Medication Therapy Review: Intravitreal Injections

Purpose:
The NPA Medication Management Work Group (MMWG) Clinical Subcommittee recognize intravitreal injections as high cost specialty medication utilization an increasing concern amongst PACE providers. The importance of maintaining acceptable visual acuity is key to helping foster independence, quality of life and to minimize falls. This document provides clinical decision-making guidance in regards to use of intravitreal injections with a focus on macular degeneration, diabetic retinopathy, and retinal vein occlusion. The goal of which is to help guide prescribers provide the best care possible at the lowest cost. It does not replace the needed communication between the Specialist and PACE Provider.

Information incorporated in this document through literature reviews of both primary and tertiary sources conducted by members of the MMWG. MMWG makes no assertion of expertise on the subject matter and final clinical decisions should be based on most updated information available. Literature review current as of August 17, 2020.

Definitions:

- **Diabetic retinopathy (DR)-** Damage to the blood vessels in the tissue at the back of the eye (retina) caused by poorly controlled blood sugar levels.
    - **Nonproliferative (NPDR):** Early stage of diabetic retinopathy with variable presentation characterized by retinal swelling. Vision loss primarily due to macular edema.
    - **Proliferative (PDR):** Presence of neovascularization arising from the disc and/or retinal vessels. May lead to both central and peripheral vision loss.
- **Diabetic macular edema**- accumulation of fluid due to leaking blood vessels in the macula (central part of the retina) that controls detailed vision abilities. Complication of diabetic retinopathy.
- **Intravitreal injection-** Inject medicine into the jelly-like fluid (vitreous) of the eye.
- **Macular degeneration (Age-Related Macular Degeneration AMD)-** A degenerative condition affecting the central part of the retina (the macula) and resulting in distortion or loss of central vision.
- **Retinal vein occlusion (RVO)-** Blockage of the small veins that carry blood away from the layer of tissue at the back of the inner eye (retina) that converts light images to nerve signals and sends them to the brain.
    - **Branch retinal vein occlusion (BRVO)-** vein in the distal retinal venous system is occluded, leading to small vessel hemorrhage
    - **Central retinal vein occlusion (CRVO)-** thrombus occlusion within the central retinal vein at the lamina cribrosa of the optic nerve, involves the entire retina

Symptoms:

Diabetic Retinopathy

- Asymptomatic until late stages
- Impaired vision/loss of visual acuity
- Characterized by abnormal permeability and vascular occlusion within the retinal vessels

Macular Degeneration

- Gradual loss of vision in one or both eyes yet can be asymptomatic early
- Acute visual distortion (metamorphosia--usually single eye)
- Loss of central vision (usually single eye)

Retinal Vein Occlusion

- Sudden change of vision
- Graying of vision
- Central vision loss
- Painful red eye (occasionally)
- May have no symptoms (esp. with BRVO)

Incidence:

Diabetic Retinopathy	• Epidemiologic studies have shown that approximately 1 in 3 persons with diabetes mellitus has DR. Based on these rates, between 100 million and 120 million people have DR worldwide.[1] • The prevalence rate for retinopathy for all adults with diabetes aged 40 and older in the United States is 28.5% (4.2 million people); worldwide, the prevalence rate has been estimated at 34.6% (93 million people). [1] • Rates in the U.S. expected to double from 7.7 million in 2010 to 14.6 million in 2050[2]
Macular Degeneration	• The number of people with AMD is estimated to reach 2.95 million in 2020. [2] • Varies with multiple factors and number of cases is projected to double by 2050 due largely to the aging population and higher incidence in older age groups.
Retinal Vein Occlusion	• In the U.S. prevalence is 0.6 percent for BRVO and 0.1 percent for CRVO and is highest in patients >80 yo (4.6%). [2] • Varies by race with highest to lowest prevalence as follows: Hispanic, Asian, Black, White.

