Ophthalmologic Policy: Vascular Endothelial Growth Factor (VEGF) Inhibitors

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➲ Instructions for Use

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Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Ophthalmologic Policy: Vascular Endothelial Growth Factor (VEGF) Inhibitors (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Pennsylvania	Refer to the state's Medicaid clinical policy

Coverage Rationale

This policy provides information about the use of certain specialty pharmacy medications administered by the intravitreal route for ophthalmologic conditions.

This policy refers to the following vascular endothelial growth factor (VEGF) inhibitors and dual VEGF/angiopoietin-2 (Ang-2) inhibitors:
- Avastin® (bevacizumab)
- Beovu® (brolucizumab-dbll)
- Byooviz™ (ranibizumab-nuna)
- Cimerli™ (ranibizumab-eqrn)
- Eylea™ (aflibercept)
- Lucentis® (ranibizumab)
- Macugen® (pegaptanib)
- Vabysmo™ (faricimab-svoa)

The following information pertains to medical necessity review:

General Requirements (applicable to all medical necessity requests)

- For initial therapy, both of the following:
  - Diagnosis; and
  - Intravitreal VEGF or dual VEGF/Ang-2 inhibitor administration is no more than 12 doses per year per eye, regardless of diagnosis
- For continuation of therapy, both of the following:
  - Documentation of positive clinical response to anti - VEGF therapy; and
  - Intravitreal VEGF or dual VEGF/Ang-2 inhibitor administration is no more than 12 doses per year per eye, regardless of diagnosis

Diagnosis-Specific Requirements

The information below indicates the list of proven and medically necessary indications.

Beovu (brolucizumab) is proven and medically necessary for the treatment of:
- Neovascular age-related macular degeneration (AMD)
- Diabetic Macular Edema (DME)

Avastin (bevacizumab) is proven and medically necessary for the treatment of:
- Choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS)
- Diabetic macular edema (DME)
- Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- Neovascular age-related macular degeneration (AMD)
- Neovascular glaucoma
- Neovascularization of the iris (NVI) (rubeosis iridis)
- Proliferative diabetic retinopathy
- Type I retinopathy of prematurity

Byooviz (ranibizumab-nuna) is proven and medically necessary for the treatment of:
- Neovascular age - related macular degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Myopic Choroidal Neovascularization (mCNV)

Cimerli™ (ranibizumab-eqrn) is proven and medically necessary for the treatment of:
- Myopic choroidal neovascularization (mCNV)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following Retinal Vein Occlusion (RVO)
- Neovascular age-related macular degeneration (AMD)

Eylea (aflibercept) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Diabetic retinopathy
- Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- Neovascular age - related macular degeneration (AMD)

Lucentis (ranibizumab) is proven and medically necessary for the treatment of:
- Choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS)
- Diabetic macular edema (DME)
- Diabetic retinopathy
- Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)

- Neovascular age - related macular degeneration (AMD)

Macugen (pegaptanib) is proven and medically necessary for the treatment of:
- Diabetic macular edema
- Neovascular age - related macular degeneration (AMD)

Vabysmo (faricimab-svoa) is proven and medically necessary for the treatment of:
- Neovascular age-related macular degeneration (AMD)
- Diabetic macular edema (DME)

Additional Information

Avastin (bevacizumab) is supplied in sterile vials containing a solution of 25 mg/mL. Doses utilized in ophthalmic conditions generally range from 6.2 mcg to 2.5 mg. Therefore, bevacizumab in vials is often divided into single-dose, prefilled syringes for intravitreal use by compounding pharmacies. Compounding pharmacies must comply with United States Pharmacopeia (USP) Chapter 797, which sets standards for the compounding, transportation, and storage of compounded sterile products (CSP).[1] The Pharmacy Compounding Accreditation Board can verify that the pharmacy is adhering to these standards.[2]

The American Society of Retinal Specialists (ASRS) is committed to ensuring that retina specialists have access to compounded drugs (such as Avastin) that are prepared with high - quality material following good quality controls and sound engineering design by appropriately trained personnel. Refer to their information page at https://www.asrs.org/advocacy-practice/access-to-safe-compounded-agents for resources pertaining to access of safe compounded agents.[14]

Refer to the U.S. Food and Drug Administration (FDA) section of this policy for information related to contamination of compounded bevacizumab. In an effort to guard against contamination during the compounding process, the United States Veterans Health Administration (USVHA) requires that only USVHA pharmacies may dispense bevacizumab for intravitreal administration to Veterans Administration beneficiaries. The medication must be dispensed directly to the VA ophthalmologist, who will then be responsible for preparing and administering the bevacizumab dose for each patient. In addition to strict labeling and storage requirements, the ophthalmologist is required to prepare only one dose of medication from each vial; if both eyes are to be treated, a separate vial and syringe must be utilized.[3]

Definitions

Type I Retinopathy of Prematurity (ROP), also known as "high-risk pre - threshold ROP", is defined as any of the following:
- Any stage ROP with plus disease in zone I
- Stage 3 ROP without plus disease in zone I
- Stage 2 or 3 ROP with plus disease in zone II

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description	Brand Name
J0178	Injection, aflibercept, 1 mg	Eylea
J0179	Injection, brolucizumab-dbll, 1 mg	Beovu
J2503	Injection, pegaptanib sodium, 0.3 mg	Macugen
J2778	Injection, ranibizumab, 0.1 mg	Lucentis
J9035	Injection, bevacizumab, 10 mg	Avastin

HCPCS Code	Description	Brand Name
J3490	Unclassified drug	Cimerli
J3590	Unclassified biologics	Cimerli
C9399	Unclassified drugs or biologics	Cimerli
J2777	Injection, faricimab-svoa, 0.1mg	Vabysmo
Q5124	Injection, ranibizumab-nuna, biosimilar, (Byooviz), 0.1 mg	Byooviz

Diagnosis Code	Description	Applies to HCPCS Code						
		J0178	J0179	J2503	J2778, J3490, J3590, C9399	J9035	J2777	Q5124
B39.5	Histoplasmosis duboisii				X	X		
B39.9	Histoplasmosis, unspecified				X	X		
E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X	
E08.319	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy without macular edema	X			X			
E08.3211	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E08.3212	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E08.3213	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E08.3219	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E08.3291	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E08.3292	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E08.3293	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E08.3299	Diabetes mellitus due to underlying condition with mild non-proliferative	X			X			

	diabetic retinopathy without macular edema, unspecified eye							
E08.3311	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E08.3312	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E08.3313	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E08.3319	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E08.3391	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E08.3392	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E08.3393	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E08.3399	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E08.3411	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E08.3412	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E08.3413	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E08.3419	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E08.3491	Diabetes mellitus due to underlying	X			X			

	condition with severe non-proliferative diabetic retinopathy without macular edema, right eye							
E08.3492	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E08.3493	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E08.3499	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E08.3511	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E08.3512	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E08.3513	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E08.3519	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E08.3521	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X			X	X		
E08.3522	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X			X	X		
E08.3523	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X			X	X		
E08.3529	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X			X	X		

E08.3531	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X			X	X		
E08.3532	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X			X	X		
E08.3533	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X			X	X		
E08.3539	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X			X	X		
E08.3541	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X			X	X		
E08.3542	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X			X	X		
E08.3543	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X			X	X		
E08.3549	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X			X	X		
E08.3551	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, right eye	X			X	X		
E08.3552	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, left eye	X			X	X		
E08.3553	Diabetes mellitus due to underlying condition with stable proliferative	X			X	X		

	diabetic retinopathy, bilateral							
E08.3559	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, unspecified eye	X			X	X		
E08.3591	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, right eye	X			X	X		
E08.3592	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, left eye	X			X	X		
E08.3593	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, bilateral	X			X	X		
E08.3599	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, unspecified eye	X			X	X		
E08.37X1	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, right eye		X	X	X	X	X	
E08.37X2	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, left eye		X	X	X	X	X	
E08.37X3	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, bilateral		X	X	X	X	X	
E08.37X9	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, unspecified eye		X	X	X	X	X	
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X	
E09.3211	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E09.3212	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E09.3213	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E09.3219	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular	X	X	X	X	X	X	

	edema, unspecified eye							
E09.3291	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E09.3292	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E09.3293	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E09.3299	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E09.3311	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E09.3312	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E09.3313	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E09.3319	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E09.3391	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E09.3392	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E09.3393	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E09.3399	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E09.3411	Drug or chemical induced diabetes mellitus with severe non-proliferative	X	X	X	X	X	X	

	diabetic retinopathy with macular edema, right eye							
E09.3412	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E09.3413	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E09.3419	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E09.3491	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E09.3492	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E09.3493	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E09.3499	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E09.3511	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E09.3512	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E09.3513	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E09.3519	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E09.3521	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X			X	X		

E09.3522	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X			X	X		
E09.3523	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X			X	X		
E09.3529	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X			X	X		
E09.3531	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X			X	X		
E09.3532	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X			X	X		
E09.3533	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X			X	X		
E09.3539	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X			X	X		
E09.3541	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X			X	X		
E09.3542	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X			X	X		
E09.3543	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment,	X			X	X		

	bilateral							
E09.3549	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X			X	X		
E09.3551	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X			X	X		
E09.3552	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X			X	X		
E09.3553	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X			X	X		
E09.3559	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X			X	X		
E09.3591	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X			X	X		
E09.3592	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X			X	X		
E09.3593	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X			X	X		
E09.3599	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X			X	X		
E09.37X1	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, right eye		X	X	X	X	X	
E09.37X2	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, left eye		X	X	X	X	X	
E09.37X3	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral		X	X	X	X	X	
E09.37X9	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye		X	X	X	X	X	
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X	

E10.3211	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E10.3212	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E10.3213	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E10.3219	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E10.3291	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E10.3292	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E10.3293	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E10.3299	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X		X	X			
E10.3311	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E10.3312	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E10.3313	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E10.3319	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E10.3391	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E10.3392	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E10.3393	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E10.3399	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E10.3411	Type 1 diabetes mellitus with severe	X	X	X	X	X	X	

	non-proliferative diabetic retinopathy with macular edema, right eye							
E10.3412	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E10.3413	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E10.3419	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E10.3491	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E10.3492	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E10.3493	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E10.3499	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E10.3511	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E10.3512	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E10.3513	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E10.3521	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X			X	X		
E10.3522	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X			X	X		
E10.3523	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X			X	X		
E10.3529	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the	X			X	X		

	macula, unspecified eye							
E10.3531	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X			X	X		
E10.3532	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X			X	X		
E10.3533	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X			X	X		
E10.3539	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X			X	X		
E10.3541	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X			X	X		
E10.3542	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X			X	X		
E10.3543	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X			X	X		
E10.3549	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X			X	X		
E10.3551	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X			X	X		
E10.3552	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X			X	X		
E10.3553	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X			X	X		
E10.3559	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X			X	X		
E10.3591	Type 1 diabetes mellitus with proliferative diabetic retinopathy without	X			X	X		

	macular edema, right eye							
E10.3592	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X			X	X		
E10.3593	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X			X	X		
E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X			X	X		
E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye		X	X	X	X	X	
E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye		X	X	X	X	X	
E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral		X	X	X	X	X	
E10.37X9	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye		X	X	X	X	X	
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X	
E11.3211	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E11.3212	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E11.3213	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E11.3219	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E11.3291	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E11.3292	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E11.3293	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E11.3299	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E11.3311	Type 2 diabetes mellitus with moderate	X	X	X	X	X	X	

	non-proliferative diabetic retinopathy with macular edema, right eye							
E11.3312	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E11.3313	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E11.3319	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E11.3391	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E11.3392	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E11.3393	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E11.3399	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E11.3411	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E11.3412	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E11.3413	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E11.3419	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E11.3491	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E11.3492	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E11.3493	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E11.3499	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E11.3511	Type 2 diabetes mellitus with	X	X	X	X	X	X	

	proliferative diabetic retinopathy with macular edema, right eye							
E11.3512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E11.3513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E11.3521	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X			X	X		
E11.3522	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X			X	X		
E11.3523	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X			X	X		
E11.3529	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X			X	X		
E11.3531	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X			X	X		
E11.3532	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X			X	X		
E11.3533	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X			X	X		
E11.3539	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X			X	X		
E11.3541	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X			X	X		
E11.3542	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment	X			X	X		

	and rhegmatogenous retinal detachment, left eye							
E11.3543	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X			X	X		
E11.3549	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X			X	X		
E11.3551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X			X	X		
E11.3552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X			X	X		
E11.3553	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X			X	X		
E11.3559	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X			X	X		
E11.3591	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X			X	X		
E11.3592	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X			X	X		
E11.3593	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X			X	X		
E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X			X	X		
E11.37X1	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye		X	X	X	X	X	
E11.37X2	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye		X	X	X	X	X	
E11.37X3	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral		X	X	X	X	X	
E11.37X9	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye		X	X	X	X	X	
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X	

