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RT Retina Today

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THREE PILLARS OF SUCCESS

in Patient and Practice Management Strategies in Diabetic Macular Edema

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INDICATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Important Safety Information

CONTRAINDICATIONS

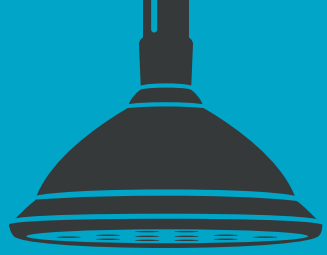
- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids including ILUVIEN may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

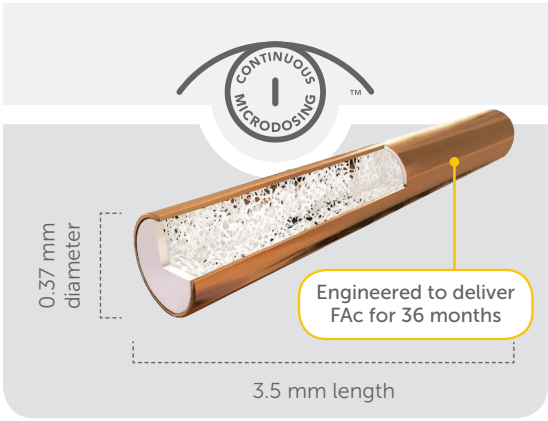
ADVERSE REACTIONS

- In controlled studies, the most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of ≥ 10 mm Hg (ILUVIEN 34%; sham 10%).



| With CONTINUOUS MICRODOSING™ Delivery |

ILUVIEN with CONTINUOUS MICRODOSING™ Delivery enables physicians to continually and consistently treat DME every day[1,2]



ILUVIEN is a CONTINUOUS MICRODOSING™ Delivery System specifically engineered for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

In pivotal studies, ILUVIEN demonstrated efficacy in visual acuity through 24 months (primary endpoint), which was sustained for up to 36 months.[1,2]

Adverse reactions in the ILUVIEN Phase 3 clinical trials were consistent with other corticosteroid treatments.[1]

Learn more at ILUVIEN.com.

References: 1. Iluvien [package insert]. Alpharetta, GA: Alimera Sciences, Inc. **2.** Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125-2132.

Please see Brief Summary of full Prescribing Information on the following page.

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ILUVIEN®
(fluocinolone acetonide intravitreal implant) 0.19mg

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg
For Intravitreal Injection

INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

Ocular or Periocular Infections: ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Glaucoma: ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Hypersensitivity: ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including **ILUVIEN** may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including **ILUVIEN** include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

Table 1: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

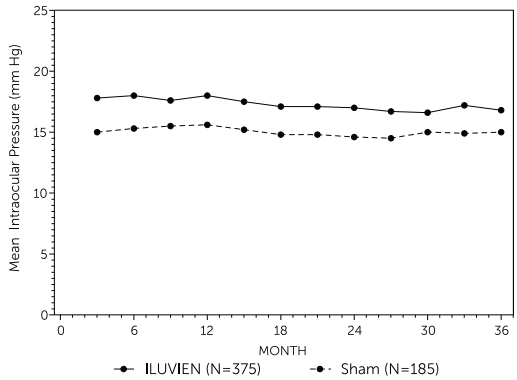
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Postmarketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of **ILUVIEN** in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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ALIMERA SCIENCES

JUGGLING ACT: MANAGING PATIENTS WITH DME

Frequent patient visits, medication management, and insurance preapprovals are among the many moving parts of treating patients with diabetic macular edema.

BY PAUL DEGROW, MSA

As chief operating officer for California Retina Consultants, managing the clinical, financial, and operational aspects of caring for patients with diabetic macular edema (DME) is a juggling act. From scheduling frequent patent visits, to buying and billing DME injections, to managing preapprovals, to supplying the drugs to all of our locations, DME is a tricky condition to treat. All of these moving parts can have both positive and negative effects on our practice.