1. Bailey ST, Fawzi A, Lim JI, et. al. Diabetic Retinopathy Preferred Practice Pattern. American Academy of Ophthalmology. AAO 2019 Oct. https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp. Accessed July 31, 2020.
2. Centers for Disease Control and Prevention. *Vision Health.* National Center for Chronic Disease Prevention and Health Promotion, 2019. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Diagnosis:

Any complaint of visual disturbance should prompt immediate evaluation starting with a history that includes the rate of vision loss, whether one or both eyes are involved, and whether the vision loss is for distance vision, near vision, or both. Patients with an acute distortion or loss of central vision may represent wet age-related macular degeneration (AMD), which requires early treatment for best outcomes. Vision loss that occurs acutely (a period of days or weeks) requires urgent ophthalmic evaluation.

Many eye conditions can be treated by optometrists, so for PACE participants, vision evaluations and treatments can begin with optometry for most indications. Optometrists not only measure visual acuity and treat deficits, they can screen for and treat glaucoma, some eye infections, and other ophthalmologic conditions. They are not authorized to perform surgery or intravitreal injections, however they can identify problems that require those interventions and make recommendations for referrals.

Classification (ICD-10):

***Not an all-inclusive list. For Detailed Diagnosis and Classification of AMD see Appendix.**

Diabetic Retinopathy	E08.3, E10.3 (Type 1 DM), E11.3 (Type 2 DM)
Macular Degeneration	H35.30 (unspecified) H35.31 (dry), H35.32 (wet), H35.35(cystoid)
Retinal Vein Occlusion	H34.81 (central), H34.83 (tributary/branch)

Treatment Overview:

Diabetic Retinopathy (DR)

General Recommendations

- Optimize control of:
  - Blood glucose
  - Blood pressure
  - Lipids
- Individualize treatment plan:
  - Severity of the proliferative DR
  - Presence or absence of DME and/or vitreous hemorrhage
  - Ability to attend scheduled visits
  - Refractory cases may warrant vitrectomy consideration

Non-proliferative DR

- Not generally treated
- May consider treatment if:
  - Concomitant diabetic macular edema (DME)
  - Severe cases to prevent progression to proliferative

Proliferative

- Panretinal laser photocoagulation (PRP) therapy
  - Durable treatment to prevent vision loss
- VEGF Inhibitors
  - More effective in the short term
  - Adherence issues may lead to progression
- Intravitreal Glucocorticoids
  - Possible monotherapy in refractory DME
  - Contraindication to VEGF
  - Inferior visual acuity outcomes
  - Increased rate of cataracts & glaucoma

Age-Related Macular Degeneration (AMD)