E13.3211	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E13.3212	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E13.3213	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E13.3219	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E13.3291	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E13.3292	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E13.3293	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E13.3299	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E13.3311	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E13.3312	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E13.3313	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E13.3319	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E13.3391	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema,	X			X			

	right eye							
E13.3392	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E13.3393	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E13.3399	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E13.3411	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E13.3412	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	
E13.3413	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E13.3419	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E13.3491	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X			X			
E13.3492	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X			X			
E13.3493	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X			X			
E13.3499	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X			X			
E13.3511	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X	
E13.3512	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X	

E13.3513	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X	
E13.3519	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X	
E13.3521	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X			X	X		
E13.3522	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X			X	X		
E13.3523	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X			X	X		
E13.3529	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X			X	X		
E13.3531	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X			X	X		
E13.3532	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X			X	X		
E13.3533	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X			X	X		
E13.3539	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X			X	X		
E13.3541	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X			X	X		
E13.3542	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X			X	X		
E13.3543	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment	X			X	X		

	and rhegmatogenous retinal detachment, bilateral							
E13.3549	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X			X	X		
E13.3551	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X			X	X		
E13.3552	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X			X	X		
E13.3553	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X			X	X		
E13.3559	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X			X	X		
E13.3591	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X			X	X		
E13.3592	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X			X	X		
E13.3593	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X			X	X		
E13.3599	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X			X	X		
E13.37X1	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, right eye		X	X	X	X	X	
E13.37X2	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, left eye		X	X	X	X	X	
E13.37X3	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral		X	X	X	X	X	
E13.37X9	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye		X	X	X	X	X	
H21.1X1	Other vascular disorders of iris and ciliary body, right eye					X		
H21.1X2	Other vascular disorders of iris and ciliary body, left eye					X		
H21.1X3	Other vascular disorders of iris and ciliary body, bilateral					X		
H21.1X9	Other vascular disorders of iris and					X		

	ciliary body, unspecified eye							
H32	Chorioretinal disorders in diseases classified elsewhere				X	X		
H34.8110	Central retinal vein occlusion, right eye, with macular edema	X			X	X		
H34.8111	Central retinal vein occlusion, right eye, with retinal neovascularization	X			X	X		
H34.8112	Central retinal vein occlusion, right eye, stable	X			X	X		
H34.8120	Central retinal vein occlusion, left eye, with macular edema	X			X	X		
H34.8121	Central retinal vein occlusion, left eye, with retinal neovascularization	X			X	X		
H34.8122	Central retinal vein occlusion, left eye, stable	X			X	X		
H34.8130	Central retinal vein occlusion, bilateral, with macular edema	X			X	X		
H34.8131	Central retinal vein occlusion, bilateral, with retinal neovascularization	X			X	X		
H34.8132	Central retinal vein occlusion, bilateral, stable	X			X	X		
H34.8190	Central retinal vein occlusion, unspecified eye, with macular edema	X			X	X		
H34.8191	Central retinal vein occlusion, unspecified eye, with retinal neovascularization	X			X	X		
H34.8192	Central retinal vein occlusion, unspecified eye, stable	X			X	X		
H34.821	Venous engorgement, right eye	X			X	X		
H34.822	Venous engorgement, left eye	X			X	X		
H34.823	Venous engorgement, bilateral	X			X	X		
H34.829	Venous engorgement, unspecified eye	X			X	X		
H34.8310	Tributary (branch) retinal vein occlusion, right eye, with macular edema	X			X	X		X
H34.8311	Tributary (branch) retinal vein occlusion, right eye, with retinal neovascularization	X			X	X		X
H34.8312	Tributary (branch) retinal vein occlusion, right eye, stable	X			X	X		X
H34.8320	Tributary (branch) retinal vein occlusion, left eye, with macular edema	X			X	X		X
H34.8321	Tributary (branch) retinal vein occlusion, left eye, with retinal neovascularization	X			X	X		X
H34.8322	Tributary (branch) retinal vein occlusion, left eye, stable	X			X	X		X
H34.8330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema	X			X	X		X
H34.8331	Tributary (branch) retinal vein occlusion, bilateral, with retinal neovascularization	X			X	X		X

H34.8332	Tributary (branch) retinal vein occlusion, bilateral, stable	X			X	X		X
H34.8390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema	X			X	X		X
H34.8391	Tributary (branch) retinal vein occlusion, unspecified eye, with retinal neovascularization	X			X	X		X
H34.8392	Tributary (branch) retinal vein occlusion, unspecified eye, stable	X			X	X		X
H35.051	Retinal neovascularization, unspecified, right eye				X	X		
H35.052	Retinal neovascularization, unspecified, left eye				X	X		
H35.053	Retinal neovascularization, unspecified, bilateral				X	X		
H35.059	Retinal neovascularization, unspecified, unspecified eye				X	X		
H35.101	Retinopathy of prematurity, unspecified, right eye					X		
H35.102	Retinopathy of prematurity, unspecified, left eye					X		
H35.103	Retinopathy of prematurity, unspecified, bilateral					X		
H35.109	Retinopathy of prematurity, unspecified, unspecified eye					X		
H35.111	Retinopathy of prematurity, stage 0, right eye					X		
H35.112	Retinopathy of prematurity, stage 0, left eye					X		
H35.113	Retinopathy of prematurity, stage 0, bilateral					X		
H35.119	Retinopathy of prematurity, stage 0, unspecified eye					X		
H35.121	Retinopathy of prematurity, stage 1, right eye					X		
H35.122	Retinopathy of prematurity, stage 1, left eye					X		
H35.123	Retinopathy of prematurity, stage 1, bilateral					X		
H35.129	Retinopathy of prematurity, stage 1, unspecified eye					X		
H35.131	Retinopathy of prematurity, stage 2, right eye					X		
H35.132	Retinopathy of prematurity, stage 2, left eye					X		
H35.133	Retinopathy of prematurity, stage 2, bilateral					X		
H35.139	Retinopathy of prematurity, stage 2,					X		

	unspecified eye							
H35.141	Retinopathy of prematurity, stage 3, right eye					X		
H35.142	Retinopathy of prematurity, stage 3, left eye					X		
H35.143	Retinopathy of prematurity, stage 3, bilateral					X		
H35.149	Retinopathy of prematurity, stage 3, unspecified eye					X		
H35.151	Retinopathy of prematurity, stage 4, right eye					X		
H35.152	Retinopathy of prematurity, stage 4, left eye					X		
H35.153	Retinopathy of prematurity, stage 4, bilateral					X		
H35.159	Retinopathy of prematurity, stage 4, unspecified eye					X		
H35.161	Retinopathy of prematurity, stage 5, right eye					X		
H35.162	Retinopathy of prematurity, stage 5, left eye					X		
H35.163	Retinopathy of prematurity, stage 5, bilateral					X		
H35.169	Retinopathy of prematurity, stage 5, unspecified eye					X		
H35.171	Retrolental fibroplasia, right eye					X		
H35.172	Retrolental fibroplasia, left eye					X		
H35.173	Retrolental fibroplasia, bilateral					X		
H35.179	Retrolental fibroplasia, unspecified eye					X		
H35.3210	Exudative age-related macular degeneration, right eye, stage unspecified	X	X	X	X	X	X	X
H35.3211	Exudative age-related macular degeneration, right eye, with active choroidal neovascularization	X	X	X	X	X	X	X
H35.3212	Exudative age-related macular degeneration, right eye, with inactive choroidal neovascularization	X	X	X	X	X	X	X
H35.3213	Exudative age-related macular degeneration, right eye, with inactive scar	X	X	X	X	X		X
H35.3220	Exudative age-related macular degeneration, left eye, stage unspecified	X	X	X	X	X	X	X
H35.3221	Exudative age-related macular degeneration, left eye, with active choroidal neovascularization	X	X	X	X	X	X	X
H35.3222	Exudative age-related macular	X	X	X	X	X	X	X

	degeneration, left eye, with inactive choroidal neovascularization							
H35.3223	Exudative age-related macular degeneration, left eye, with inactive scar	X	X	X	X	X		X
H35.3230	Exudative age-related macular degeneration, bilateral, stage unspecified	X	X	X	x	x	x	x
H35.3231	Exudative age-related macular degeneration, bilateral, with active choroidal neovascularization	x	x	x	x	x	x	x
H35.3232	Exudative age-related macular degeneration, bilateral, with inactive choroidal neovascularization	X	X	X	X	X	X	X
H35.3233	Exudative age-related macular degeneration, bilateral, with inactive scar	X	X	X	X	X		X
H35.3290	Exudative age-related macular degeneration, unspecified eye, stage unspecified	X	X	X	X	X	X	X
H35.3291	Exudative age-related macular degeneration, unspecified eye, with active choroidal neovascularization	X	X	X	X	X	X	X
H35.3292	Exudative age-related macular degeneration, unspecified eye, with inactive choroidal neovascularization	X	X	X	X	X	X	X
H35.3293	Exudative age-related macular degeneration, unspecified eye, with inactive scar	X	X	X	X	X	X	X
H35.33	Angioid streaks of macula	X		X	X	X		
H35.351	Cystoid macular degeneration, right eye	X	X	X	X	X	X	X
H35.352	Cystoid macular degeneration, left eye	X	X	X	X	X	X	X
H35.353	Cystoid macular degeneration, bilateral	X	X	X	X	X	X	X
H35.81	Retinal edema	X			X	X		
H40.89	Other specified glaucoma				X	X		
H44.20	Degenerative myopia, unspecified eye				X	X		
H44.21	Degenerative myopia, right eye				X	X		
H44.22	Degenerative myopia, left eye				X	X		
H44.23	Degenerative myopia, bilateral				X	X		
H44.2A1	Degenerative myopia with choroidal neovascularization, right eye				X	X		X
H44.2A2	Degenerative myopia with choroidal neovascularization, left eye				X	X		X
H44.2A3	Degenerative myopia with choroidal neovascularization, bilateral eye				X	X		X
H44.2A9	Degenerative myopia with choroidal neovascularization, unspecified eye				X	X		X
H44.2B1	Degenerative myopia with macular hole, right eye				X	X		

H44.2B2	Degenerative myopia with macular hole, left eye				X	X		
H44.2B3	Degenerative myopia with macular hole, bilateral eye				X	X		
H44.2B9	Degenerative myopia with macular hole, unspecified eye				X	X		
H44.2C1	Degenerative myopia with retinal detachment, right eye				X	X		
H44.2C2	Degenerative myopia with retinal detachment, left eye				X	X		
H44.2C3	Degenerative myopia with retinal detachment, bilateral eye				X	X		
H44.2C9	Degenerative myopia with retinal detachment, unspecified eye				X	X		
H44.2D1	Degenerative myopia with foveoschisis, right eye				X	X		
H44.2D2	Degenerative myopia with foveoschisis, left eye				X	X		
H44.2D3	Degenerative myopia with foveoschisis, bilateral eye				X	X		
H44.2D9	Degenerative myopia with foveoschisis, unspecified eye				X	X		
H44.2E1	Degenerative myopia with other maculopathy, right eye				X	X		
H44.2E2	Degenerative myopia with other maculopathy, left eye				X	X		
H44.2E3	Degenerative myopia with other maculopathy, bilateral eye				X	X		
H44.2E9	Degenerative myopia with other maculopathy, unspecified eye				X	X		

Maximum Allowed Frequencies

The allowed frequencies in this section are based upon the FDA approved prescribing information for the applicable medications. For indications without FDA approved dosing, the frequencies are derived from available clinical evidence. This list may not be inclusive of all medications listed and is subject to change.

