INTRAVITREAL ANGIOGENESIS INHIBITORS FOR RETINAL VASCULAR CONDITIONS

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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INTRAVITREAL ANGIOGENESIS INHIBITORS FOR RETINAL VASCULAR CONDITIONS (cont.)

Description:

Angiogenesis inhibitors bind to and inhibit vascular endothelial growth factor (VEGF) to prevent the formation of new blood vessels. VEGF inhibitors are also referred to as anti-vascular endothelial growth factors (anti-VEGF) or angiogenesis inhibitors.

The anti-VEGF agents Avastin® (bevacizumab), EYLEA™ (aflibercept), Lucentis™ (ranibizumab) and Macugen® (pegaptanib) are used to treat choroidal neovascularization associated with age-related macular degeneration (AMD) and have been investigated for the treatment of disorders of retinal circulation (e.g., diabetic macular edema [DME], diabetic retinopathy, macular edema following retinal vein occlusion, retinopathy of prematurity [ROP]).

Avastin is approved for the treatment of metastatic cancers including colorectal and lung cancer. Avastin is the full-length monoclonal antibody from which the Lucentis fragment is derived. Use of Avastin is included in the American Academy of Ophthalmology (AAO) preferred practice pattern for Age-Related Macular Degeneration (AMD). Although prospective randomized trials with bevacizumab for AMD have not yet been conducted, community experience demonstrating the beneficial impact on vision have resulted in acceptance as standard in the medical community.

Diabetic Retinopathy:
At its earliest stage (nonproliferative retinopathy), microaneurysms occur. With disruption of the blood-retinal barrier, macular retinal vessels become permeable, leading to exudation of serous fluid and lipids into the macula (macular edema). As the disease progresses, blood vessels that provide nourishment to the retina are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from vitreous hemorrhage. Moderate vision loss can also arise from macular edema (fluid accumulating in the center of the macula) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main blinding complication of diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

Central and Branch Retinal Vein Occlusions:
Retinal vein occlusions are classified by whether there is a central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO). CRVO is also categorized as ischemic or non-ischemic. Ischemic CRVO is associated with a poor visual prognosis, with macular edema and permanent macular dysfunction occurring in virtually all individuals. Non-ischemic CRVO has a better visual prognosis, but many individuals will have macular edema, and it may convert to the ischemic type within 3 years. Most of the vision loss associated with CRVO results from the main complications, macular edema and intraocular neovascularization. BRVO is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more commonly than CRVOs. Macular edema is the most significant cause of central visual loss in BRVO.
INTRAVITREAL ANGIOGENESIS INHIBITORS FOR RETINAL VASCULAR CONDITIONS (cont.)

Description: (cont.)

Retinopathy of Prematurity:
This is a neovascular retinal disorder that primarily affects premature infants of low birth weight. It is one of the most common causes of childhood blindness in the United States. Typically, retinal vascularization begins at the optic nerve when the eye begins to develop (16 weeks’ gestation) and reaches the edge of the retina at 40 weeks’ gestation. If an infant is born prematurely, normal vessel growth may stop, followed by neovascularization at the interface between the vascular and avascular retinal areas.

Other Retinal Vascular Conditions:
Other retinal vascular conditions that have been investigated for treatment with VEGF inhibitors are cystoid macular edema resulting from vasculitis, Coats disease, Eales disease, idiopathic macular telangiectasia type II, neovascularization of the iris/neovascularization of the angle/neovascular glaucoma, pseudoxanthoma elasticum, radiation retinopathy, retinal neovascularization, rubeosis, Von Hippel- Lindau and vitreous hemorrhage secondary to retinal neovascularization.

Criteria:

For Avastin, Eylea, Lucentis and Macugen for choroidal vascular conditions, see BCBSAZ Medical Coverage Guideline #O718, “Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions”.

- Intravitreal injection of Avastin (bevacizumab), Eylea (aflibercept) or Lucentis (ranibizumab) is considered *medically necessary* with documentation of **ANY** of the following:
  1. Diabetic macular edema
  2. Diabetic retinopathy in individuals with DME
  3. Macular edema following retinal vein occlusion
  4. Neovascular glaucoma
  5. Rubeosis (neovascularization of the iris)

- Intravitreal injection of Avastin (bevacizumab), Eylea (aflibercept) or Lucentis (ranibizumab) for the treatment of all other retinal vascular disorders not previously listed is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.
INTRAVITREAL ANGIOGENESIS INHIBITORS FOR RETINAL VASCULAR CONDITIONS (cont.)

Criteria: (cont.)

- Intravitreal injection of Macugen (pegaptanib) for treatment of retinal vascular disorders is considered experimental or investigational based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Branch retinal vein occlusion (BRVO)
- Central retinal vein occlusion (CRVO)
- Diabetic macular edema
- Proliferative diabetic retinopathy

Resources:

Literature reviewed 04/25/17. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 04/16/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

INTRAVITREAL ANGIOGENESIS INHIBITORS FOR RETINAL VASCULAR CONDITIONS (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Dílí kwe’ é atah nilnigíí Blue Cross Blue Shield of Arizona haada yitt’éego bíná’ídiłkidgo éí doodago Háída bíjá aniyeedígíí t’aadoo le’é yina’ídiłkidgo bee haaz’áânii hólo díí t’áa haazad’ëhí háká a’dooowolgo bee haaz’á doo bąąh ilinígóó. Atá’ halné’ígií koj’ bíchj’ hódiilihí 877-475-4799.

Chinese: 您，或是您正在幫助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話，在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعدك أسماء بخصوص خصوصيات الضرورية بلغتك، من دون أي تكلفة للتحدث مع متبرع المصلب ب 877-475-4799.
INTRAVITREAL ANGIGENESIS INHIBITORS FOR RETINAL VASCULAR CONDITIONS (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay may mga katawagan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통해서 매기기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если вы или лицо, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言葉でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799までお電話ください。

Farsi: اگر شما یا کمککننده یا هرکسی می‌خواهید در مورد اطلاعاتی که در مورد Blue Cross Blue Shield of Arizona وارد می‌کنید، در مورد که کمک می‌شود، سوال‌پردازی را بپذیرید، و درخواست‌ها را داشته باشید. در مورد‌ها که به گوش‌هایتان وارد می‌کنید، 877-475-4799 می‌توانید به آنها پاسخگو شوید.

Assyrian: Blue Cross Blue Shield of Arizona ئی‌وی‌سی یکیی دیگری رو که بکایی کردن جخش‌ها و پاسخگویی به سوال‌ها که به جوانان وارد می‌کنید، در مورد‌ها که به گوش‌هایتان وارد می‌کنید، 877-475-4799 می‌توانید به آنها پاسخگو شوید.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่เสียภาย โปรดโทรสาย โทร 877-475-4799.