General Recommendations

- Smoking cessation
- Avoid laser therapy in dry AMD

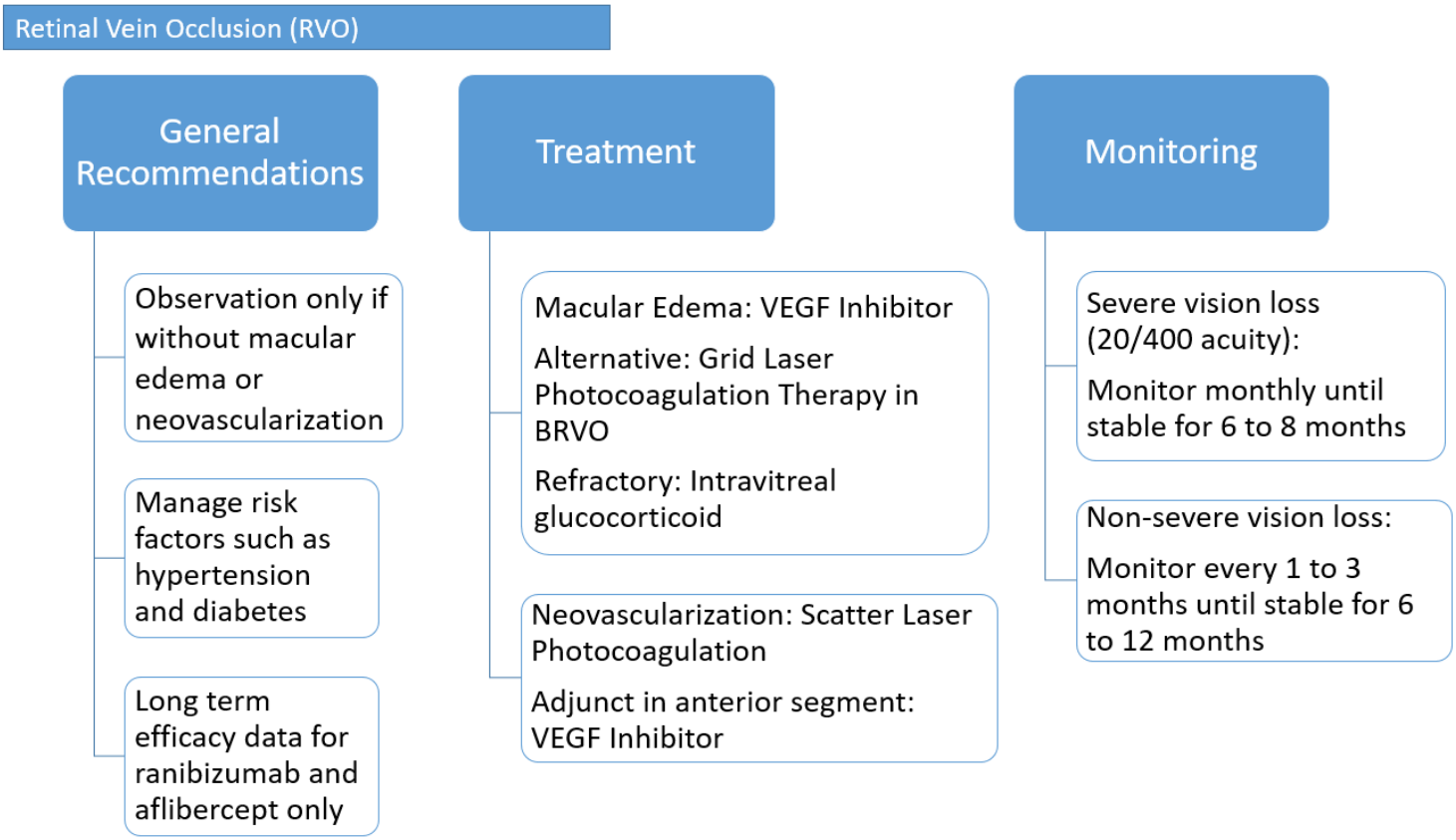
Intermediate or Advanced dry AMD or Wet AMD

- AREDS2 Vitamin and Mineral Supplement
- AREDS formulation with beta-carotene alternative in non-smokers

Neovascular AMD

- VEGF Inhibitors
  - Aflibercept
  - Bevacizumab
  - Brolucizumab
  - Ranibizumab
  - Initiate within 7 weeks of wet symptoms for better vision outcomes(Lim, 2012)
- Photodynamic Therapy (PDT)
  - Contraindication to VEGF
  - Chronic exudative lesions

*References: Arroyo, Flaxel, and National Institute for Health Care Excellence



Adapted from UpToDate: Han, D., & Ahmed, B. (2020). Retinal vein occlusion: Treatment. *UpToDate.* Retrieved August 17, 2020, from https://www.uptodate.com/contents/retinal-vein-occlusion-treatment

Pharmacologic Treatment

Drug	Route	Cost (AWP)	FDA Approved Indications
Vascular Endothelial Growth Factor (VEGF) Inhibitor			
Aflibercept (Eylea®)	Intravitreal	$2200/month reduced to $1100/month if given Q8 weeks	Age-related Macular Degeneration Diabetic Macular Edema Macular Edema Diabetic Retinopathy
Bevacizumab (Avastin®, Mvasi®, Zirabev®)	Intravitreal	$239/month $203/month $184/month	No ophthalmic FDA approved indications. Used off-label for diabetic macular edema and age-related Macular Degeneration.
Brolucizumab (Beovu®)	Intravitreal	$2,220.00/month reduced as interval decreases	Neovascular (wet) age-related macular degeneration
Pegaptanib (Macugen®)	Intravitreal	$600/month ($900/6 weeks)	Age-related Macular Degeneration
Ranibizumab (Lucentis®)	Intravitreal	$2300/month (0.5 mg dose) $1400/month (0.3 mg dose)	Age-related Macular Degeneration Diabetic Macular Edema Macular Edema Diabetic Retinopathy Myopic Choroidal Neo-Vascularization