Medication Name		Diagnosis	Maximum Frequency
Brand	Generic		
Avastin	bevacizumab	Choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome	The recommended dose is 1.25 mg (0.05 mL) near-monthly into affected eyes during the first 12 months, with fewer injections needed in subsequent years. Maximum of 12 doses per year per eye.
		Diabetic macular edema	
		Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)	
		Neovascular age-related macular degeneration	

Medication Name		Diagnosis	Maximum Frequency
Brand	Generic		
		Neovascular glaucoma	
		Neovascularization of the iris (rubeosis iridis)	
		Proliferative diabetic retinopathy	
		Type I retinopathy of prematurity	
Beovu	brolucizumab	Neovascular age-related macular degeneration	The recommended dose is 6 mg (0.05 mL) into affected eye(s) once monthly (approximately every 25 to 31 days) for the first 3 doses, then 6 mg every 8 to 12 weeks thereafter. Maximum of 12 doses per year per eye.
		Diabetic macular edema	The recommended dose is 6 mg (0.05 mL) into affected eye(s) every six weeks (approximately every 39 to 45 days) for the first 5 doses, then 6 mg every 8 to 12 weeks thereafter. Maximum of 12 doses per year per eye.
Byooviz	ranibizumab-nuna	Neovascular age-related macular degeneration	The recommended dose is 0.5 mg (0.05 ML) administered by intravitreal injection once a month (approximately 28 days). Patients may be treated with 3 monthly doses followed by less frequent dosing. Patients may also be treated with one dose every 3 months after 4 monthly doses. Maximum of 12 doses per year per eye.
		Macular Edema Following Retinal Vein Occlusion (RVO)	The recommended dose is 0.5 mg (0.05 ML) administered by intravitreal injection once a month (approximately 28 days). Maximum of 12 doses per year per eye.
		Myopic Choroidal Neovascularization (mCNV)	The recommended dose is 0.5 mg (0.05 ML) administered by intravitreal injection once a month (approximately 28 days) for up to 3 months. May be retreated if necessary. Maximum of 12 doses per year per eye.
Cimerli	ranibizumab-eqrn	Myopic choroidal neovascularization (mCNV)	The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days) for up to 3 months. May be retreated if necessary. Maximum of 12 doses per year per eye.
		Diabetic macular edema (DME)	The recommended dose is 0.3 mg to affected eye(s) once a month (approximately every 28 days). Maximum of 12 doses per year per eye.
		Diabetic retinopathy (DR)	
		Macular edema following retinal vein occlusion (RVO)	The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days). Maximum of 12 doses per year per eye.
		Neovascular (wet) age-related macular	The recommended dose is 0.5 mg to

Medication Name		Diagnosis	Maximum Frequency
Brand	Generic		
		degeneration (AMD)	affected eye(s) once a month (approximately every 28 days). Treatment may be reduced to 3 once monthly doses, followed by an average of 4 to 5 injections over the subsequent 9 months. Maximum of 12 doses per year per eye.
Eylea	aflibercept	Diabetic macular edema Diabetic retinopathy	The recommended dose is 2 mg (0.05 mL) into affected eye(s) every 4 weeks (approximately every 28 days, monthly) for the first 20 weeks (5 months), then 2 mg every 8 weeks (2 months). Maximum of 12 doses per year per eye.
		Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)	The recommended dose is 2 mg (0.05 mL) once every 4 weeks. Maximum of 12 doses per year per eye.
		Neovascular age-related macular degeneration	The recommended dose is 2 mg (0.05 mL) into affected eye(s) every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Maximum of 12 doses per year per eye.
Lucentis	ranibizumab	Choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome	The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days) for up to 3 months. May be retreated if necessary. Maximum of 12 doses per year per eye.
		Diabetic macular edema Diabetic retinopathy	The recommended dose is 0.3 mg to affected eye(s) once a month (approximately every 28 days). Maximum of 12 doses per year per eye.
		Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)	The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days). Maximum of 12 doses per year per eye.
		Neovascular age-related macular degeneration	The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days). Treatment may be reduced to 3 once monthly doses, followed by an average of 4 to 5 injections over the subsequent 9 months. Maximum of 12 doses per year per eye.
Macugen	pegaptanib	Diabetic macular edema	The recommended dose is 0.3 mg to affected eye(s) near-monthly during the first 12 months, with fewer injections needed in subsequent years. Maximum of 12 doses per year per eye.
		Neovascular age-related macular degeneration	The recommended dose is 0.3 mg to affected eye(s) once every 6 weeks. Maximum of 12 doses per year per eye.
Vabysmo	Faricimab	Diabetic macular edema	The recommended dose is one of the

Medication Name		Diagnosis	Maximum Frequency
Brand	Generic		
			following regimens: 1) 6 mg administered by intravitreal injection every 4 weeks for at least 4 doses, followed by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments based on response; or 2) 6 mg administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injections at intervals of every 8 weeks over the next 28 weeks. Although most patients require dosing every 8 weeks, some patients may need dosing every 4 weeks. Maximum of 12 doses per year per eye.
		Neovascular age-related macular degeneration	The recommended dose is 6 mg by intravitreal injection every 4 weeks for the first 4 doses, followed by one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36, and 48; or 3) Weeks 20, 28, 36 and 44. Although most patients require dosing every 8 weeks, some patients may need dosing every 4 weeks. Maximum of 12 doses per year per eye.

Background

Vascular endothelial growth factor (VEGF) is a protein that stimulates the growth, proliferation and survival of vascular endothelial cells. VEGF plays a critical role in the development of new blood vessels (angiogenesis), increases vascular permeability in small blood vessels and prevents apoptosis of vascular endothelial cells in immature blood vessels. VEGF has been implicated in blood retinal barrier breakdown and pathological ocular neovascularization.[4]

Clinical Evidence

Proven

Neovascular Age-Related Macular Degeneration (AMD)

Aflibercept, brolucizumab, pegaptanib, ranibizumab, ranibizumab-eqrn, ranibizumab-nuna, and faricimab are indicated for the treatment of neovascular age-related macular degeneration.[5-7,71, 76-77]

Solomon et al evaluated the ocular and systemic effects of, and quality of life associated with, intravitreally injected anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) for the treatment of neovascular AMD compared with no anti-VEGF treatment; and the relative effects of one anti - VEGF agent compared with another when administered in comparable dosages and regimens.[10] A database search identified 12 randomized controlled trials which included 5496 patients with neovascular AMD. Patients treated with any of the three anti - VEGF agents more often experienced improved vision, less often lost vision, and were less likely to be legally blind than patients treated with control interventions after one year of treatment. Additionally, these patients also showed improvements in structural areas of the eye that doctors use to monitor disease progression and treatment response compared with untreated patients. Compared with control treatments, treatment with ranibizumab or bevacizumab yielded larger improvements than pegaptanib. No trial compared pegaptanib directly with other anti-VEGF agents. When bevacizumab and ranibizumab were compared with each other, there were no major differences with respect to vision-related outcomes; there was, however, a large difference in cost between the two agents. Inflammation and increased pressure in the eye were the most common vision-related adverse events with anti-VEGF agents. Endophthalmitis was reported in < 1% of anti-VEGF-treated patients and no cases were reported in control groups. The occurrence of serious adverse health effects, such as high blood pressure and internal bleeding, was comparable across anti-VEGF-treated groups and control groups;

however, the number of events was small relative to the number of people in the studies making it difficult to detect any meaningful differences between groups. Few data were available for visual function (e.g., reading speed and critical print size), quality of life, and economic outcomes. The overall quality of the evidence was very good, with most trials having an overall low risk of bias. The results of the review indicated the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; ranibizumab and bevacizumab were also shown to improve visual acuity. The information available on the adverse effects of each medication do not suggest a higher incidence of potentially vision - threatening complications with intravitreal injection compared with control interventions; however, clinical trial sample sizes may not have been sufficient to detect rare safety outcomes.

In a multicenter, prospective, noninferiority, double-masked, randomized clinical trial, the relative efficacy and safety profile of bevacizumab versus ranibizumab intravitreal injections for the treatment of neovascular age-related macular degeneration (AMD) was evaluated.[62] Patients (n = 501) aged ≥ 50 years were eligible if they presented with subfoveal neovascular AMD, with best-corrected visual acuity (BVCA) in the study eye of between 20/32 and 20/320 measured on the Early Treatment of Diabetic Retinopathy Study chart, and a lesion area of less than 12 optic disc areas (DA). Subjects were randomly assigned to intravitreal administration of bevacizumab (1.25 mg) or ranibizumab (0.50 mg), then followed for one year. A loading dose of three-monthly intravitreal injections was administered to all subjects, followed by an as-needed regimen (one injection in case of active disease) for the remaining 9 months with monthly follow-up. The main outcome measure was the mean change in visual acuity at one year, with a noninferiority limit of five letters. In the per protocol analysis, bevacizumab was noninferior to ranibizumab (bevacizumab minus ranibizumab + 1.89 letters; 95% confidence interval [CI], -1.16 to + 4.93, p < 0.0001). The intention-to-treat analysis was concordant. The mean number of injections was 6.8 in the bevacizumab group and 6.5 in the ranibizumab group (p = 0.39). Both drugs reduced the central subfield macular thickness, with a mean decrease of 95 µm for bevacizumab and 107 µm for ranibizumab (p = 0.27). There were no significant differences in the presence of subretinal or intraretinal fluid at final evaluation, dye leakage on angiogram, or change in choroidal neovascular area. The proportion of patients with serious adverse events was 12.6% in the bevacizumab group and 12.1% in the ranibizumab group (p = 0.88). The proportion of patients with serious systemic or ocular adverse events was similar in both groups. Based on these results, bevacizumab was determined to be noninferior to ranibizumab for visual acuity at one year with similar safety profiles. Ranibizumab tended to have a better anatomic outcome.

A multi-center, single-blind, non-inferiority study was conducted by the CATT Research Group in 1,208 patients with neovascular age-related macular degeneration (AMD).[8] Participants were randomly assigned to receive intravitreal injections of either ranibizumab or bevacizumab on a monthly schedule or as needed with monthly evaluations. The primary outcome of the study was the mean change in visual acuity at one year, with a non-inferiority limit of 5 letters on the eye chart. The investigators reported that monthly administration of bevacizumab was equivalent to monthly administration of ranibizumab, with 8.0 and 8.5 letters gained, respectively. Results of as needed administration of the agents were determined to be equivalent, with bevacizumab recipients gaining 5.9 letters and ranibizumab recipients gaining 6.8 letters. Ranibizumab as needed was equivalent to monthly ranibizumab, while the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 µm) than in the other groups (152 to 168 µm, p = 0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either treatment (p > 0.20). However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. Therefore, the investigators recommended that differences in rates of serious adverse events should be further studied. At one year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly.

