



Intravitreal Anti-VEGF Treatment for Adults Patients: Risk Management Recommendations

OMIC is grateful to the ophthalmologists on our Board for their expertise. This specific document reflects the input of the following Board and staff members: Anne M. Menke, RN, PhD; George Williams, MD, Trexler M. Topping, MD; Pauline Merrill, MD, Denise Chamblee, MD, Paul Weber, JD, Hans Bruhn, MHS, and Michelle Pineda, MBA.

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.

Version 6/30/15

Vascular endothelial growth factor, or VEGF, is a protein that stimulates the growth of new blood vessels. Ophthalmologists administer intravitreal anti-VEGF agents for a variety of indications. Sometimes the indication has been approved by the Food and Drug Administration (FDA), other times it is off-label, or the medication itself may never have been approved for any eye indication. This risk management document presents suggestions to increase patient safety and decrease the likelihood of lawsuits related to these drugs. It also provides information about our revised sample consent documents for anti-VEGF agents.

A. Approved indications for anti-VEGF drugs

The Food and Drug Administration (FDA) has approved a few drugs for the treatment of ophthalmic VEGF-mediated diseases. For ease of reading, the first reference to a drug will give its trade and generic name; thereafter, only the trade name will be given. Three other drugs that are not anti-VEGF agents are approved for some of the same indications.

- Age-related macular degeneration (AMD):
 - Macugen™ (pegaptanib), Lucentis™ (ranibizumab), and Eylea™ (aflibercept) are all anti-VEGF agents approved to treat AMD. Visudyne™ (verteporfin) is also approved to treat AMD.
- Diabetic macular edema (DME):
 - Lucentis and Eylea are approved to treat DME. Ozurdex™ (dexamethasone) and Iluvien® (fluocinolone acetonide) are also approved to treat DME.
- Diabetic retinopathy (DR):
 - Lucentis and Eylea are approved to treat DR in patients with diabetic macular edema.
- Retinal vein occlusion (RVO):
 - Lucentis and Eylea are approved to treat macular edema following retinal vein occlusion (RVO); Ozurdex is also approved for this.

Explaining to patients how these drugs work

The indications on the labels for these drugs state the conditions they are designed to treat. We have learned from field testing our revised forms that patients may have a difficult time understanding the names of these diseases, or get confused about which one they have. To make our consent forms easier to understand, we incorporated “plain language” principles. The goal is simple, short explanations. Here is how we describe the indications in our new sample forms:

- Eye surgeons treat some types of eye problems with a medication called [name of drug]. [Name of drug] can help prevent vision loss due to 2 types of eye problems:
 - 1) the growth of harmful blood vessels in your eyes
 - 2) swelling in the back of the eye (macular edema).

OMIC-insured ophthalmologists are not required to use our consent forms, and are encouraged to adapt them as needed. Sample forms can be found at www.omic.com/avastin/, www.omic.com/lucentis/, and www.omic.com/eylea/.

B. Off-label use of drugs

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.

- Ophthalmologists use the FDA-approved medications just discussed to treat other eye conditions. All such use is off-label.
- Eye surgeons use Avastin™ (bevacizumab), which has not been approved for intravitreal use or for eye conditions. All ophthalmic use of Avastin is off-label.
- Use of any anti-VEGF drug in the pediatric population is off-label.

OMIC recommends that you obtain consent for off-label use of anti-VEGF drugs. The OMIC website has sample consent forms for these medications, as well as risk management recommendations and a sample consent form for the use of anti-VEGF drugs to treat ROP. The Avastin consent form already addresses this off-label use. Here is sample language that can be added if Lucentis or Eylea are used off-label:

- The Food and Drug Administration (FDA) approved [name of drug] for treating some eye diseases. These diseases may cause the growth of harmful blood vessels in your eye and swelling (macular edema). Eye surgeons also use [name of drug] to treat other diseases that cause similar problems. This is called off-label use.

C. Preparation of Avastin

The medication comes in preservative-free vials intended for intravenous use at a much higher concentration on a single cancer patient. Avastin needs to be repackaged for intravitreal use. This repackaging must be done in compliance with the Drug Quality and Security Act (DQSA), which was passed on November 27, 2013. Under this law, repackaging must be done either by a compounding pharmacy or a federally-registered outsourcing facility.