Drug	Route	Cost (AWP)	FDA Approved Indications
Ophthalmic Corticosteroid			
Dexamethasone (Ozurdex®)	Intravitreal implant	$267/month ($1600/6mo)	Diabetic macular edema Macular edema following BRVO, CRVO Non-infective uveitis affecting the posterior segment of the eye
Preservative-free Triamcinolone (Triesence®)	Intravitreal	$60/month (180/3 months)	Ocular disease (Second line therapy in Macular Edema & Retinal Vein Occlusion) May combine with PDT in AMD

Note – The cost above is the AWP as listed in Lexi-Comp® as of August 2020. This cost will vary depending on contracting agreements and administration fees of the physicians.

Medication Dosing

Drug	Dosing	Side Effects	Monitoring
Vascular Endothelial Growth Factor (VEGF) Inhibitor **Class Monitoring Parameters:** Intraocular pressure; signs of infection; optic nerve head perfusion; visual acuity			
Aflibercept (Eylea®)	Inject 2 mg (0.05 mL) once every 4 weeks (monthly) for 3 to 5 injections followed by 2 mg (0.05 mL) once every 8 weeks (every 2 months)	Conjunctival hemorrhage, cataract, eye pain	After 12 months of treatment, the injection intervals may be prolonged, depending on the functional and anatomical condition of the individual patient. Visual acuity improvements may decrease with as needed dosing in CRVO after 24 weeks.
Bevacizumab (Avastin®, Mvasi®, Zirabev®)	Inject 1.25 mg (0.05 mL) monthly for 3 months, then may be given scheduled (monthly) or as needed based on monthly ophthalmologic assessment	Serious eye infections and vision loss	Monthly dosing favored over PRN monthly assessment due to slight decline in visual acuity gains with PRN dosing in neovascular AMD
Brolucizumab (Beovu®)	Inject 6 mg once per month (approximately every 25 to 31 days) for 3 months, followed by 6 mg once every 8 to 12 weeks	Antibody development, arterial thromboembolism, blurred vision	Successful 12 week interval dosing during year 1 should be maintained for year 2
Pegaptanib (Macugen®)	Inject 0.3 mg into affected eye once every 6 weeks	Hypertension, anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema	Shown less effective compared to ranibizumab or bevacizumab in AMD
Ranibizumab (Lucentis®)	Inject 0.3 or 0.5mg monthly per indication	Arterial thromboembolism, headache, anemia, arthralgia, conjunctival hemorrhage, eye pain	Use up to 2 years. Monthly SD-OCT (spectral domain optical coherence tomography) monitoring. Retreatment with any evidence of fluid noted by retinal imaging. Monthly intravitreal injections continued until maximum VA is achieved for three consecutive monthly assessments. Both monthly and “as needed” treatment approaches are efficacious in RVO

Drug	Dosing	Side Effects	Monitoring
Ophthalmic Corticosteroid			
Dexamethasone (Ozurdex®)	Inject 0.7 mg implant in affected eye once every 6 months (slow-release)	Hypertension, cataract, increased intraocular pressure, conjunctival hemorrhage, corneal edema	Intraocular pressure elevations (peak ~8 weeks following injection)
Preservative-free Triamcinolone (Triesence ®)	Inject 4 mg as a single dose once every 3 to 4 months	Increased intraocular pressure, progression of cataract	Increased intraocular pressure and endophthalmitis; biomicroscopy between 2 to 7 days after injection

Intravitreal Injections: Non-Clinical Factors Affecting Prescribing

Purpose: The NPA Medication Management Workgroup Non-Clinical Subcommittee recognizes intravitreal injections as high cost specialty medications. As intravitreal injections are administered by contracted specialists, it may be increasingly difficult to track their utilization for clinical appropriateness and acceptable duration. The following is a general guideline that provides insight on best practices to track utilization of these costly medications and potential cost saving alternatives

