



Triamcinolone Acetonide (Kenalog™ Triesence™ Trivaris™): 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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Steroids and their effect on the eye have been studied for nearly fifty years.¹ Some steroids are specifically approved by the Food and Drug Administration (FDA) for use in the eye. This list now includes triamcinolone acetonide (TA) injectable suspension, marketed as Triesence™ (Alcon, Ft. Worth, TX) or Trivaris™ (Allergan, Riverside, CA). The indications noted in the approval are limited, however, to sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. As a result, ophthalmic use of TA will still largely be “off-label.” Moreover, now that an FDA-approved form of TA is available, some ophthalmologists have contacted OMIC to inquire about the medicolegal consequences of continued “off-label” use of Kenalog™. OMIC responded to similar queries about Avastin™ when Lucentis™ was approved for age-related macular degeneration.

OMIC's Legal/Risk Management Department recognizes that “off-label” use of approved medications is a legal and necessary part of the practice of medicine. In the event of a lawsuit, ophthalmologists who are challenged about their use of one medication over another will continue to rely upon expert witnesses, peer-reviewed literature, and well-documented efforts to provide quality care. Furthermore, OMIC feels that the ophthalmologist is in the best position to determine how to treat an individual patient, and whether it is appropriate to take the cost of a

¹ Lewis, Richard A, MD. Intravitreal Kenalog™ and Glaucoma. *Glaucoma Today*.
<http://www.glaucomatoday.com/pages/0305/06.html>.

medication into account. Our professional liability policy provides coverage for such use, including ongoing use of Kenalog,TM as well as off-label use of TriesenceTM and Trivaris.TM

The remainder of this document further clarifies OMIC's understanding of "off-label" use of approved medications, and offers risk management recommendations specific to intravitreal administration of triamcinolone acetonide. A **sample consent form** for IVTA can be found on the OMIC website. If you are using TriesenceTM or TrivarisTM for on-label use only, delete the paragraph that addresses off-label use as well as the first bullet point on it in the consent section. If you are using Kenalog,TM include both the section on off-label use, and the second bullet point in the consent section.

"OFF-LABEL" USE OF AN APPROVED MEDICATION

As Dr. E. Randy Craven and attorney Elizabeth C. Moran note in "The Medicolegal Risks of Using Off-Label Drugs and Devices," the production, sale, and clinical research of new drugs and medical devices are subject to regulation by the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS).² When a drug or device is approved for medical use by the FDA, the manufacturer produces a "label" to explain the indications, dose, side effects, and complications.

The FDA has clarified that once it approves a device/medication, physicians may use it "off-label" for other purposes if they are well-informed about the product, base its use on firm scientific information and sound medical evidence, and maintain records of its use and effects.³ The FDA considers such use to be "the practice of medicine," which it does not directly regulate. The FDA does, however, expect physicians to practice in a manner that is designed solely to insure the well-being of the individual patient. Accordingly, the FDA generally does not oversee or interfere with a physician's individual practice decisions unless a physician is himself marketing or selling a drug or device, acting as an investigator in clinical research, or gathering information about safety or efficacy.⁴

PERFORM A RISK ANALYSIS

Craven and Moran suggest performing a risk analysis before first using a drug "off-label," a recommendation echoed by OMIC Staff Attorney Kimberly Wittchow in "When FDA Leaves Physicians to Its Own Devices."⁵ If the medication is an existing drug used in a non-approved manner, first consider whether its use poses significantly increased risks to the patient. Second, consider whether its use can be expected to bring good results without a higher complication

² Craven, E. Randy, MD and Moran, Elizabeth C, JD. The Medicolegal Risks of Using Off-Label Drugs and Devices. *OMIC Digest*. Winter, 1006. http://www.omic.com/resources/risk_man/deskref/clinical/printVer.cfm?margin=yes&body=_28&pathmod=../../../../

³ Information Sheets. Guidance for Institutional Review Boards and Clinical Investigators. 1998 Update. "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices. <http://www.fda.gov/oc/ohrt/irbs/offlabel.html>.

⁴ For more information on distinguishing between "off-label" and investigational use, see the above article as well as Menke, Anne M., RN, PhD, Research Versus the Practice of Medicine http://www.omic.com/resources/risk_man/forms/medical_office/Research%20or%20Practice%20of%20Medicine%20041906.rtf.

