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**ROP Safety Net:**

**Anti-VEGF for ROP**

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**OMIC policyholders who provide care must comply with the ROP Safety Net.**

OMIC’s ROP Safety Net is based on our claims experience. It is designed to address the causes of ROP lawsuits in order to protect the infant and the ophthalmologist. The ROP Safety Net Toolkit contains sample protocols, which may need to be customized, and refers to ROP clinical care guidelines. These protocols and guidelines are recommendations and do not constitute the standard of care. Ophthalmologists should use their professional judgment in determining the applicability of a given recommendation to their particular patients and practice situation.

The Toolkit does not provide legal advice. Consult an attorney if legal advice is desired or needed. 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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OMIC is committed to helping ophthalmologists provide safe care for infants at risk for retinopathy of prematurity (ROP). To that end, we have developed and published our ROP Safety Net, which includes an analysis of ROP malpractice claims, toolkits for both hospital- and office-based care, and sample consent forms for laser and anti-VEGF injection. To further reduce the risk and severity of ROP malpractice claims, OMIC conducts an underwriting review on a regular basis of all insured physicians who provide ROP care, and has mandated certain loss prevention actions that are summarized in “ROP conditions of coverage” (all documents available at <http://www.omic.com/rop-safety-net/>).

# **Treatment of ROP**

Ophthalmologists have been treating ROP with laser surgery for many years. Some babies are too sick to tolerate the anesthesia needed during the surgery. In others, the abnormal vessels are in an area that the laser cannot safely reach, or the view is obstructed by blood or a persistent tunica vasculosa lentis. Some infants have disease that persists despite laser. Other means of arresting ROP are thus needed.

Adult patients with retinal conditions due at least in part to VEGF have been successfully treated with intravitreal injections of anti-VEGF agents such as AvastinTM (bevacizumab), Macugen**TM** (pegaptanib), Lucentis**TM** (ranibizumab), and Eylea**TM** (aflibercept); intravitreal injection of anti-VEGF agents is hereafter referred to as **IVAV**. The similarity between ROP and adult retinal conditions prompted clinical trials on the use of IVAV in neonatal populations. Published reports from both clinical trials and “off-label” use of IVAV for ROP suggest that it can be effective and does not—so far—appear to produce many serious short or long-term side effects. **The efficacy, safety, and long-term consequences have not yet been proven.**

Concerns about IVAV both as primary or salvage therapy have been addressed in the literature and at eye society meetings. In addition, many questions are currently being studied and debated, such as agent, dosage amount, volume, timing of injections, length of follow-up, and contraindications. The 2018 ROP Screening Policy Statement (PS)[[1]](#endnote-1) addresses these issues. The PS recommends that infants treated with IVAV be followed closely until at least 65 weeks postmenstrual age (PMA).

Despite these uncertainties, when faced with aggressive or refractive ROP, ophthalmologists at times feel there is no other prudent choice but to treat ROP with IVAV. Given the extremely high indemnity payments often required to settle ROP malpractice claims, physicians are understandably concerned: they feel they are caught between the need to administer vision-preserving care and the risk of litigation—even decades later—for doing so. This document will address those concerns, and provide risk management recommendations specific to the use of anti-VEGF agents “off-label” for the treatment of ROP.

## **“Off-label” use of medications**

The Food and Drug Administration (FDA) approves and regulates the production, sale, and clinical research of medical drugs and devices. As a condition of approval, the manufacturer produces a “label” that summarizes the results of the research upon which the approval is based, as well as the indications, contraindications, known complications, and special warnings.

The FDA does not directly regulate the practice of medicine. Rather this oversight is provided by state legislatures, which pass medical practice acts generally granting the physician the right to use any and all means to diagnose and treat disease. Medical practice is further regulated by state medical boards, which issue licenses to practice medicine, and set conditions for license maintenance and renewal.

The FDA has explicitly addressed “off-label” use in an Information Sheet.[[2]](#endnote-2) The Sheet starts by declaring “Good medical practice and the best interests of the patient **require** that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment (emphasis added).” The FDA advises physicians who use approved products “off-label” to “be well-informed about the product, base its use on firm scientific method and sound medical evidence, and maintain records of its use andeffects.”