HAWK and HARRIER were two double-masked, multicenter, active-controlled, randomized phase 3 trials that compared brolucizumab, with aflibercept to treat neovascular age-related macular degeneration (nAMD). In the studies, patients (n = 1817) had untreated, active choroidal neovascularization due to age-related macular degeneration in the study eye. Patients were randomized to intravitreal brolucizumab 3 mg or 6 mg or aflibercept 2 mg. After loading with 3 monthly injections, brolucizumab-treated eyes received an injection every 12 weeks. If disease activity was present, dosing was adjusted to every 8 weeks. Patients receiving aflibercept were dosed every 8 weeks. The study was evaluating noninferiority in mean best-corrected visual acuity (BCVA) change from baseline to 48 weeks. Other key end points included the percentage of patients who maintained every 12 - week dosing through 48 weeks and anatomic outcomes. At 48 weeks, each brolucizumab arm demonstrated noninferiority to aflibercept in BCVA change from baseline. Greater than 50% of brolucizumab 6 mg-treated eyes were maintained on every 12 - week dosing for 48 weeks. At 16 weeks, after the same treatment exposure, fewer brolucizumab 6 mg-treated eyes had disease activity versus aflibercept in HAWK (24.0% vs. 34.5%; p = 0.001) and HARRIER (22.7% vs. 32.2%; p = 0.002). Greater central subfield thickness reductions from baseline to 48 weeks were observed with brolucizumab 6 mg versus aflibercept in HAWK (LS mean -172.8 µm vs. -143.7 µm; p = 0.001) and HARRIER (LS mean -193.8 µm vs. -143.9 µm; p < 0.001). Anatomic retinal fluid outcomes favored brolucizumab over aflibercept. Overall, adverse event rates were generally the same with the two agents. The authors concluded that brolucizumab was noninferior to aflibercept in visual function at 48 weeks, and > 50% of brolucizumab 6 mg-treated eyes were maintained on every 12 - week dosing through 48 weeks. Anatomic outcomes favored brolucizumab over aflibercept. Overall safety was similar for the two agents.[71]

Two identically designed, randomized, multi-center, double-masked, active comparator-controlled, 2-year studies (TENAYA – NCT03823287 and LUCERNE – NCT03823300) assessed the safety and efficacy of faricimab in patients with nAMD. Patients (n = 1329) were newly diagnosed and treatment-naïve with ages ranging from 50 to 99 (mean = 75.9 years). Patients were randomized in a 1:1 ratio to one of two treatment arms: 1) aflibercept 2 mg administered fixed every 8 weeks after three initial monthly doses; and faricimab 6 mg administered by intravitreal injection every 4 weeks for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to determine whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44 (Q16W dosing); 2) Weeks 24, 36, and 48 (Q12W dosing); or 3) Weeks 20, 28, 36, and 44 (Q8W dosing). At week 48, after 4 initial monthly doses in the faricimab arm, 45% of patients received Q16W dosing, 33% of patients received Q12W dosing, and the remaining 22% of patients received Q8W dosing. Both studies demonstrated non-inferiority to the comparator control (aflibercept) at the primary endpoint, defined as the mean change from baseline in Best Corrected Visual Acuity (BCVA) when averaged over the week 40, 44, and 48 visits and measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and the faricimab arm. In both studies, faricimab-treated patients had a non-inferior mean change from baseline in BCVA compared to patients treated with aflibercept. The clinical efficacy for the second year of the study has not been reviewed.[78]

Woo et al. evaluated the equivalence of efficacy, similar safety, and similar immunogenicity of a ranibizumab biosimilar product (SB11) compared with the reference ranibizumab with neovascular age-related macular degeneration in a randomized, double-masked, parallel-group phase 3 equivalence study. The study was conducted in 75 centers in 9 countries from March 14, 2018 to December 9, 2019, among 705 participants 50 years or older with neovascular age-related macular degeneration with active subfoveal choroidal neovascularization lesions. Patients were randomized in a 1:1 ratio to receive intravitreous injection of either SB11 or ranibizumab, 0.5 mg, every 4 weeks through week 48. Preplanned interim analysis after all participants completed the week 24 assessment of primary efficacy end points at week 8 for change from baseline in best-corrected visual acuity (BCVA) and week 4 for central subfield thickness (CST), with predefined equivalence margins for adjusted treatment differences of −3 letters to 3 letters for BCVA and −36 µm to 36 µm for CST. Least-squares mean (SE) changes in BCVA from baseline at week 8 were 6.2 (0.5) letters in the SB11 group vs 7.0 (0.5) letters in the ranibizumab group. Least-squares mean (SE) changes in CST from baseline at week 4 were −108 (5) µm in the SB11 group vs −100 (5)µm in the ranibizumab group. Incidences of treatment-emergent adverse events (231 of 350 [66.0%] vs 237 of 354 [66.9%]), including serious treatment-emergent adverse events (44 of 350 [12.6%] vs 44 of 354 [12.4%]) and treatment-emergent adverse events leading to study drug discontinuation (8 of 350 [2.3%] vs 5 of 354 [1.4%]), were similar in the SB11 and ranibizumab groups. Immunogenicity was low, with a cumulative incidence of antidrug antibodies up to week 24 of 3.0% (10 of 330) in the SB11 group and 3.1% (10 of 327) in the ranibizumab group. These findings of equivalent efficacy and similar safety and immunogenicity profiles compared with ranibizumab support the use of SB11 for patients with neovascular age-related macular degeneration.[80]

The clinical equivalence of ranibizumab-eqrn and reference ranibizumab was evaluated in a prospective, evaluation-masked, parallel-group, 48-week, phase 3 randomized study in patients with treatment-naïve, subfoveal choroidal neovascularization caused by neovascular age-related macular degeneration (nAMD). A total of 477 patients were randomly assigned to receive ranibizumab-eqrn (n = 238) or reference ranibizumab (n = 239) 0.5mg by intravitreal (IVT) injection in the study eye every 4 weeks. The primary end point was change from baseline in best-corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopahty Study (ETDRS) letters at 8 weeks before the third IVT injection. Biosimilarity of ranibizumab-eqrn to its originator was assess via a 2-sided equivalence test, with an equivalence margin in BCVA of 3 ETDRS letters. The BCVA improved in both groups, with a mean improvement of + 5.1 (FYB201) and + 5.6 (reference ranibizumab) ETDRS letters at week 8. The analysis of covariance (ANCOVA) least squares mean difference for the change from baseline between ranibizumab-eqrn and reference ranibizumab was -0.4 ETDRS letters with a 90% confidence interval (CI) of -1.6 to 0.9. Primary end point was met as the 90% CI was within the predefined equivalence margin of -3.5 to 3.5. In the post hoc analysis, the ANCOVA least squares mean difference for the change from baseline in BCVA at week 8 between ranibizumab-eqrn and reference ranibizumab was –0.4

ETDRS letters, with a 95% CI of −1.9 to 1.1, again meeting the criteria for equivalence between drugs. In the per-protocol sensitivity analysis, the ANCOVA least squares mean difference for change in BCVA between ranibizumab-eqrn and reference ranibizumab at week 8 was −0.4 ETDRS letters, with a 90% CI of −1.7 to 0.9, also contained within the predefined equivalence margin. The frequency and type of ocular adverse events were comparable between treatment groups. Most adverse events were of mild or moderate intensity, and no clinically relevant differences were identified. The most frequent study drug-related adverse events in the ranibizumab-eqrn and reference ranibizumab groups, respectively, were cataract (0.0% and 2.1%), retinal pigment epithelium tear (0.4% and 1.3%), reduced visual acuity (0.0% and 1.3%), punctate keratitis (0.0% and 0.8%), vitreous hemorrhage (0.4% and 0.4%), eye pain (0.8% and 0.0%), increased gamma-glutamyl transferase level (0.4% and 0.4%), and increased intraocular pressure (1.3% and 0.8%). A total of 21.4% (ranibizumab-eqrn) and 27.6% (reference ranibizumab) of patients experienced adverse events related to the IVT injection procedure. The prevalence of treatment-emergent AEs associated with MedDRA preferred terms for intraocular inflammation was similar between FYB201 and reference ranibizumab groups. Of the patients treated with FYB201, 8.4% (20/238) experienced treatment-emergent AEs associated with intraocular inflammation terms, compared with 8.4% (20/239) of patients treated with reference ranibizumab. In both treatment groups, 0.8% of patients experienced treatment-emergent AEs possibly related to the investigational medicinal product, specifically iridocyclitis (n = 1) and conjunctivitis (n = 1) in the FYB201 group, and punctate keratitis (n = 2) in the reference ranibizumab group. Frequency and type of systemic AEs were also similar between FYB201 and reference ranibizumab groups, with the most frequent, respectively, being nAMD in the fellow eye (7.6% and 8.8%), nasopharyngitis (5.0% and 6.7%), hypertension (1.3% and 5.9%), and increased C-reactive protein level (4.2% and 2.1%). A slightly higher incidence of systemic serious AEs was observed in the reference ranibizumab arm (12.1%) compared with the FYB201 arm (7.1%). Three patients discontinued the study because of AEs, 1 in the FYB201 group (worsening of nAMD) and 2 in the reference ranibizumab group (unrelated benign pancreatic neoplasm and malignant tongue neoplasm of unspecified stage). In addition, AEs led to permanent or temporary withdrawal of study drug in an additional 9 patients, 5 in the FYB201 group and 4 in the reference ranibizumab group. In the FYB201 group, 3 patients had interruption of treatment due to mild nonserious AEs (1 with upper respiratory tract infection and 2 with conjunctivitis), and 2 patients had moderate AEs; 1 had a chalazion for which treatment was resumed at the subsequent visit without omitting an injection, and 1 had conjunctivitis for which the patient did not receive the last planned injection. In the reference ranibizumab group, mild nonserious AEs resulted in interruption of treatment in 3 patients (1 each of blepharospasm and visual acuity reduced, vascular anastomosis, and complications associated with device and viral infection), and 1 patient had severe endophthalmitis. Three patients died during the study (n = 2 in FYB201 group and n = 1 in the reference ranibizumab group), but none of the deaths were considered related to the study drug. [82-83]

Diabetic Macular Edema

Aflibercept, brolucizumab-dbll, faricimab, ranibizumab, and ranibizumab-eqrn are indicated for the treatment of diabetic macular edema (DME).[5,7]

Virgili et al. evaluated the effects in preserving and improving vision and acceptability, including the safety, compliance with therapy and quality of life, of antiangiogenic therapy with anti - VEGF modalities for the treatment of diabetic macular oedema (DMO).[61] A database search was conducted which included randomized controlled trials (RCTs) comparing any antiangiogenic drugs with an anti-VEGF mechanism of action versus another treatment, sham treatment or no treatment in people with DMO. The primary outcome measured was the proportion of people improving or losing vision by three or more lines. Eighteen studies were included in this review. Approximately one in five people gained 3 lines of vision, using antiangiogenic therapy compared with laser, using seven to nine intraocular injections in the first year, and three or four injections in the second year. Benefits were also detected when the drug was compared to no treatment and when it was added to photocoagulation and compared to photocoagulation alone. Antiangiogenic treatment was well tolerated in these studies, with few reported injection-related adverse events and no increase in the number of reported overall and cardiovascular adverse events. Researchers concluded that the evidence utilized in the review was of high - quality regarding efficacy compared to laser photocoagulation, the standard treatment, because the effects were large and consistent between studies. The evidence was also of moderate quality regarding safety, since safety had to be confirmed in patients with higher morbidity, particularly regarding cardiovascular risk.