The Operational Shuffle

Our practice is affected by patients with DME primarily by the number of staff, training, patient education, and supply of drugs necessary for managing this disease. Patients with DME frequently visit our practice for use of anti-vascular endothelial growth factor (anti-VEGF) injections. In order to meet this flow of visits, additional staff was needed, including technicians, receptionists, and billers — the greater volume of visits means the greater number of staff, and these staff members need to be trained.

The newer technology and treatments coming through for DME affect staff training and patient education. These are newer treatments, with new preparations for the injection. Overall, the staff needs to understand the nature of the procedure and be able to communicate that to the patient.

The next step is having the medication available for the patient visit. We are very fortunate to have one individual who orders the drug on a daily basis and manages the supply of drugs for our various locations. Our technicians populate shared spreadsheets on usage, which the staff members can access on the cloud. The schedules are then reviewed, and the medications are supplied to appropriate locations based on need. The person who handles this process has been with our practice for 13 years, and we are very lucky to have him managing this operation. That said, I believe that we will eventually migrate to a digitally oriented solution, such as PODUS. If we eventually decide to move to a more automated system to simplify inventory control, there are several options from which to choose, including ones using barcodes. These types of systems will integrate well with our electronic health record program and financial program. For practices not fortunate enough to have someone on staff to manage the supply of drugs to your facilities, I would highly recommend a barcode system that tracks inventory for most practices.

WATCH IT NOW

Juggling Act: Managing Patients with DME

Paul Degrow, MSA, and Nathan Steinle, MD, discuss the many moving parts of treating patients with DME.

Financial Implications

Along with managing the inventory to ensure the drugs are where they are needed, it is critical to take the drugs' expiration dates into consideration. Otherwise, there will be exceptionally negative impacts across the board. Because of the costs of the injectable anti-VEGF drugs, you must be very cognizant of when they expire. Some drug manufacturers are willing to work with practices to replace expired medication, but this does not happen with all manufacturers or all drugs.

(Continued on page 7)

TREAT THE PATIENT, NOT JUST THE DISEASE

It is vital to consider the patient's complete history — medical, financial, and social — when choosing treatment options for patients with DME.

BY NATHAN C. STEINLE, MD

The more we learn about diabetic macular edema (DME), the more we learn about the complexity of the disease. There are a variety of treatment options available for patients with DME, and all of these options incur their own benefits and challenges. There is a well-known quote from Sir William Osler that says, "The good physician treats the disease; the great physician treats the patient who has the disease." When choosing treatment options for patients, it is critical to take not only the patient's medical history into consideration, but their financial and social situations as well.

Treatment Options

The release of atypical cytokines occurs early in the development of DME, and vascular endothelial growth factor (VEGF) is one of many mediators involved. This means we should consider two different types of treatments, an anti-VEGF to treat the overabundance of VEGF, as well as a corticosteroid for the inflammatory portion of DME.

There are several multimodal imaging options available to help assess which treatment is best for each patient: fluorescein angiography (FA) (especially widefield imaging), optical coherence tomography (OCT), and OCT angiography (OCTA). However, despite the plethora of information gleaned from these different imaging modalities, it is difficult to enact a maximally effective treatment plan for DME based on imaging alone. Instead, I prefer to look at a combination of images, as well as the anatomy of the patient and the patient's lifestyle, so that I can customize the best treatment plan for each patient.

Selection Bias

Anti-VEGF injections are generally well tolerated by most patients, and they have a long safety profile.[1-3] However, I also believe there is a selection bias that comes into play. Over time, retina specialists recognize which patients come into the office most frequently. They realize these are the patients who are willing to get injections, and they are able to tolerate the injections.

In contrast to this, however, are the patients who miss appointments, or never reschedule, or perhaps leave the practice for reasons we often never know. As retina specialists, we have a selection bias that these injections are so well-tolerated, when in fact there is certainly a subset of the patient population that has significant difficulty with chronic injections — especially those patients with chronic dry eye or patients with ocular surface reactions to povidone iodine.