Compounding pharmacies (CFs) operate under Section 503A of the law and are governed by their state board of pharmacy. They must be in compliance with USP (United States Pharmacopeia) Chapter 797, which regulates the compounding, transportation, and storage of compounded sterile products (CSP). CFs require a patient-specific prescription.

Section 503B of the DQSA created outsourcing facilities (OFs), which must register with the FDA, which governs them. OFs must comply with current good manufacturing practices as well as USP 797. OFs do not require a patient-specific prescription, so ophthalmologists may order in bulk from them.

“Credential” the compounding pharmacy or outsourcing facility:

- Ask the compounding pharmacy for:
 - Evidence of licensure in the state in which it is dispensing
 - Assurance that it maintains strict compliance with USP chapter 797 mandates
- Verify with the outsourcing facility that:
 - It has registered with the FDA
 - It maintains strict compliance with current good manufacturing practices

The pharmacy or outsourcing facility should provide prepare the medication for ophthalmic use, confirm the dose and sterility, identify a syringe suitable for this protein, provide storage and “beyond-use-date” instructions, and the lot number of the vial. The FDA is still determining the “beyond-use-date” requirements for repackaged Avastin.

D. Preventing endophthalmitis

The prescribing information for the anti-VEGF agents contain statements about actions ophthalmologists should take to prevent and manage known complications. These statements tend to reflect protocols in place during clinical trials for these drugs. Aspects of the protocols may not be necessary in clinical practice outside of the research setting. And guidelines published since the drug was approved make different recommendations, especially in relation to infection prophylaxis. Physicians should use their clinical judgment to determine what recommendations to follow.

FDA-approved labels for both Lucentis and Eylea state that the “intravitreal injection should be administered under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eye speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.” An expert panel reviewed published studies of intravitreal injection technique and monitoring and released guidelines in 2014.¹ The panel reached different conclusions about gloves, drapes, speculum, and antibiotics than the recommendations included in the label for Lucentis and Eylea.

Lack of evidence to support some labeling instructions

- The experts concluded that “there is insufficient evidence to support the routine use of pre-, peri-, or postoperative antibiotics to reduce the rate of endophthalmitis.”¹
- Sterile or non-sterile gloves may be used even though they have not been shown to reduce the risk of endophthalmitis.
- There is no evidence to support the routine use of a drape.

Recommendations to reduce the risk of endophthalmitis

The experts did make recommendations. Here are some key guidelines. Please see the article for full details.

- External infections
 - Postpone injection until active external infections, including blepharitis, have been treated and cleared, unless the benefits of injection clearly outweigh the risk of endophthalmitis.
- Povidone-iodine
 - Ensure that povidone-iodine (5-10%) is the last agent applied to the intended injection site before injection.
 - If a gel anesthetic is used, apply povidone-iodine both before and after application of the gel.
 - Povidone-iodine may also be applied to the eyelids, including the eyelid margins and eyelashes.
 - Avoid eyelid scrubbing or expressing material from the meibomian glands.
 - Prevent contact of the eyelashes and eyelid margins with both the injection site and the injection needle after final application of povidone-iodine and especially during the actual injection.
 - Use either a speculum or other technique, such as manual lid retraction.
- Aerosolized droplets
 - Reduce the spread of aerosolized droplets during the injection preparation and procedure.
 - Use a surgical mask or minimize speaking by the physician, assistants, and patients.
- Bilateral injections on the same day
 - Exercise caution when performing bilateral injections on the same day.

¹ Avery RL et al. Intravitreal Injection Technique and Monitoring. Updated Guidelines of an Expert Panel. *Retina*. 2014; 34, number 12, S1-S18.

- Consider the injection for each eye as a separate procedure.
- Use separate site preparation, individual syringes, needles, etc.
- Use a different medication batch if using a compounded medication such as Avastin.
- Patient education and monitoring
 - Monitor patients for symptoms suggestive of endophthalmitis.
 - Instruct patients to contact you immediately if the eye becomes red, sensitive to light, painful, or develops a change in vision. Consider giving these instructions in writing.

E. Informed consent and documentation

Intravitreal injections carry many of the same risks as other intraocular procedures (i.e., infection, IOP changes, etc). There are a few risks specific to these drugs that raise questions for ophthalmologists.