OMIC has analyzed the FDA guidance and our claims history, and concurs that it is not only legal but necessary for ophthalmologists to administer medications “off-label” when treating their patients.Moreover, OMIC feels that the ophthalmologist is in the best position to determine how to treat an individual patient. Accordingly, our professional liability policy provides coverage for such use.In the event of a lawsuit related to “off-label” use, ophthalmologists who are challenged will rely upon the expert witness testimony of ophthalmologists, peer-reviewed literature, and their well-documented efforts to provide quality care.

## **Obtaining informed consent for IVAV for ROP**

Intravitreal administration of anti-VEGF agents requires the informed consent of the infant’s parents or legal guardians. Informed consent discussions are often difficult, but rarely more so than in situations like this. Ophthalmologists who screen infants for ROP may not meet the parents during the screening process, and may thus be talking to the parents for the first time when they need to obtain consent. Once the need for treatment is identified, the eye surgeon needs to provide it within 72 hours to prevent progression to a retinal detachment; this timeline may make parents uncomfortable about making an informed choice. Premature infants run the risk of serious cardiac and respiratory complications with invasive treatment. In addition, the VEGF that causes ROP is vital for the development of the infant’s brain, lungs, and kidneys. When the treatment being proposed is relatively new and has unknown long-term risks, it is even more difficult for physicians to discuss and parents to consent.

OMIC has resources to help prepare parents for this discussion. In response to allegations made by plaintiffs in ROP malpractice lawsuits that they did not know that the infant was at risk for ROP, OMIC requires that insured physicians provide parents with a brief explanation of ROP prior to discharge from the hospital and at the first outpatient visit (the letters are in both toolkits).

Our sample protocols also advise educational efforts by the neonatologist and neonatal nurses. Neonatologists are a vital partner in the decision to use IVAV. Discuss the decision to use IVAV with the infant’s neonatologist to help determine the risk/benefit ratio in the particular child. Document the discussion, and relay it to the parents. Consider asking the neonatologist to be present during the informed consent discussion.

OMIC has also developed a sample consent form in English (included) and Spanish (in development) for IVAV for ROP, which is in the hospital toolkit, and at the end of this document. As always, our sample forms need to be reviewed and may need to be revised to meet current PS standards. The hospital may need to have the form approved by its Forms Committee.

While the consent of the parent or legal guardian is legally required to treat a child, lack of consent may constitute child neglect if the proposed care is needed to prevent significant harm to the minor. Physicians must take action if there is a reasonable belief that there is child neglect or abuse. The consent form includes a paragraph that states the surgeon must discuss the refusal with other physicians and Child Protective Services.

# **Managing parents who insist on IVAV**

While IVAV has an imprecise safety profile, it does not ablate the peripheral retina and may allow for better overall vision. Some parents prefer this treatment option. OMIC’s Risk Management Department has fielded calls from ophthalmologists who are uncomfortable with demands made by parents to use IVAV when laser surgery is, in the physician’s judgment, the best treatment. As in any case where the patient or legal guardian wants a different course of treatment, clarify the reasons for the preference. Explain your reservations. Enlist the assistance of other members of the patient’s healthcare team, and document all discussions. If after careful discussion and consideration you feel you cannot provide the treatment that is requested, arrange for an ophthalmologist with current competency in ROP to assume care of the infant and provide treatment in the appropriate time interval before withdrawing from care. Conduct and document the transfer of care, and send the parent a letter confirming the end of the physician-patient relationship. OMIC has sample termination of care letters at [www.omic.com](http://www.omic.com).

# **Follow up**

Some studies and presentations have indicated that IVAV changes the natural history of ROP. Significantly, the disease may reoccur months later than expected. As a result, infants who receive IVAV need to be examined for longer periods. The need for longer and additional follow-up may increase the risk for noncompliance with some parents. Consider whether IVAV with laser or IVAV alone is the best choice in the setting of unreliable parents. Carefully monitor appointments and promptly involve Child Protective Services if needed. The office toolkit includes recommendations for tracking appointments, and sample letters to parents that warn of the possible need to contact the authorities.