Two randomized, multi-center, double-masked, active comparator-controlled 2-year studies (YOSEMITE – NCT03622580 and RHINE – NCT03622593) assessed the safety and efficacy of faricimab in patients with DME. Patients (n = 1891) with diabetes were enrolled in the two studies with a total of 1262 patients treated with at least one dose of faricimab. Patient ages ranged from 24 to 91 years old (mean = 62.2 years). The overall population included both anti-VEGF naïve patients (78%) and patients who had been previously treated with a VEGF inhibitor prior to study participation (22%). The studies were identically designed, 2 year studies. Patients were randomized in a 1:1:1 ratio to one of three treatment regimens: 1) aflibercept Q8W, patients received fixed aflibercept 2 mg administered every 8 weeks (Q8W) after the first five monthly doses; 2) faricimab Q8W, patients received fixed faricimab 6 mg administered Q8W after the first six monthly doses; and 3) faricimab variable, patients received faricimab 6 mg administered every 4 weeks for at least four doses and until the central subfield thickness (CST) of the macula measured by optical coherence tomography was less than approximately 325 microns, then the interval of dosing was modified by up to 4 week interval extensions or reductions in up to 8 week interval increments based on CST and visual acuity disease activity criteria at study drug dosing visits. After 4 initial monthly doses, the patients in the faricimab variable arm could have received between the minimum of three and the maximum of eleven total injections through Week 56 inclusive. At Week 56, 32% of patients had completed at least one Q12W interval followed by one full Q16W interval. Seventeen percent (17%) of patients were treated on Q8W and/or Q4W dosing intervals through Week 56 (7% only on Q4W). These percentages are reflective of what happened within the conduct of these trials, but the percentages are not generalizable to a broader DME population due to the inclusion/exclusion criteria limited enrollment to a select subset of DME patients and that there is no empirical data that a similar magnitude would be observed if eligibility criteria allowed for broader enrollment. Both studies demonstrated non-inferiority to the comparator control (aflibercept) at the primary endpoint, defined as the mean change from baseline in BCVA at year 1 (average of the week 48, 52, and 56 visits), measured by the ETDRS Letter Score. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and faricimab groups. In both studies, faricimab Q8W and faricimab variable treated patients had a mean change from baseline in BCVA that was non-inferior to the patients treated with aflibercept Q8W. Clinical efficacy for the second year study has not been reviewed.[79]

Bevacizumab

Shoebi et al. reported the long-term results of intravitreal bevacizumab (IVB) injection alone or combined, at the time of first IVB injection, with intravitreal triamcinolone acetonide (IVT) for treatment of refractory diabetic macular edema (DME).[63] This randomized clinical trial enrolled 115 eyes of 101 patients with refractory DME and utilized three study arms: the IVB group (41 eyes) received three consecutive injections of 1.25 mg IVB at 6-week intervals; the IVB/IVT group (37 eyes) additionally received 2 mg of IVT at the time of first IVB injection; and the control (sham injection) group. Patients in the IVB and IVB/IVT groups were followed for a mean of 13.3 months and received retreatment with IVB alone whenever indicated. Main outcome measures were best corrected visual acuity (BCVA) and central macular thickness (CMT). The investigators found that at last follow up, CMT decreased significantly in the IVB group ($p = 0.013$), but it was not significant ($p = 0.13$) in the IVB/IVT group. Mean CMT improvement was 91 (95% CI, 20 to 161) microns and 57 (95% CI, -18 to 133) microns in the IVB and IVB/IVT groups, respectively. Mean BCVA improvement from baseline was 0.28 (95% CI, 0.18 to 0.38) logMAR ($p = 0.017$) in the IVB group and 0.19 (95% CI, 0.08 to 0.30) logMAR ($p = 0.001$) in the IVB/IVT group. There was no difference between the two groups in terms of visual improvement ($p = 0.42$). In generalized linear mixed model, only the time interval between the last injection and CMT measurement was statistically significant ($p = 0.04$). The same results were repeated for visual acuity ($p = 0.03$). Based upon these findings, the authors concluded that three loading doses of IVB (added doses if required) have long - term beneficial effects for treatment of refractory DME and that adding triamcinolone to this regimen provides no additional long-term benefit.

Nepomuceno et al. compared visual acuity and spectral domain optical coherence tomography (SDOCT) outcomes associated with intravitreal (IV) bevacizumab versus IV ranibizumab for the management of diabetic macular edema (DME) in a prospective, randomized trial.[64] Forty-eight patients (63 eyes) with center-involved DME were randomly assigned to receive 1.5 mg (0.06 cc) IV bevacizumab or 0.5 mg (0.05 cc) IV ranibizumab at baseline and monthly if central subfield thickness was greater than 275 μm. Forty-five patients (60 eyes) completed 48 weeks of follow - up. At baseline, mean ±standard error best-corrected visual acuity (BCVA) (logMAR) was 0.60 (20/80) ±0.05 in the IV bevacizumab group and 0.63 (20/85) ±0.05 in the IV ranibizumab group. A significant improvement in mean BCVA was observed in both groups at all study visits ($p < 0.05$); this improvement was significantly greater in the IV ranibizumab group compared with the IV bevacizumab group at weeks 8 ($p = 0.032$) and 32 ($p = 0.042$). A significant reduction in mean central subfield thickness was observed in both groups at all study visits compared with baseline ($p < 0.05$), with no significant difference in the magnitude of macular thickness reduction between groups. The mean number of injections was significantly higher ($p = 0.005$) in the IV bevacizumab group (9.84) than in the IV ranibizumab group (7.67). The investigators concluded that IV bevacizumab and IV ranibizumab are associated with similar effects on central subfield thickness in patients with DME through 1 year of follow-up. IV ranibizumab is associated with greater improvement in BCVA at some study visits, and the mean number of injections is higher in the IV bevacizumab group.

Pegaptanib

Sultan et al. conducted a randomized, multicenter, parallel-group trial to confirm safety and compare efficacy of intravitreal pegaptanib sodium versus placebo in subjects with diabetic macular edema (DME) involving the center of the macula associated with vision loss not due to ischemia.[12] During year one of the study, subjects received pegaptanib 0.3 mg or placebo every 6 weeks (total = 9 injections) and were eligible to receive focal/grid photocoagulation beginning at week 18. Subjects received injections as often as every 6 weeks per pre-specified criteria in the second year of the study. The primary efficacy endpoint was the proportion of subjects gaining ≥ 10 letters of visual acuity (VA) from baseline to year one. In total, 260 (pegaptanib, n = 133; placebo, n = 127) and 207 (pegaptanib, n = 107; placebo, n = 100) subjects were included in years 1 and 2 intent-to-treat analyses, respectively. A total of 49 of the 133 (36.8%) subjects from the pegaptanib group and 25 of the 127 (19.7%) from the placebo group experienced a VA improvement of ≥ 10 letters at week 54 compared with baseline (odds ratio [OR], 2.38; 95% confidence interval, 1.32-4.30; p = 0.0047). In the pegaptanib-treated subjects, change in mean VA from baseline by visit was superior (p < 0.05) to sham at weeks 6, 24, 30, 36, 42, 54, 78, 84, 90, 96, and 102. At week 102, pegaptanib-treated subjects gained, on average, 6.1 letters versus 1.3 letters for placebo (p < 0.01). Fewer pegaptanib- than placebo-treated subjects received focal/grid laser treatment (week 54, 31/133 [23.3%] vs 53/127 [41.7%], respectively, p = 0.002; week 102, 27/107 [25.2%] vs 45/100 [45.0%], respectively, p = 0.003). The pegaptanib treatment group showed significantly better results on the National Eye Institute-Visual Functioning Questionnaire than sham for subscales important in this population. Pegaptanib was well tolerated; the frequencies of discontinuations, adverse events, treatment-related adverse events, and serious adverse events were comparable in the pegaptanib and placebo groups.

In a randomized, double-masked, multicenter, dose-ranging, controlled trial, Cunningham et al. evaluated the safety and efficacy of pegaptanib sodium injection in the treatment of diabetic macular edema (DME).[13] Study subjects (n = 172) included those with a best-corrected visual acuity (VA) between 20/50 and 20/320 in the study eye, DME involving the center of the macula, and for whom the investigator judged photocoagulation could be safely withheld for 16 weeks. The primary outcome measures were best-corrected VA, central retinal thickness at the center point of the central subfield as assessed by optical coherence tomography measurement, and the need for additional therapy with photocoagulation between weeks 12 and 36. Intravitreous pegaptanib 0.3 mg (n = 44), pegaptanib 1 mg (n = 44), pegaptanib 3 mg (n = 42), or placebo (n = 42) injections were administered upon study entry, at week 6, and at week 12 with additional injections and/or focal photocoagulation as needed for another 18 weeks. Final assessments were conducted at week 36. Median VA was better at week 36 with 0.3 mg (20/50), as compared with placebo (20/63) (p = 0.04). A larger proportion of those receiving 0.3 mg gained VAs of ≥ 10 letters (approximately 2 lines) (34% vs. 10%, p = 0.003) and ≥ 15 letters (18% vs. 7%, p = 0.12). Mean central retinal thickness decreased by 68 microm with 0.3 mg, versus an increase of 4 microm with placebo (p = 0.02). Larger proportions of those receiving 0.3 mg had an absolute decrease of both ≥ 100 microm (42% vs. 16%, p = 0.02) and ≥ 75 microm (49% vs. 19%, p = 0.008). Photocoagulation was deemed necessary in fewer subjects in each pegaptanib arm (0.3 mg vs. placebo, 25% vs. 48%; p = 0.04). All pegaptanib doses were well tolerated. Endophthalmitis occurred in 1 of 652 injections (0.15% per injection; i.e., 1/130 [0.8%] pegaptanib subjects) and was not associated with severe visual loss. Overall, subjects assigned to pegaptanib had better VA outcomes, were more likely to show reduction in central retinal thickness and were deemed less likely to need additional therapy with photocoagulation at follow-up.

Macular Edema Secondary to BRVO/CRVO

Aflibercept, ranibizumab, ranibizumab-eqrn, and ranibizumab-nuna are indicated for the treatment of macular edema following retinal vein occlusion (RVO).[5,7, 77]

The efficacy and safety of intravitreal bevacizumab injections into eyes with macular edema secondary to central retinal vein occlusion (CRVO) was evaluated in a prospective clinical trial (n = 45 eyes) by Zhang et al.[15] Study subjects were treated with 3 initial intravitreal bevacizumab injections of 1.25 mg at monthly intervals. Retreatment was based on central retinal thickness (CRT) measured by optical coherence tomography (OCT) performed monthly, while fluorescein angiography was performed every 3 months. Main outcome parameters were visual acuity (VA, using the Early Treatment of Diabetic Retinopathy Study protocol) and CRT in an 18-month follow-up period. Mean VA increased from 40.9 letters at baseline to 61.9 letters (+ 21 letters; p < 0.001) at month 18; CRT decreased from 572.3 µm at baseline to 273.2 µm at month 18 (-299.1 µm; p < 0.001). Neither age, duration of CRVO, baseline VA, nor baseline CRT was correlated with the change in VA. No drug-related systemic or ocular side effects were observed following intravitreal bevacizumab treatment.

The efficacy of intravitreal bevacizumab as the primary treatment of macular edema due to retinal vein occlusions was evaluated by Figueroa et al. in a study of patients diagnosed as having central retinal vein occlusion (CRVO) (n = 18 eyes) or branch retinal vein occlusion (BRVO) (n = 28 eyes) with visual acuity of less than 20/40 and macular edema (> 300 microm central retinal thickness).[16] After an initial intravitreal injection of bevacizumab, re-treatment was performed if intraretinal or subretinal fluid with distortion of the foveal depression was found in optical coherence tomography. During a 6-month period, the mean number of injections per patient was 3.7 (BRVO group) and 4.6 (CRVO group). In the BRVO group, mean baseline logMAR visual acuity was 0.80 (SD 0.38) and macular thickness was 486.9 microm (SD 138.5 microm). After 6 months, mean logMAR visual acuity improved significantly to 0.44 (SD 0.34), $p < 0.001$. Mean macular thickness decreased significantly to 268.2 microm (SD 62.5 microm), $p < 0.001$. In the CRVO group, mean baseline logMAR visual acuity was 1.13 (SD 0.21) and macular thickness was 536.4 microm (SD 107.1 microm). Mean final logMAR visual acuity improved significantly to 0.83 (SD 0.45), $p < 0.001$. Mean macular thickness decreased significantly to 326.17 microm (SD 96.70 microm), $p < 0.001$. The investigators concluded that intravitreal bevacizumab is an effective primary treatment option for macular edema due to retinal occlusions. However, multiple injections are necessary to maintain visual and anatomic improvements.