Arterial thromboembolic events (ATEs)

Anti-VEGF agents have been safely administered to hundreds of thousands of patients. Clinical trials of Lucentis, Avastin, and Eylea have shown a low incidence of ATEs, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death, including deaths of unknown cause. The relationship between administration of anti-VEGF agents and these events is unclear, as patients receiving these drugs have co-morbidities associated with ATEs.

Nonetheless, the labels for Lucentis and Eylea indicate that anti-VEGF drugs have a potential risk of ATEs. ATEs are also included in the warnings on the label for intravenous Avastin. The Lucentis label indicates that the risk for ATEs may be higher in patients with diabetes. Further research is needed to confirm this. We recommend warning all patients with diabetes who receive anti-VEGF drugs of this possible increased risk. OMIC recommends that you discuss the risk of ATEs with patients. We have addressed this risk in our sample consent forms for these drugs.

In addition to ATEs, the prescribing information for intravenous Avastin contains warnings about gastrointestinal perforations/wound healing complications, hemorrhage, hypertension, proteinuria, and congestive heart failure. These complications have not been related to intravitreal use, so OMIC has removed any discussion of them from our sample Avastin consent form.

Potential harm to the fetus

The FDA changed the safety labeling for intravenous Avastin, adding a section on embryo-fetal toxicity in June, 2015. The warning states that “Avastin may cause fetal harm based on the drug’s mechanism of action and findings from animal studies.”² Pregnant rabbits were given Avastin IV 10 mg/kg or more every three days, and congenital abnormalities were noted. It went on to say that “animal models link angiogenesis and VEGF...to critical aspects of female reproduction, embryo-fetal development, and postnatal development.” The FDA instructs physicians to “advise

² <http://www.fda.gov/safety/medwatch/safetyinformation/ucm287610.htm>

females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin.”

The FDA does not know if intravenous Avastin causes harm to the human fetus. The FDA warning did not address intravitreal Avastin, as this use is off-label. The risk for intravitreal use is even less clear, however, as the intravitreal dose of Avastin is a fraction of this, and is only administered monthly. If the effect on the fetus is inherent to anti-VEGF agents, then Lucentis and Eylea may pose a similar risk. In any event, the warning would only apply to the small number of women who are pre-menopausal.

The warning was only issued for Avastin. Nonetheless, to reduce the potential liability for ophthalmologists using anti-VEGF drugs, we feel it is prudent to discuss the FDA warning with pre-menopausal women.

- Explain that the warning was issued for IV use, not for use in the eye.
- Explain that the FDA does not know if IV Avastin causes harm to the human fetus.
- Explain that the FDA does not know if intravitreal anti-VEGF drugs pose a risk for the human fetus.
- Advise the woman to talk to her regular doctor about whether to use birth control while she is getting Avastin, Eylea, or Lucentis, and for six months after the last dose.
- Ask the woman to sign a document discussing this possible risk, which is available at www.omic.com/avastin_risk_to_fetus/, www.omic.com/lucentis_risk_to_fetus/, and www.omic.com/eylea_risk_to_fetus/.

Treatment of both eyes on the same day

- Document your decision-making process in the medical record.
- Inform the patient of the possibility of vision-threatening complications in both eyes.
- Explain the measures you will take to reduce the risk of infection (i.e., you will use a new syringe, needle, etc.).
- Ensure that the patient has a ride home before administering the injections.

Consent for ongoing treatment

In general, informed consent is considered valid until 1) the patient revokes the consent or 2) the patient’s medical or ocular condition change so as to materially affect the nature of the procedure or the risk/benefit ratio. This means that unless either of these situations materialize, you need only obtain the patient’s informed consent once as long as you document that the consent is for ongoing treatment, and the consent form states the same.

- Obtain consent for each eye.
- Obtain and document informed consent again if the patient’s medical or ocular condition changes to the point that the risk/benefit ratio is affected.
- Review the risks and benefits on a regular basis, such as yearly.

Documentation

- Document the decision-making process that led to choosing the particular drug as the treatment for the patient. Note results of earlier attempts at treatment and the

results of diagnostic tests.

- Evaluate and document the continued need, effectiveness, and safety of the medication prior to each injection.
- 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.

RISK MANAGEMENT ASSISTANCE

OMIC policyholders may obtain confidential risk management help by contacting OMIC's Risk Management Hotline at 800.562-6642, option 4, or by emailing us at riskmanagement@omic.com.