**OMIC policyholders have specific obligations if an infant is treated with IVAV:**

* Follow infants closely until at least 65 weeks PMA.
* At 65 weeks PMA, may end screening if either of these endpoints has been reached:
	+ Full vascularization in close proximity to the ora serrata for 360° **OR**
	+ The avascular retina has been successfully treated with laser (e.g., no skip areas).
* Use professional judgment on continued monitoring in the following circumstances if no treatment endpoint has been reached at 65 weeks PMA:
	+ Low-grade disease that is clearly and slowly improving
	+ Stage 1 disease that is unchanged for 2 months
	+ No disease, no ROP, but incomplete vascularization
	+ Infant has a DNR order

# **Keep current and keep a file of resources**

Screening and treatment of ROP is a rapidly evolving discipline. Keep current by reviewing pertinent journals and attending lectures. Keep a file containing such articles or notes from talks given at eye society meetings. Consider taking a course that provides advanced training in the diagnosis and treatment of ROP. OMIC has identified such a course, and will pay enrollment fees for insured physicians who provide ROP care. If you are interested, please contact Linda Nakamura at lnakamura@omic.com, or at 800.562-6642, extension 652.

If you have any concerns about the underwriting requirements for ROP, please contact your Underwriting representative. For questions about any other aspect of ROP care, please contact our Risk Management Hotline by calling 800.562-6642, option 4, or via email at riskmanagement@omic.com; the assistance is confidential.

**Informed consent for injection to treat ROP (retinopathy of prematurity)**

This form is intended as a sample. It does not constitute the standard of care nor does it provide legal advice. It contains the information OMIC recommends the surgeon personally discuss with the patient.

**How to use this sample**

* Please modify it to fit your actual practice.
* **Remove this instruction box.**
* Add your letterhead to the first page of the consent form.
* Change font size if necessary.

**After the patient signs the form**

* Give the patient a copy of the signed form.
* Send a copy to the hospital or surgery center as verification that you have obtained informed consent.
* Keep the original in the patient’s medical record.

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Your baby has a condition of the retina (the back of the eye) called ROP.When a baby is born prematurely (too early), the retina has not had time to finish forming. After the premature birth, the blood vessels at the back of the eye stop growing. Soon the eye starts to make a chemical called VEGF (vascular endothelial growth factor). This chemical makes the blood vessels start growing again, but these are not normal blood vessels. These abnormal blood vessels can bleed. They can also pull (detach) the retina away from its normal position. This is called an RD (retinal detachment), and it can cause blindness.

**Treatment with Medication**

Some babies are too sick to have surgery or anesthesia. In other babies, the abnormal blood vessels are too far back in the eye to use the laser safely. Other parts of the eye or blood in the eye may block the path to the abnormal blood vessels.

Ophthalmologists can inject a medication in the baby’s eye to treat ROP.This is called an intravitreal injection. The medication, called anti-VEGF, stops the eye from making the VEGF chemical. There are three anti-VEGF medications: Avastin, Eylea, and Lucentis. The ophthalmologist will talk to you about which medication will be injected.

The goal of the injection is to keep the retina attached and save the baby’s vision. Some babies lose vision or go blind even if they have the injection. Sometimes, the abnormal vessels keep growing after the injection. The baby may need another injection or laser surgery to stop the growth of the abnormal blood vessels. If the abnormal blood vessels continue to grow they can pull the retina off the eye and cause an RD. If an RD develops, the baby will need surgery to treat the RD. An ophthalmologist will need to keep examining the baby’s eyes for at least 6 months after the injection to make sure the ROP is gone. You will need to take the baby to the ophthalmologist’s office for these exams after the baby goes home.

Your baby could have very poor vision or go blind if the ROP is not treated. Your baby cannot choose whether to have treatment. You have the legal right to choose if your baby will get treatment for ROP. Your ophthalmologist has a legal duty to treat the baby. If you decide not to treat the ROP, your ophthalmologist must talk to other doctors and child protective services about your choice.

**Anti-VEGF injection for ROP has not been approved by the FDA (Food and Drug Administration) to treat children. This is called off-label use.**

Some anti-VEGF medications have been approved by the FDA to treat eye conditions in adults. Ophthalmologists started to treat ROP with anti-VEGF medication in 2006. Ophthalmologists continue to study how well anti-VEGF works to treat ROP and how much medication to give babies.