Proliferative Diabetic Retinopathy

Aflibercept,ranibizumab, and ranibizumab-eqrn are indicated for diabetic retinopathy [(Non - Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR)].[5,7]

Intravitreal bevacizumab has been studied as an adjunct to laser photocoagulation, to facilitate pars plana vitrectomy, and as a monotherapy for treatment of proliferating diabetic retinopathy (PDR).[17,59-60]

Ahmadieh et al. evaluated the effect of preoperative intravitreal bevacizumab (IVB) injections on the rate of early (≤ 4 weeks) post vitrectomy hemorrhage in patients (n = 68) with proliferative diabetic retinopathy.[18] Subjects were randomly assigned to receive either 1.25 mg IVB (n = 35) one week prior to surgery or control (n = 33). The primary outcome measure was the incidence of early post vitrectomy hemorrhage. Secondary outcome measures included changes in best-corrected visual acuity (BCVA) and IVB-related adverse events. In the intention-to-treat analysis, the incidence of post vitrectomy hemorrhage 1 week and 1 month after surgery was significantly lower in the IVB group compared with the control group ($p = 0.023$ and $p = 0.001$, respectively). Mean BCVA improved from 1.88 logarithm of minimum angle of resolution (logMAR) units in both study groups before surgery to 0.91 logMAR units and 1.46 logMAR units 1 month after vitrectomy in the IVB and control groups, respectively ($p = 0.001$). Resolution of vitreous hemorrhage was observed in 9 eyes (25.7%) after IVB injection, obviating the need for vitrectomy; the corresponding figure was 2 eyes (6.1%) in the control group ($p = 0.028$). The per-protocol analysis included 16 eyes in the IVB group and 18 eyes in the control group; post vitrectomy hemorrhage occurred less frequently 1 week and 1 month after surgery in the IVB group compared with the control group ($p = 0.033$ and $p = 0.003$, respectively). Mean improvement in BCVA 1 month after vitrectomy was -1.05 logMAR units in the IVB group and -0.42 logMAR units in the control group ($p = 0.004$). No IVB-related complication was observed in the treatment group. The investigators concluded that IVB one week before vitrectomy appears to reduce the incidence of early post vitrectomy hemorrhage in diabetic patients. The need for vitrectomy may be decreased significantly in these cases as well.

In order to evaluate the safety and effectiveness of intravitreal bevacizumab (IVB) as an adjunct to vitrectomy, di Lauro et al. performed a randomized controlled trial on 72 eyes of 68 patients affected by vitreous hemorrhage (VH) and tractional retinal detachment (TRD) which occurred as a consequence of active proliferative diabetic retinopathy (PDR).[19] Participants were assigned in a 1:1:1 ratio to receive a placebo injection or an intravitreal injection of 1.25 mg of bevacizumab, either 7 or 20 days before the vitrectomy. Complete ophthalmic examinations and color fundus photography were performed at baseline and 1, 6, 12, and 24 weeks after the surgery. In the placebo group, intraoperative bleeding occurred in 19 cases (79.1%), the use of Endo diathermy was necessary in 13 patients (54.1%), relaxing retinotomy was performed on one patient (4.1%), and in four cases (16.6%) iatrogenic retinal breaks occurred. The surgical mean time was 84 minutes (SD 12 minutes). In subjects receiving IVB seven days prior to vitrectomy, intraoperative bleeding occurred in two cases (8.3%) and the use of Endo diathermy was necessary in two patients (8.3%). No iatrogenic breaks occurred during the surgery. The surgical mean time was 65 minutes (SD 18 minutes). For those subjects receiving IVB twenty days before vitrectomy, intraoperative bleeding occurred in three cases (12.5%), the use of Endo diathermy was necessary in three patients (1.5%), and an iatrogenic break occurred in one patient (4.1%) while the delamination of fibrovascular tissue was being performed. The surgical mean time was 69 minutes (SD 21 minutes). The average difference in the surgical time was statistically significant between the placebo group and the 7-day IVB group ($p = 0.025$), and between the placebo group and the 20-day IVB group ($p = 0.031$). At completion of surgery, the retina was completely attached in all eyes. The researchers concluded that best surgical results are achieved performing the IVB 7 days preoperatively.

Neovascular Glaucoma & Rubeosis Iridis

Ghosh et al. present the outcome of concomitant treatment with diode laser cyclophotocoagulation (CPC) and intravitreal bevacizumab (IVB) in painful eyes with poor visual potential in a case series of consecutively diagnosed neovascular glaucoma (NVG).[20] Twelve patients (14 eyes) were treated with CPC and concurrent IVB 0.05 mL (1.25 mg). Study endpoints were lowering of intraocular pressure (IOP), regression of anterior segment neovascularization, and resolution of pain. The mean preoperative IOP was 42.1 ±11.4 and was lowered to 16.6 ±7.1 mmHg at 1-month post-CPC. Anterior segment neovascularization regressed dramatically within 1 week of IVB in 12 eyes. Thirteen eyes reported persistent relief of ocular pain at 6 months following treatment. The authors concluded that combined IVB and CPC treatment for NVG provides rapid control of anterior segment neovascularization and may lead to improved symptomatic relief and IOP control.

To evaluate the effect of intravitreal bevacizumab injection in cases of neovascular glaucoma, Ghanem et al. studied 16 eyes of 16 patients with rubeosis iridis and secondary glaucoma.[21] Patients were administered an intravitreal injection of bevacizumab (2.5 mg) and were followed for 2 months. Partial or complete regression of iris neovascularization was noted 1 week after injection of bevacizumab. Reproliferation of new vessels was detected in 25% of the cases after 2 months. The mean intraocular pressure (IOP) before injection was 28 ±9.3 mm Hg under topical β-blocker and systemic acetazolamide. One week after injection, the IOP decreased to 21.7 ±11.5 mm Hg (5 cases without anti-glaucoma drugs, 6 cases with topical β-blocker and 5 cases with both topical β-blocker and systemic acetazolamide). The authors concluded that intravitreal bevacizumab injection leads to regression of iris neovascularization with subsequent drop of IOP in eyes with neovascular glaucoma.

Moraczewski et al. report a retrospective, non-comparative, consecutive, interventional case series of the treatment of neovascular glaucoma with intravitreal bevacizumab in 56 eyes at the University of Miami, Florida, Bascom Palmer Eye Institute.[22] The authors' impression both clinically and from a review of available literature is that early diagnosis and treatment of NVG with intravitreal bevacizumab may lead to improved outcomes. If bevacizumab is administered when the anterior chamber angle is open at the time of NVG diagnosis, it is postulated that IOP may be controlled without the need for surgical procedures. This study underscores the concept that, if followed long enough, the majority of patients regardless of initial angle status and initial IOP lowering, will require surgical intervention for the control of IOP. The cumulative proportion of eyes requiring a second injection of bevacizumab increases linearly with time and is related to recurrent or persistent iris neovascularization or angle neovascularization. Bevacizumab induced regression of neovascularization is often temporary, and recurrence is possible, while panretinal photocoagulation provides a more permanent reduction of the ischemic angiogenic stimulus. At this institution, treatment of NVG with intravitreal bevacizumab is the standard of care, including: 1) Administering intravitreal bevacizumab at the time of diagnosis of NVG; 2) Administering panretinal photocoagulation shortly thereafter, and; 3) lowering IOP medically and via placement of a drainage device if necessary.

Choroidal Neovascularization

Choroidal Neovascularization Secondary to Pathologic Myopia

Ranibizumab, ranibizumab-eqrn, and ranibizumab-nuna are indicated for the treatment of choroidal neovascularization secondary to pathologic myopia.[7, 57, 77]

Cha DM et al compared the long-term efficacy of versus bevacizumab for myopic choroidal neovascularization (CNV) in retrospective, multicenter, comparative, non-randomized study in 64 consecutive patients [ranibizumab (n = 22) or bevacizumab (n = 42 patients)].[9] Best-corrected visual acuity (BCVA) and central foveal thickness (CFT) on optical coherence tomography were evaluated before and after treatment. All the patients were followed for at least 12 months. BCVA (logarithm of the minimal angle of resolution) improved from 0.63 ±0.30 to 0.43 ±0.27, 0.41 ±0.37, 0.40 ±0.39, 0.39 ±0.43, and 0.39 ±0.42 at 1, 2, 3, 6, and 12 months after treatment in the ranibizumab group, and from 0.67 ±0.28 to 0.52 ±0.31, 0.49 ±0.31, 0.47 ±0.31, 0.42 ±0.32, and 0.46 ±0.43 in the bevacizumab group (all $p < 0.05$ compared with baseline BCVA in each group). CFT decreased by 20.21%, 19.58%, and 22.43% from the baseline 304 ±76 μm at 3, 6, and 12 months after treatment in the former group, and by 15.20%, 15.67%, and 15.56% from the baseline 297 ±62 μm in the latter group (all $p < 0.05$ compared with baseline CFT in each group). BCVA improvement and CFT reduction did not statistically differ when compared at the same periods from treatment between 2 groups. Neither ocular nor systemic safety problems appeared during follow up. Researchers concluded that the outcomes of the study showed a similar functional and anatomical improvement after treatment for ranibizumab and bevacizumab in patients with myopic CNV over a 12 - month follow - up period.

In a phase III, 12-month, randomized, double-masked, multicenter, active-controlled study, researchers evaluated the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients (n = 277) with visual impairment due to myopic choroidal neovascularization (CNV).[11] Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n = 106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n = 116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n = 55). Primary outcomes measured included average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3 (primary) and 6, mean BCVA change and safety over 12 months. Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 (group I: + 10.5, group II: + 10.6 vs. group III: + 2.2 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; both p < 0.0001). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: + 11.7 vs. group I: + 11.9 ETDRS letters; p < 0.00001). Mean BCVA change from baseline to month 12 was + 13.8 (group I), + 14.4 (group II), and + 9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred. CONCLUSIONS: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was noninferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.

Yoon et al. compared visual outcomes after treatment with intravitreal anti - vascular endothelial growth factor (anti-VEGF) injection or photodynamic therapy (PDT) in patients with myopic choroidal (CNV).[23] One hundred and forty-two eyes of 128 consecutive patients treated with anti-VEGF (ranibizumab or bevacizumab) and/or PDT for myopic choroidal neovascularization were retrospectively reviewed. Patients were categorized into 3 groups: PDT (51 eyes), anti - VEGF (63 eyes), and a combination group (PDT with anti-VEGF) (28 eyes). Corrected visual acuity values at baseline and 3, 6, 9, and 12 months after treatment were compared. The anti-VEGF group showed significant postoperative improvement in visual acuity compared with the PDT and combination groups (p = 0.01 and 0.04, respectively). The anti-VEGF group demonstrated visual improvement from baseline at every follow-up visit after treatment (p = 0.04, 0.02, 0.01, and 0.002, respectively). The anti-VEGF group showed visual improvement (Snellen equivalent) from 0.57 logarithm of the minimum angle of resolution (0.27) to 0.33 logarithm of the minimum angle of resolution (0.47) (p = 0.01). Furthermore, 98.4% of patients in the anti-VEGF group and 92.8% of those in the combination group lost < 15 letters from baseline visual acuity compared with 72.6% in the PDT group (p = 0.001 and 0.02, respectively). In the anti-VEGF group, 39.7% of patients improved from baseline by 15 or more letters compared with 17.7% in the PDT group (p = 0.02) and 21.4% in the combination group (p = 0.07). Based on these findings, the investigators concluded that intravitreal anti - VEGF injection is superior to PDT alone or a combination of PDT with anti - VEGF for treating myopic choroidal neovascularization.

Vadalà et al. assessed the efficacy and safety of ranibizumab in the treatment of choroidal neovascularization (CNV) caused by pathologic myopia (PM) in a prospective, multicenter, interventional case series.[24] Forty eyes of 39 consecutive patients with PM and CNV were treated with 'on demand' intravitreal injection of ranibizumab 0.5 mg. Final best corrected visual acuity (BCVA) and its change from baseline were the main outcome measures. Median follow-up was 13.3 ±2 (range 12 - 18) months. Fifteen eyes (37.5%) had previously been treated with photodynamic therapy (PDT). The mean baseline logarithm of the minimum angle of resolution (logMAR) BCVA was 0.68 ±0.34 (Snellen equivalent 20/131) and 21 ±6 letters. The final mean logMAR BCVA was 0.27 ±0.2 (p = 0.008) (20/42) and 40.5 ±14 letters (p = 0.01). Mean final VA improved in 82.5% of patients, in 60% by 3 or more lines (median number of lines gained 2.9). Age and previous PDT did not influence the results (p > 0.05). The mean number of injections was 2.8 ±1.2 (range 1 - 6). No ocular or systemic side effects were observed. Ranibizumab was an effective treatment for stabilizing and improving vision with a low number of injections in 92.5% of patients with myopic CNV in a long - term follow - up.