Financial Considerations

One of the unfortunate aspects of DME is that it strikes younger, working-age individuals. Cost is a consideration when treating these patients. When you think of the anti-VEGF agents, it is hard to argue against use of bevacizumab (Avastin; Genentech) for the baseline low cost of the drug itself. However, some patients require repeat injections over many years, and there is a cost associated with that, including for the patient to miss work, for family members who must take off time from work to accompany patients, and also for the cost of the injections and the office visits.

There have been studies that show the average patient with diabetes has 24 physician visits a year, overall. Not only are they seeing their ophthalmologist, they are also seeing their cardiologist, nephrologist, and internist. As physicians caring for these patients with diabetes, we must consider all these chronic conditions and long-term treatments, such as laser therapy, or a long-term corticosteroid, such as the fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences). I focus on minimizing that treatment burden for these patients in regard to their time commitment and financial situation.

Short-term vs Long-term Injections

The anti-VEGF era has been around for more than 10 years now, and with it we have seen the degradation of the conjunctiva and the ocular surface in patients treated with anti-VEGFs. A long-term sustained-delivery device is ideal for DME, and we are fortunate to have the fluocinolone implant

> It is important to remember all aspects of the patient. It is easy to get caught up in the task of treating retinal thickness... but in fact, you are treating the whole person.

at our disposal. As opposed to either triamcinolone (Kenalog 40; Bristol-Myers Squibb) or dexamethasone (Ozurdex; Allergan) which generally last about 3 months, the fluocinolone implant can last up to 3 years. It provides patients 3 years of slow, sustained release of fluocinolone, so it helps with the inflammatory component of their DME.

When it comes to the treatment of the patient in front of you, I believe many retina specialists reach first for anti-VEGF therapy. Whether it be bevacizumab, ranibizumab (Lucentis; Roche/Novartis), or aflibercept (Eylea; Regeneron), these are all reasonable options for initial therapy for DME. For patients who are either suboptimal responders or nonresponders to anti-VEGF, other options should be considered. In our practice, we identify a suboptimal responder as an individual who gains only a few letters on the Snellen visual acuity chart or has a 10% or less improvement on OCT retinal thickness. A nonresponder has absolutely no change in OCT thickness or no visual acuity gains after repeated anti-VEGF injections.

I typically administer three to five injections of one anti-VEGF and then switch to another anti-VEGF agent before I label this patient as either a suboptimal or a nonresponder. It is at that point that I consider adding a corticosteroid to address the inflammatory component of their DME. If it appears they are not a significant responder to corticosteroids, I begin considering ways to bridge this patient to a long-term corticosteroid implant, such as fluocinolone.

I am willing to try almost anything to minimize that time commitment burden on the patient and their family. It is important to remember all aspects of the patient. It is easy to get caught up in the task of treating retinal thickness as shown on the OCT, but in fact you are treating the whole person. ■

1. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120(10):2013-2022.
2. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M, Beck RW; Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology*. 2016;123(6):1351-1359.
3. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, Boyer DS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Vitti R, Berliner AJ, Zeitz O, Metzig C, Holz FG. Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies. *Ophthalmology*. 2016;123(11):2376-2385.

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(Continued from page 5)

We take the expiration date as a hard cost with a negative financial impact to the practice. That said, one of the things we do at our facilities is manage the supply of drugs to our locations with the expiration date in mind. We are a very prolific organization, and if one location's drugs are beginning to expire, we will move that product to another location with a more urgent need and ensure they are used prior to the expiration date.

From a patient perspective, managing the preapproval process for these drugs also has financial implications. From a billing standpoint, it is very onerous for us to deal with insurance companies that require preapprovals for drugs. In general, the more expensive the drug, the more rigorous the preapproval process. Our practice is located in California, and we deal regularly with HMOs, many of which require a preapproval process. The more expensive DME treatments trigger the most investigations, compared with the less expensive DME treatment options.