**Doctors do not know if anti-VEGF medication injected in the eye harms other parts of the baby’s body.**

Anti-VEGF medication injected in the eye reaches the brain, lungs, and kidneys. These organs need the VEGF chemical to grow. The anti-VEGF medication may harm the brain, lungs, and kidneys.

* Ophthalmologists and neonatologists (doctors who care for newborns) are studying babies who get anti-VEGF to see if they develop other health issues with the development of their brain, lungs, and kidneys after injections.
* Premature babies often have problems with their brains, lungs, and kidneys and can be very sick. Sick babies may experience other health issues after injections.
* It is not known if problems that show up later in life are caused by being born prematurely or from getting the anti-VEGF medication.
* The ophthalmologist will talk to the neonatologist about whether it is safe for your baby to have anti-VEGF medication.

**This injection has risks and can cause problems**

There are risks with all injections and with all medications. These risks can cause vision loss or blindness. Here are some common or serious ones:

* The injection might not stop the ROP.
* The ROP can come back. The baby may need another injection or laser surgery to treat the ROP.
* Your baby could lose vision or go blind.
* When ROP is treated with laser surgery, the ophthalmologist knows in a few weeks if the ROP will return. The ophthalmologist may not know for months or years if the ROP will come back after an injection. The ophthalmologist must keep checking the eyes for ROP for at least 6 months after the injection. The baby may need laser surgery if the retina does not grow completely after the injection.
* In rare instances anesthesia can cause heart or breathing problems, or even death.
* The injection can cause other eye problems:
	+ An eye infection that could lead to blindness
	+ RD (detached retina)
	+ Cataracts (clouding of the eye’s lens)
	+ Glaucoma (high eye pressure)
	+ Hypotony (low eye pressure)
	+ Damage to the retina
	+ Damage to the cornea (clear covering of the front of the eye)
	+ Bleeding in the eye
	+ Bright redness in the white part of the eye
	+ Eye irritation, inflammation and lots of tears
* Some adult patients who have had anti-VEGF injections have had heart attack, stroke, or death. The FDA does not know if the anti VEGF medication caused these problems.

**Consent**. By signing below, you consent (agree) that:

* You read this informed consent form, or someone read it to you.
* You understand the information in this form.
* The eye surgeon or staff offered you a copy of this form.
* You are aware that the baby may lose vision or go blind from the ROP even with treatment.
* You are aware that the baby may need another injection or laser surgery.
* You are aware that the FDA has not approved this medicine for treatment of ROP.
* The eye surgeon or staff answered your questions about the injection for ROP.
* You understand that it is your right to refuse (say no to) this treatment for your baby. You also understand that if you do refuse the treatment, the ophthalmologist must ask other doctors or child protective services to talk to you about your decision.
* You agree to the injection.

**I want the ophthalmologist to give my baby an injection of \_\_\_\_\_\_\_\_\_\_\_(insert medication name- Avastin, Eylea or Lucentis) for ROP in:**

**\_\_\_\_\_\_\_ the right eye**

**\_\_\_\_\_\_\_ the left eye**

**\_\_\_\_\_\_\_ both eyes.**

Parent (or person authorized to sign for patient) Date

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Relationship to child if other than parent

# **Please contact risk management for Spanish translation.**

We welcome questions about the ROP Safety Net as well as suggestions on how to improve it. We can help OMIC policyholders to customize the procedures to their practice and hospitals. Please contact our Risk Management Hotline at 800-562-6642, option 4, or at riskmanagement@omic.com.

1. Fierson WM, American Academy of Pediatrics (AAP) Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening Examination of Premature Infants for Retinopathy of Prematurity. [Policy Statement.] *Pediatrics*. 2018;142(6):e20183061. Available at: <http://pediatrics.aappublications.org/content/142/6/e20183061> (Accessed: 3/16/22). [↑](#endnote-ref-1)
2. Food and Drug Administration. Regulatory Information: “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet,” available at <https://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm>. Accessed 8/17/18.. [↑](#endnote-ref-2)