Choroidal Neovascularization Secondary to Angioid Streaks/Pseudoxanthoma Elasticum

Finger et al. investigated the long - term effectiveness of intravitreal bevacizumab for treating active choroidal neovascularization in pseudoxanthoma elasticum (PXE).[25] Fourteen patients (16 eyes) received intravitreal bevacizumab (1.5 mg), were evaluated monthly, and received further treatments depending on disease activity. Examinations included best-corrected visual acuity, bio microscopy, optical coherence tomography, fluorescein angiography and indocyanine green angiography, fundus autofluorescence, and digital fundus photography. Areas of atrophy of the retinal pigment epithelium and retinal fibrosis were quantified using semiautomated detection on fundus autofluorescence images. Mean age of the cohort was 55 ±13 years, and mean best-corrected visual acuity at baseline was 20/80 (logarithm of the minimum angle of resolution, 0.56, SD, 0.51). At last follow-up, after an average of 6.5 ±5.7 injections over 28 months, best-corrected visual acuity was 20/40 (logarithm of the minimum angle of resolution, 0.31, SD, 0.32; p = 0.04). Central retinal thickness was reduced from 254 ±45 µm to 214 ±40 µm (p = 0.035). The size of retinal pigment epithelial atrophy and retinal fibrosis measured on fundus autofluorescence images increased in both the treated eye and the fellow eye (p < 0.05). Best-corrected visual acuity of patients with early disease compared with that of those with advanced disease improved significantly more over the treatment course (20/25 vs. 20/63; p = 0.008). The authors reported that intravitreal bevacizumab therapy demonstrates long-term effectiveness by preserving function in advanced disease and improving function in early disease. Best results of treating active choroidal neovascularization in PXE are achieved when treatment starts as early in the disease as possible.

El Matri et al. evaluated the efficacy and safety of intravitreal bevacizumab for the treatment of choroidal neovascularization associated with angioid streaks in a retrospective case series of eighteen eyes of 17 patients treated between October 2006 and May 2008.[26] Ophthalmic evaluation, including best corrected visual acuity (BCVA), slit lamp biomicroscopic examination, optical coherence tomography (OCT) and fluorescein angiography, was performed before and after treatment. Retreatment was allowed every 4 - 6 weeks in case of persistent symptoms or CNV activity on OCT. Main outcome measures were changes in BCVA and central retinal thickness on OCT. The mean number of injections was 4.8 at one year. Twelve eyes (66.6%) received five injections or more. The mean BCVA at baseline was 20⁄80 (range 20⁄400 to 20⁄32) and improved to 20⁄44 (range 20⁄160 to 20⁄20) at 1 year (p = 0.014). The BCVA improved by three or more lines in eleven eyes (61.11%) and remained within two lines of baseline in seven eyes (38.8%). Mean central retinal thickness was 404.2 µm (range 160 - 602 µm) at baseline and decreased to 300.5 µm (range 150 - 523 µm) at 1 year (p = 0.022). No ocular or systemic complications were noted. The 1-year outcomes suggest intravitreal bevacizumab to be a promising treatment for CNV associated with angioid streaks, resulting in both functional and anatomical improvements. Repeated injections are needed to maintain these results. Further long - term studies are required to confirm these findings.

Mimoun et al. retrospectively analyzed the efficacy of intravitreal ranibizumab injections for the management of choroidal neovascularization (CNV) in patients with angioid streaks.[27] In a nonrandomized, double-center, retrospective, interventional case series, patients were treated with intravitreal ranibizumab injections (0.5 mg/0.05 mL). The primary end point was the percentage of eyes with stable or improved visual acuity at the end of follow-up. Secondary end points were the percentage of eyes with stable or decreased macular thickness on optical coherence tomography and the percentage of eyes with persistent leakage on fluorescein angiography at the last follow-up examination. Thirty-five eyes of 27 patients were treated with repeated intravitreal ranibizumab injections (mean, 5.7 injections; range, 2 to 14 injections) for a mean of 24.1 months (range, 6 to 37 months). At the end of follow - up, visual acuity was stabilized or improved in 30 (85.7%) of 35 eyes. Macular thickness had stabilized or decreased in 18 (51.5%) of 35 eyes. At the last follow-up examination, on fluorescein angiography, no further leakage was observed in 23 (65.7%) of 35 eyes.

Myung et al. reported long-term results of intravitreal anti - vascular endothelial growth factor therapy in the management of choroidal neovascularization in patients with angioid streaks associated with pseudoxanthoma elasticum.[28] Nine eyes of nine consecutive patients were managed with either bevacizumab 1.25 mg/0.05 mL or ranibizumab 0.5 mg/0.05 mL. The main outcome measures were visual acuity and greatest lesion height as measured by optical coherence tomography. During the mean follow-up period of 28.6 months, eyes received an average of 8.4 injections. At baseline, the mean visual acuity was 20/368 (median, 20/60) and improved to 20/281 (median, 20/40) at the last visit (p = 0.14). Visual acuity either improved or stabilized in all 9 eyes (100%). Serial optical coherence tomography measurements showed a mean of 353 mum at baseline and decreased to 146 mum at the last visit (p = 0.005). No complications were noted. These long-term results support the use of intravitreal anti - vascular endothelial growth factor therapy for the management of choroidal neovascularization in patients with pseudoxanthoma elasticum.

Choroidal Neovascularization Secondary to Ocular Histoplasmosis Syndrome (OHS)

Cionni et al. conducted a retrospective, comparative case series of 150 eyes in 140 patients treated with intravitreal bevacizumab (IVB) for choroidal neovascularization (CNV) secondary to presumed ocular histoplasmosis syndrome (POHS).[29] Subjects received either IVB monotherapy (n = 117 eyes) or combination IVB and verteporfin photodynamic therapy (IVB/PDT) (n = 34 eyes). Visual acuity (VA) at 12 and 24 months was analyzed. Secondary outcome measures included the number of injections per year and treatment-free intervals. For all patients, the average pretreatment logarithm of minimum angle of resolution (logMAR) was 0.63 (Snellen equivalent 20/86) with a 12-month logMAR VA of 0.45 (Snellen equivalent 20/56) and a 24-month logMAR VA of 0.44 (Snellen equivalent 20/55). The mean follow-up was 21.1 months with an average of 4.24 IVB injections per year. There was no significant difference in initial VA, VA at 12 months, VA at 24 months, or number of eyes with a 3-line gain between the IVB monotherapy and IVB/PDT groups. Thirty-eight percent (39/104) of eyes gained 3 lines or more, and 81.2% (84/104) of subjects had maintained or improved their starting VA at 1 year. The proportion of subjects maintaining a 3-line gain in VA was relatively preserved at 2 years (29.8%, 17/57) and 3 years (30.3%, 10/32) follow-up. There was no increase in the proportion of subjects losing 3 lines or more over 3 years of follow-up. The authors concluded that there is no significant difference in VA outcomes between IVB monotherapy versus IVB/PDT combination therapy. The use of IVB alone or in combination with PDT results in significant visual stabilization in the majority of patients with CNV secondary to POHS.

Shadlu et al., conducted a retrospective chart review of 28 eyes of 28 patients who underwent intravitreal administration of bevacizumab for treatment of choroidal neovascularization secondary to OHS.[30] The mean follow-up period was 22.43 weeks with patients receiving an average of 1.8 intravitreal injections. The investigators found that the treatment was of benefit to improve or stabilize the visual acuity in a significant majority (24 eyes, 85.7%) of patients with neovascular complications of OHS.

In a retrospective chart review of 54 eyes, Nielsen et al. studied the effect of treatment with intravitreal anti-VEGF therapy for choroidal neovascularization in ocular histoplasmosis syndrome.[31] Either bevacizumab or ranibizumab were administered on an average of 4.5 injections per patient per year of follow-up. Mean visual acuity improved from 20/53 to 20/26 over an average of 26.8 months. Vision loss was seen in only three eyes with loss limited to a single line of vision. Patients experienced no serious complications from treatment. Long-term intravitreal anti-VEGF therapy with bevacizumab or ranibizumab is beneficial in treatment of choroidal neovascularization in ocular histoplasmosis syndrome.

There are additional small, published studies and reports that provide support for the use of both bevacizumab and ranibizumab to treat choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS).[32-46]

Retinopathy of Prematurity

Geloneck et al. conducted a prospective, stratified, randomized, controlled, masked, multicenter clinical trial examining the efficacy of bevacizumab versus laser therapy for the treatment of zone I or zone II posterior stage 3 + retinopathy of prematurity (ROP) or aggressive posterior ROP (APROP) in preterm infants. Infants either received intravitreal bevacizumab or laser therapy, randomized by infant, also underwent cycloplegic retinoscopic refraction at an average age of 2.5 years. Pediatric and vitreoretinal ophthalmologists in 15 level 3 neonatal intensive care units in academic centers participated. Of the originally enrolled 150 infants (300 eyes) in the clinical trial, 13 infants (26 eyes) died (6 received intravitreal bevacizumab; 7 received laser) and 19 eyes had intraocular surgery (6 infants bilaterally). Thus, 45 eyes (19 infants bilaterally) were excluded, leaving 131 infants (255 eyes, including 21 eyes that received a successful second treatment for recurrence). The primary outcomes were spherical equivalent refractive outcomes and their distribution by ROP zone and treatment. Of the 131 eligible infants, refractions were available for only 109 (83.2%) and 211 of 255 eyes (82.7%). Mean (SD) spherical equivalent refractions were as follows: zone I, -1.51 (3.42) diopters (D) in 52 eyes that received intravitreal bevacizumab and -8.44 (7.57) D in 35 eyes that received laser treatment ($p < .001$); and zone II posterior, -0.58 (2.53) D in 58 eyes that received intravitreal bevacizumab and 5.83 (5.87) D in 66 eyes that received laser treatment ($p < .001$). Very high myopia (-8.00 D) occurred in zone I in 2 of 52 (3.8%) eyes that received intravitreal bevacizumab and in 18 of 35 (51.4%) eyes that received laser treatment ($p < .001$). Very high myopia occurred in zone II posterior in 1 of 58 (1.7%) eyes that received intravitreal bevacizumab and in 24 of 66 (36.4%) eyes that received laser treatment ($p < .001$). The authors concluded that more very high myopia was found in eyes that received laser treatment than in eyes that received intravitreal bevacizumab. This difference is possibly related to anterior segment development that is present with intravitreal bevacizumab but minimal or absent following laser treatment.

In a prospective, controlled, randomized, stratified, multicenter trial, Mintz-Hittner et al. studied the efficacy of intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3 + retinopathy of prematurity (ROP). One hundred fifty infants were randomized to receive intravitreal bevacizumab (0.625 mg/0.025 ml) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of ROP in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. Of the 150 infants, 143 survived to 54 weeks. The 7 infants who died were not included in the primary outcome analysis. ROP recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%]), $p = 0.002$). A significant treatment effect was found for zone I ROP ($p = 0.003$) but not for zone II disease ($p = 0.27$). The authors concluded that intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3 + retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina.

Professional Societies

The Royal College of Ophthalmologists released a scientific statement on bevacizumab use in medical ophthalmology in December 2011.[52] A working group of the Scientific Committee of the College considered the published literature relating to the efficacy and safety of bevacizumab (Avastin) and ranibizumab (Lucentis) in the treatment of the neovascular form of age-related macular degeneration (AMD). The College view is that the current published literature is consistent with the conclusion that bevacizumab and ranibizumab are equally effective in the treatment of neovascular age - related macular degeneration and there is no convincing evidence of a clinically significant difference in the incidence of serious adverse events between the two groups. Since then, the College has made a revised statement stating there is clear evidence that, despite the lack of a license, bevacizumab is a safe and effective drug for the treatment of neovascular AMD.