A specific J code for DME for use with fluocinolone acetonide (Iluvien; Alimera) was recently introduced in early 2017. Use of the specific code results in fewer paperwork requirements for the preapproval process, and it takes some of the onus off of records being sent to the insurance companies. Payments also tend to be processed faster using the new J code. ■

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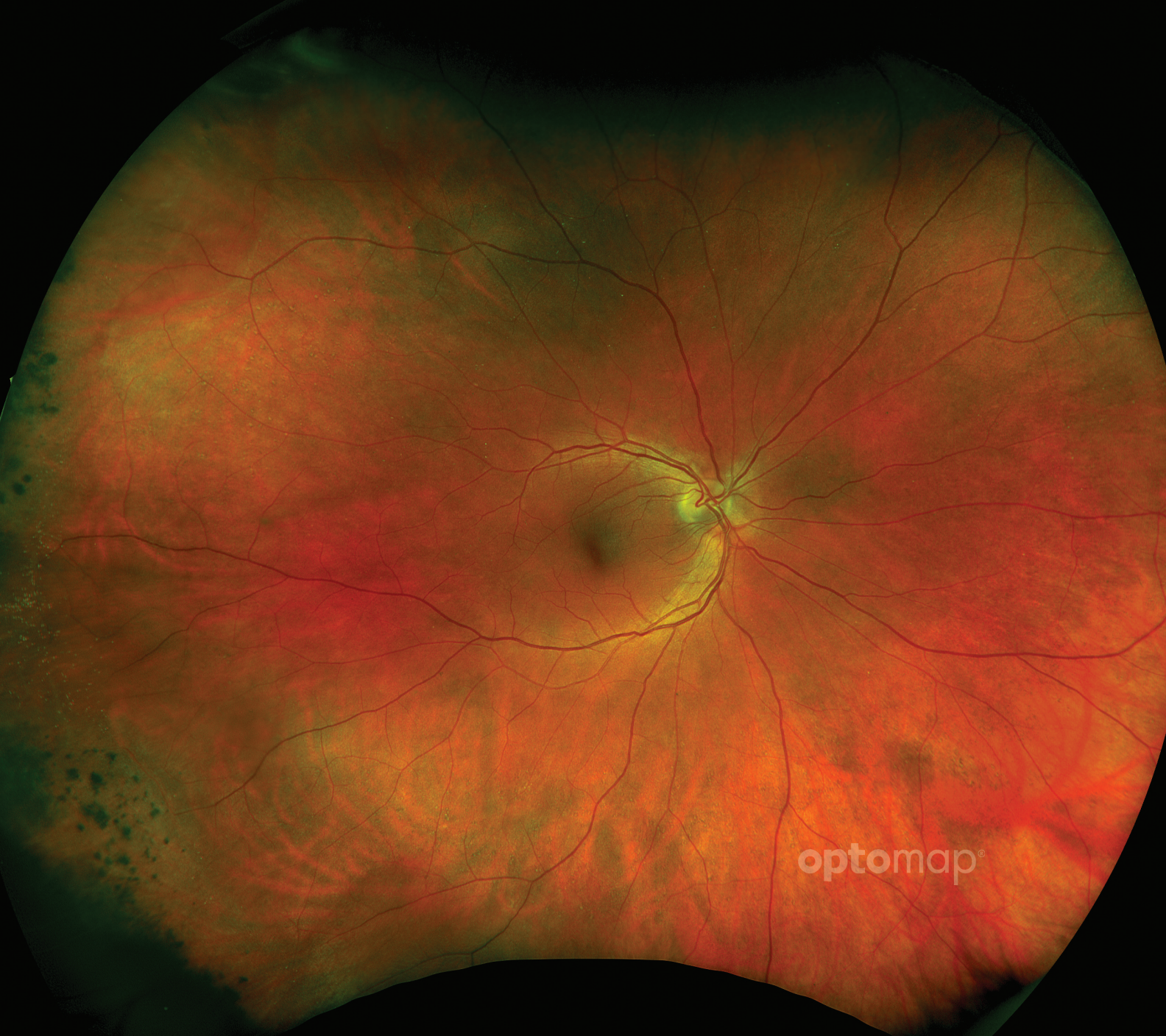
- financial interest: none acknowledged



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