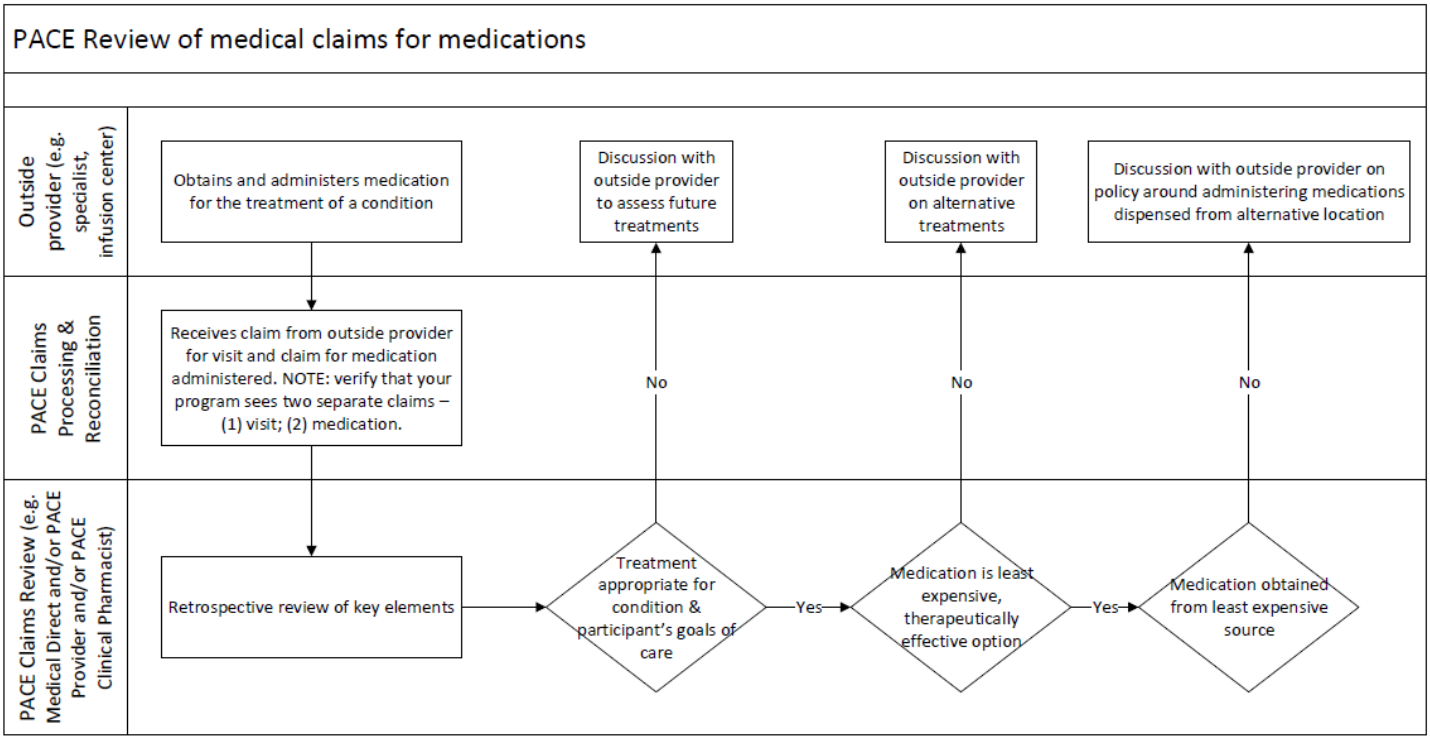
Definitions:

- **Drug Utilization:** Authorized, structured system that involves ongoing evaluation of provider prescribing, pharmacist dispensing and patient use of a drug. A comprehensive review of retrospective, concurrent and prospective clinical data to ensure appropriate use and positive patient outcome.

Background: Most often intravitreal injections are billed to PACE finance departments bundled with the actual office visit cost or as a separate line item. The visit is authorized according to the actual referral from the PACE provider to the specialist. These medications will not be on the Prescription Drug Event (PDE) file submitted to CMS for separate Part D reimbursement.

