Ophthalmology* 2005;112:1035-1047.
 - In another study, patients treated with intravitreal Avastin™ for AMD and macular edema did not have these elevations. See Rosenfeld, PJ, Moshfeghi AA, Puliafito CA. Optical Coherence Tomography Findings After an Intravitreal Injection of

Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration. *Ophthalmic Surg Lasers Imaging* 2005; 36:331-335, and Rosenfeld, PJ, Fung AE, Puliafito CA. Optical Coherence Tomography Findings After Intravitreal Injection of Bevacizumab (Avastin) for Macular Edema From Central Retinal Vein Occlusion. *Ophthalmic Surg Lasers Imaging* 2005; 36:336-339.

- The International Intravitreal Bevacizumab Safety Survey used the internet to compile reports from physicians of adverse events potentially associated with Avastin injections. Seventy centers in 12 countries reported on a total of 7113 injections in 5228 patients. The following systemic adverse events, in increasing order of frequency, occurred: transient ischemic attacks (TIA) and deep vein thrombosis (DVT), both at 0.01%; death (0.03%); cerebrovascular accident (CVA; 0.03%), and mild increases in blood pressure (0.21%). See Fung AE, Rosenfeld PJ Reichel E. The International Intravitreal Bevacizumab Safety Survey: Using the internet to assess drug safety. *Br J Ophthalmol* 2006; 90: 1344-1349.
- “Off-label” status.
 - Intravitreal Avastin™ for AMD, conditions with similar manifestations, and refractory macular edema is not an approved use, so patients should be informed of its “off-label” status.
 - Now that the related Genentech medication Lucentis™ has been approved, inform patients that a very similar medication has been approved for this condition and route.
- Consent for ongoing treatment
 - In general, informed consent may be considered to have ongoing force and effect until 1) the patient revokes the consent or 2) circumstances (i.e., the patient’s medical or ocular condition) change so as to materially affect the nature of the procedure or the risk/benefit ratio.
 - Prior to subsequent injections, the continued need, effectiveness, and safety of the medication should be evaluated and documented.
 - If the patient’s medical or ocular condition changes to the point that the risk/benefit ratio is affected, it would be prudent to either discontinue treatment or obtain and document informed consent again.
 - Documentation
 - Document the decision-making process that led to choosing Avastin™ as the treatment for the patient. Note results of earlier attempts at treatment and the results of diagnostic tests.
 - Note the dose, lot number of the vial, any reactions to the injection and how they were handled, and the discharge and follow-up instructions.

OMIC policyholders who have additional questions about this topic are encouraged to utilize our confidential Risk Management Hotline by calling 1.800.562-6642, extension 651 or 662.