⁵ Wittchow, Kimberly, JD. When FDA Leaves Physicians to Their Own Devices. *OMIC Digest* Spring 2003. http://www.omic.com/new/digest/DigestSpri_03.pdf. For a sample analysis form, see Menke, Anne M. RN, PhD, Risk Analysis of Unapproved Devices at <http://www.omic.com/new/announce/unapproveddevices.rtf>.

rate. If it presents no more risk to the patient than that of daily living, proceed with its use, as, for example, the use of aspirin for anticoagulation after a central retinal vein occlusion. If there is an increased risk to the patient, ask yourself if at least a reasonable number of physicians in your specialty are using the treatment; e.g., have peer reviewed articles been published supporting the use of the new treatment and is the treatment being used by a reasonable number of other practitioners with the same level of training as you? As part of the risk analysis, consider what you will tell the patient before initiating treatment. If the proposed treatment consists primarily of an “off-label” medication, the physician should obtain the patient’s informed consent and disclose the FDA non-approved status.

RISK PROFILE OF TRIAMCINOLONE ACETONIDE

A risk analysis of TA shows that while there are known, serious risks, its use in ophthalmology is both widespread and well-studied.⁶ IVTA is the subject of dozens of studies in the peer-reviewed scientific literature as well as two ongoing National Eye Institute randomized clinical trials. This drug is used to treat a wide range of proliferative, inflammatory, occlusive, and edematous diseases of the retina and eye. Conditions treated with IVTA include diabetic macular edema, exudative age-related macular degeneration, edema from central retinal and branch retinal vein occlusions, chronic uveitis, and pseudophakic cystoid macular edema.^{1,7} Anterior segment and retinal specialists have also used it as a surgical adjunct “to help visualize the vitreous during epiretinal peels or internal limiting membrane peels.”⁸ For some of these conditions, TA is considered the first line of treatment; for others, it is the only available medical modality. Its use reduces edema, vascular leakage, and vascular growth, resulting in improved visual acuity. In November, 2007, and June, 2008, the FDA approved two TA products for ophthalmic use, TriesenceTM and Trivaris.TM

Steroids are associated with significant risk, regardless of why they are prescribed or their route of administration. Intravitreal and other ophthalmic administration techniques were developed to minimize the risk of systemic steroids and maximize the effectiveness of the drug. As studies have shown, however, these routes are also linked to adverse events. Intravitreal injections, for example, are known to result in infection (endophthalmitis), retinal detachment, secondary glaucoma, and lens trauma/acute cataract. Rare complications of this technique include hemorrhage, precipitated angle closure, elevated intraocular pressure with perfusion compromise, wound leak with hypotony, and anaphylactic reaction to either the agent or the periprocedural materials.⁹

Steroids themselves lead to the development of cataracts and glaucoma, risks that may increase with repeated injections.⁸ Some patients are “steroid responders,” and may develop a dramatic rise in IOP.¹ Additionally, benzyl alcohol, the preservative in KenalogTM (triamcinolone acetonide), has anecdotally been reported to cause a sterile, inflammatory reaction.⁹ Animal

⁶ As a service to its members, Dr. Flora Lum, Director, Quality of Care and Knowledge Base Development at the AAO compiled a bibliography of articles and studies.

(<http://www.aao.org/education/library/memberalert/index.cfm>).

⁷ Ip, Michael S, MD. Intravitreal Injection of Triamcinolone: An Emerging Treatment for Diabetic Macular Edema. *Diabetes Care* 27: 1794-1797, 2004. <http://care.diabetesjournals.org/cgi/content/full/27/7/1794>.

⁸ Stephenson, Michelle. Kenalog: Does It Still Fit Into Clinical Practice? *Review of Ophthalmology*. 2006. 13: August 5, 2006. http://www.revophth.com/index.asp?page=1_993.htm.

⁹ Brucker, Alexander J, MD, and Hopkins, Tim B., MD. Maximizing the Safety of Intravitreal Injections. AMD Expert Column Series. *Medscape Ophthalmology*. 2006; 7(2). http://www.medscape.com/viewarticle/548070_print.

studies have shown evidence of retinal toxicity that was avoided when using preservative-free formulations; adverse outcomes were likewise absent in some clinical studies.^{10,11,12,13}

RISK MANAGEMENT RECOMMENDATIONS

In line with previous recommendations from OMIC about “off-label” use, we encourage ophthalmologists to follow these suggestions to promote patient safety and reduce liability exposure.

- **Patient and treatment selection**
- Determine what is in the best interests of the particular patient.
- If there is an alternative FDA-approved medication for the patient’s ophthalmic condition, consider first treating the patient with it. Consider using Triesence™ or Trivaris.™ Conduct and document pertinent diagnostic/monitoring tests, such as fluorescein angiogram and OCT, as part of the evaluation. If applicable, note lesion type, location, size, and presence of subretinal fluid.
- Document prior treatment efforts, if any, and the decision-making process that led to the choice of triamcinolone acetonide.
- **Preparation of the medication**
- Proper aseptic technique should be utilized during the preparation and administration of the injection.
- KENALOG™ USE
- Most ophthalmologists use the commercially available form of Kenalog™. A minority, however, choose to administer a preservative-free form that is usually prepared by a compounding pharmacy, a process that may introduce other risks. Compounding pharmacies must comply with Chapter 797 of the United States Pharmacopeia (USP), 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. To ensure safe compounding and administration, ophthalmologists should ask the compounding pharmacy 1) to prepare the medication under aseptic conditions, 2) to confirm the dose and sterility, 3) to label each container or syringe with the strength, lot number, storage, and “beyond use” instructions, 4) to verify that it is licensed/registered in the state in