According to the American Society of Retina Specialists (ASRS), bevacizumab is being used by a large number of retinal specialists who believe that it is reasonable and medically necessary for the treatment of some patients with macular edema and abnormal retinal and iris neo-vascularization.[53]

The American Academy of Ophthalmology (AAO) supports the use of intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.[54]

In their Diabetic Retinopathy Preferred Practice Pattern, the AAO states that intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have been shown to be an effective treatment for center-involving diabetic macular edema and also as an alternative therapy for proliferative diabetic retinopathy.[55]

In their Retinal Vein Occlusions Preferred Practice Pattern, the AAO states that Macular edema may complicate both CRVOs and BRVOs. The safest treatment for the associated macular edema is the use of anti - vascular endothelial growth factors (anti-VEGFs). Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation in BRVO has a potential role in treatment.[65]

In 2014 the AAO released a clinical statement entitled ‘Verifying the Source of Compounded Bevacizumab for Intravitreal Injections – 2014.[56] Their recommendations are as follows:
To reduce the risk of infection to patients, the following steps are recommended when sourcing bevacizumab (Avastin) for intravitreal injections:

- Select a compounding pharmacy accredited by the PCAB, which adheres to quality standards for aseptic compounding of sterile medications (USP <797>). Note: PCAB does not track or keep record of specific medications that a pharmacy can compound.
- Record the lot numbers of the medication in the patient’s record and in a logbook or spreadsheet in case the numbers are needed for tracking later.

In addition, Ophthalmic Mutual Insurance Company’s (OMIC) Risk Management Recommendations for Preparations of Avastin specify:

- Using proper aseptic technique during the preparation and administration of the injection.
- “Credentialing” the compounding pharmacy where you send the prescription for intravitreal bevacizumab (Avastin) by:
    - Verifying that the compounding pharmacy is licensed/registered in the state it is dispensing.
    - Inquiring how the pharmacy compounds bevacizumab (Avastin). (The pharmacy should state that it complies with USP <797>.)
    - Asking the pharmacy if it is an accredited compounding pharmacy.
- Requesting that the compounding pharmacy prepare the medication for ophthalmic use, confirms the dose and sterility, identifies a syringe suitable for the protein, provides storage and “beyond-use” instructions, and indicates the vial lot number.

The informed consent process with the patient should include a discussion of the risks and benefits of treatment and treatment alternatives where the off-label status of bevacizumab (Avastin) for neovascular AMD should be included in the discussion.

Technical Assessments

Retinopathy of Prematurity

In 2017, the American Academy of Ophthalmology (AAO) published an Ophthalmic Technology Assessment (OTA) to review and evaluate the evidence on the ocular safety and efficacy of anti-VEGF agents for the treatment of retinopathy of prematurity (ROP) compared with laser photocoagulation therapy. The OTA compared retinal structural outcomes, visual and refractive outcomes, ocular complications and systemic morbidity. The OTA included 13 citations, out of 37 citations that were deemed clinically relevant for review. A panel methodologist assigned ratings (I to III) to the selected articles according to the level of evidence. Of the 13 citations, articles on 5 randomized clinical trials provided level II evidence supporting the use of anti-VEGF agents, either as monotherapy or in combination with laser therapy. The primary outcome for these articles included recurrence of ROP and the need for retreatment (3 articles), retinal structure (2 articles), and refractive outcome (1 article). Seven articles were comparative case series that provided level III evidence. The primary outcomes included the effects of anti-VEGF treatment on development of peripheral retinal vessels (1 article), refractive outcomes (1 article), or both structural and refractive or visual outcomes (5 articles). The authors concluded that the recent literature suggests that the short-term efficacy and ocular safety are similar to those of laser photocoagulation therapy. The advantages of using anti-VEGF agents include less time to administer treatment, faster improvement in plus disease and regression of ROP, less treatment-related destruction of the peripheral retina, and a lower likelihood of myopia, high myopia, and astigmatism. The disadvantages of anti-VEGF therapy include a longer required follow-up as a result of delayed or incomplete vascularization, significant rates of recurrence and the potential need for later retreatment, and the possibility of developmentally abnormal or atypical retinal vascular patterns. With respect to the severity of ROP, there seems to be several potential advantages for primary treatment with anti-VEGF agents for eyes with zone I ROP or eyes with aggressive posterior ROP. However, there is no clear advantage over laser photocoagulation for eyes with more peripheral zone II ROP, and there is no clear advantage for first-line combination therapy.

In 2018, a Cochrane review was published to evaluate the efficacy and safety of anti-VEGF drugs when used either as monotherapy (without concomitant cryotherapy or laser therapy) or in combination with planned cry/laser therapy in preterm infants with type 1 retinopathy of prematurity (ROP), (defined as zone I any stage with plus disease, zone I stage 3 with or without plus disease, or zone II stage 2 or 3 with plus disease). The review included randomized or quasi-randomized controlled trials that evaluated the efficacy or safety of administration, or both, of anti-VEGF agents compared with conventional therapy in preterm infants with ROP.

Six trials involving a total of 383 infants fulfilled the inclusion criteria. Five trials compared intravitreal bevacizumab (n = 4) or ranibizumab (n = 1) with conventional laser therapy (monotherapy), while the sixth study compared intravitreal pegaptanib plus conventional laser therapy with laser/cryotherapy (combination therapy). When used as monotherapy, bevacizumab/ranibizumab did not reduce the risk of complete or partial retinal detachment (3 studies; 272 infants; risk ratio (RR) 1.04, 95% confidence interval (CI) 0.21 to 5.13; risk difference (RD) 0.00, 95% CI -0.04 to 0.04; very low-quality evidence), mortality before discharge (2 studies; 229 infants; RR 1.50, 95% CI 0.26 to 8.75), corneal opacity requiring corneal transplant (1 study; 286 eyes; RR 0.34, 95% CI 0.01 to 8.26), or lens opacity requiring cataract removal (3 studies; 544 eyes; RR 0.15, 95% CI 0.01 to 2.79). The risk of recurrence of ROP requiring retreatment also did not differ between groups (2 studies; 193 infants; RR 0.88, 95% CI 0.47 to 1.63; RD -0.02, 95% CI -0.12 to 0.07; very low-quality evidence). Subgroup analysis showed a significant reduction in the risk of recurrence in infants with zone I ROP (RR 0.15, 95% CI 0.04 to 0.62), but an increased risk of recurrence in infants with zone II ROP (RR 2.53, 95% CI 1.01 to 6.32). Pooled analysis of studies that reported eye-level outcomes also revealed significant increase in the risk of recurrence of ROP in the eyes that received bevacizumab (RR 5.36, 95% CI 1.22 to 23.50; RD 0.10, 95% CI 0.03 to 0.17). Infants who received intravitreal bevacizumab had a significantly lower risk of refractive errors (very high myopia) at 30 months of age (1 study; 211 eyes; RR 0.06, 95% CI 0.02 to 0.20; RD -0.40, 95% CI -0.50 to -0.30; low - quality evidence). When used in combination with laser therapy, intravitreal pegaptanib was found to reduce the risk of retinal detachment when compared to laser/cryotherapy alone (152 eyes; RR 0.26, 95% CI 0.12 to 0.55; RD -0.29, 95% CI -0.42 to -0.16; low-quality evidence). The incidence of recurrence of ROP by 55 weeks' postmenstrual age was also lower in the pegaptanib + laser therapy group (76 infants; RR 0.29, 95% CI 0.12 to 0.7; RD -0.35, 95% CI -0.55 to -0.16; low-quality evidence). There was no difference in the risk of perioperative retinal hemorrhages between the two groups (152 eyes; RR 0.62, 95% CI 0.24 to 1.56; RD -0.05, 95% CI -0.16 to 0.05; very low-quality evidence). However, the risk of delayed systemic adverse effects with any of the three anti-VEGF drugs is not known.

The authors concluded that intravitreal bevacizumab/ranibizumab, when used as monotherapy, reduces the risk of refractive errors during childhood but does not reduce the risk of retinal detachment or recurrence of ROP in infants with type 1 ROP. Bevacizumab/ranibizumab can potentially result in higher risk of recurrence requiring retreatment in those with zone II ROP. Intravitreal pegaptanib, when used in conjunction with laser therapy, reduces the risk of retinal detachment as well as the recurrence of ROP in infants with type 1 ROP. However, the quality of the evidence was very low too low for most outcomes due to risk of detection bias and other biases. The effects on other critical outcomes and, more importantly, the long-term systemic adverse effects of the drugs are not known. Insufficient data precludes strong conclusions favoring routine use of intravitreal anti-VEGF agents - either as monotherapy or in conjunction with laser therapy - in preterm infants with type 1 ROP.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Avastin (Bevacizumab)

The statements below are for information only. Oncology indications for bevacizumab are listed in the NCCN Drugs & Biologics Compendium.

- Bevacizumab, in combination with intravenous 5 – fluorouracil - based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.[57]
- Bevacizumab, in combination with fluoropyrimidine - irinotecan - or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients with metastatic colorectal cancer who have progressed on a first - line bevacizumab-containing regimen.[57]
- Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.[57]
- Bevacizumab for treatment of recurrent glioblastoma.[57]
- Bevacizumab, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.[57]
- Bevacizumab, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.[57]
- Bevacizumab, in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent, is indicated for the treatment of platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[57]
- Bevacizumab, in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.[57]
- Bevacizumab, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than 2 prior chemotherapy regimens.[57]

Beovu (Brolucizumab)

Brolucizumab is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).[71]

Byooviz (Ranibizumab-Nuna)

Ranibizumab-nuna is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following vein occlusion (RVO, and myoptic choroidal neovascularization (mCNV).[77]

Cimerli (Ranibizumab-Eqrn)

Ranibizumab-eqrn is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), and myopic choroidal neovascularization (mCNV).[82]

Eylea (Aflibercept)

Aflibercept is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy.[5]

Lucentis (Ranibizumab)

Ranibizumab is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy, and myopic choroidal neovascularization (mCNV).[7]

Macugen (Pegaptanib)

Pegaptanib is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD).[6]

Vabysmo (Faricimab)

Faricimab is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME).[76]

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Policy History/Revision Information

Date	Summary of Changes

12/01/2022	**Coverage Rationale**
	• Revised list of applicable vascular endothelial growth factor (VEGF) inhibitors and dual VEGF/angiopoietin-2 (Ang-2) inhibitors; added Cimerli™ (ranibizumab-eqrn)
	• Added language to indicate Cimerli™ (ranibizumab-eqrn) is proven and medically necessary for the treatment of:
	  ○ Myopic choroidal neovascularization (mCNV)
	  ○ Diabetic macular edema (DME)
	  ○ Diabetic retinopathy (DR)
	  ○ Macular edema following retinal vein occlusion (RVO)
	  ○ Neovascular age-related macular degeneration (AMD)
	Applicable Codes
	• Added HCPCS codes C9399, J3490, and J3590
	• Identified the ICD-10 diagnosis codes that apply to Cimerli (HCPCS codes C9399, J3490, and J3590)
	• Added *Maximum Allowed Frequencies* for Cimerli (ranibizumab-eqrn):
	  ○ Myopic choroidal neovascularization (mCNV): The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days) for up to 3 months and may be retreated if necessary; maximum of 12 doses per year per eye
	  ○ Diabetic macular edema (DME) and diabetic retinopathy (DR): The recommended dose is 0.3 mg to affected eye(s) once a month (approximately every 28 days); maximum of 12 doses per year per eye
	  ○ Macular edema following retinal vein occlusion (RVO): The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days); maximum of 12 doses per year per eye
	  ○ Neovascular (wet) age-related macular degeneration (AMD): The recommended dose is 0.5 mg to affected eye(s) once a month (approximately every 28 days) and treatment may be reduced to 3 once monthly doses, followed by an average of 4 to 5 injections over the subsequent 9 months; maximum of 12 doses per year per eye
	Supporting Information
	• Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information
	• Archived previous policy version CS2022D0042Y

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.