Reconciliation of Payments: Medications that are not self-administered (infusion or injection-related) by participants are typically paid for by the PACE plan. Thus, these are not submitted to CMS on the PDE file for additional reimbursement. These medications may only be on the medical claims file the PACE plan receives from outside providers. As such, medications administered at outside provider offices may not have the same level of oversight as Medicare Part D claims. *All reviews completed from outside medical claims are retrospective in nature.* Lack of internal review by a PACE provider and/or pharmacist may lead to missed opportunities in identifying alternative therapeutic treatment options that may be less costly.

It can be inferred that the cost of multiple ocular injections could accrue significantly. Tracking these referrals and reviewing the therapy recommended is prudent to assess medical necessity and appropriate utilization. For example, are any biosimilars available that would be an appropriate alternative to treat the medical condition. Reviewing medical claims for drugs that have a similarly efficacious, more cost-effective alternatives may help reduce the overall expenditure while still appropriately treating the condition. This review may often be completed in collaboration with an internal clinical pharmacist.



Key considerations: The primary focus of the review should center on the following, which may be discussed with the specialist, if necessary:

1. **When reviewing the treatment currently in place, be sure to include a description of the participant's functional level and one-year mortality risk.**
    a. Inform the specialist if the participant's level of care may change within the next year **(i.e. long-term care conversion)**.
2. **Take the following questions into consideration when reviewing the claims and potentially speaking to the specialist:**
    a. Is the diagnosis associated with the request in accordance with an FDA approved indication or medically accepted off-label use?
    b. Does the specialist recommendation follow medically accepted treatment algorithms?
    c. How do the participant's comorbidities affect treatment?
    *Note that specialists may not inclusively review the participant's other disease states and only focus on the condition specific to them.
3. **Other important questions to clarify with the specialist and/or PACE interdisciplinary team:**
    a. How should we jointly monitor participant progress?
    b. What treatments have already been trialed? Why did these treatments fail and were they administered for a proper period? Are there other therapies currently available at a lower cost with similar outcomes?
    c. Are there clinically relevant drug-drug or drug-disease interactions that may compromise treatment?
    d. Are consult notes from the specialist appropriately documented in the electronic clinical record that justifies the course of treatment?
    e. Is the disease state in question adequately noted in the participant's individual care plan?

Procurement of Intraocular Injections

May be beneficial to reach out to the specialist office, specialty pharmacy, contracted vendor pharmacy or institutional pharmacy to see who has the best pricing available for the product in question. This process may be extrapolated to many infused medications as rates may differ significantly.

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APPENDIX

Detailed Diagnosis and Classification of AMD:

Early Age-Related Macular Degeneration (AMD)- Classified by risk of progression	• Low risk: medium drusen (63 micrometres or more and less than 125 micrometres) **or** pigmentary abnormalities • Medium risk: large drusen (125 micrometres or more) **or** reticular drusen **or** medium drusen with pigmentary abnormalities • High risk: large drusen (125 micrometres or more) with pigmentary abnormalities **or** reticular drusen with pigmentary abnormalities **or** vitelliform lesion without significant visual loss (best-corrected acuity better than 6/18) **or** atrophy smaller than 175 micrometres and not involving the fovea
Late AMD (indeterminate)	• Retinal pigment epithelial (RPE) degeneration and dysfunction (presence of degenerative AMD changes with subretinal **or** intraretinal fluid in the absence of neovascularization), and serous pigment epithelial detachment (PED) without neovascularization
Late AMD (wet active)	• Classic choroidal neovascularization (CNV), occult (fibrovascular PED and serous PED with neovascularization), mixed (predominantly or minimally classic CNV with occult CNV), retinal angiomatous proliferation (RAP), polypoidal choroidal vasculopathy (PCV)
Late AMD (wet inactive)	• Fibrous scar, sub-foveal atrophy or fibrosis secondary to an RPE tear, atrophy (absence or thinning of RPE and/or retina), cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment)
Late AMD (dry)	• Geographic atrophy (in the absence of neovascular AMD), significant visual loss (6/18 or worse) associated with dense **or** confluent drusen **or** advanced pigmentary changes **and/or** atrophy **or** vitelliform lesion