¹⁰ Narayanan, Raja et al. Toxicity of Triamcinolone Acetonide on Retinal Neurosensory and Pigment Epithelial Cells. *Investigative Ophthalmology and Visual Science*. 2006; 47: 722-728. <http://www.iovs.org/cgi/content/abstract/47/2/722>.

¹¹ Morrison, Victoria et al. Intravitreal Toxicity of the Kenalog vehicle (benzyl alcohol) in rabbits. *Retina*. 2006, 26(3): 339-344.

¹² Kim, H et al. Safety and pharmacokinetics of a preservative-free triamcinolone acetonide formulation for intravitreal administration. *Retina*. 2006 May-June 26(5): 523-30.

¹³ Bakri, SH et al. Intravitreal preservative-free triamcinolone acetonide for the treatment of macular oedema. *Eye* (2005) 19, 686-688.

¹⁴ Be familiar with the latest guidelines on care before, during, and after administration In addition to the Brucker and Hopkins article referred to above, see Flynn, Harry W. and Scott, Ingrid U., Evolving Guidelines For Intravitreal Injections. *Retina* 24: S3-S19, 2004.

which it is dispensing, 5) to describe how they compound the TA, and 6) if it is an accredited compounding pharmacy.

- **Preventing and managing complications from intravitreal injections of TA¹⁴**
 - Intravitreal injections have caused endophthalmitis, retinal detachment, and increased intraocular pressure.
 - BEFORE. Pre-treat obvious sources of infections, measure IOP, and prep with povidone iodine.
 - DURING. Use a sterile lid speculum and calipers and standard aseptic technique. Inject in the inferotemporal quadrant, and aim the needle towards the geometric center of the eye.
 - AFTER. Monitor for hemorrhage, rise in IOP, wound leak, and infection, and treat accordingly.
 - Educate the patient about the warning signs of complications and how to contact you. Consider giving these instructions in writing.
 - Inform the patient of complications, and document all discussions. Contact OMIC's Risk Management Department for confidential assistance with disclosure discussions and adverse events.
 - Refer the patient to sub-specialists as needed, e.g., they are not responding to treatment. If patients are sent to sub-specialists, request formal consultation reports.
 - Stay in touch with the patient while complications are being treated, even if the patient is being followed by a sub-specialist.

 - **Informed consent discussion and documentation**
 - Inform the patient of the known risks associated with the injection technique as well as the medication (**see sample consent form** at www.omic.com).
 - Forewarn patients at particular risk for specific complications e.g., increased risk of infection in diabetics, increased risk of elevated IOP and worsening of glaucoma in patients who are steroid-responders or who have glaucoma.
 - If using TriesenceTM or TrivarisTM off-label
 - Inform the patient that the drug was not approved for the condition they have, but that off-label use is a legal and necessary aspect of the practice of medicine.
 - If using KenalogTM, discuss "off-label" status.
 - Inform patients of this form of TA's off-label status and told that the manufacturer has recommended against ophthalmic use, but that the FDA and attorneys have confirmed that ongoing use is legal as part of the "practice of medicine." Inform the patient that a two products of TA have been approved for use in the eye.
 - Consent for ongoing treatment
 - In general, informed consent may be considered to have ongoing force and effect until 1) the patient revokes the consent (by refusing subsequent injections) 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. If the patient refuses subsequent injections, ascertain and address the reasons, and document the conversation and treatment
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decisions.

- **Documentation of care**

- Document the diagnostic process, as well as the decision-making process that led to choosing TA as the treatment for the patient.
- Note the results of earlier attempts at treatment and the results of diagnostic tests.
- Document the informed consent discussion in the chart and ask the patient to sign a procedure-specific consent form. Document any refusal of care, and include the reason.
- Note the dose, lot number of the vial, and any reactions to the injection and how they were handled.
- Provide discharge and follow-up instructions, and document that they were given.
- Document efforts to monitor for and respond to complications.
- Document referrals to sub-specialists, and place a copy of the consultation letter in the medical record.
- Document all communication to and from the patient, even if it occurs after a sub-specialist has taken over the care.

OMIC policyholders who have additional questions or concerns about this issue may call OMIC's Risk Management Hotline for confidential assistance at (800) 562-6642, option 4.