WellMed Doctors helping patients for more than 25 years	**Effective Date: 01/02/2024**	**Revision Date(s):** 10/24/18, 03/12/20, 03/11/21, 10/21/21, 12/15/22, 12/19/23
Department: PHARMACY	**MMC Review/Approval Date(s):** 11/13/18, 06/23/20, 03/19/21, 11/09/21, 12/28/22, 12/27/23	**Page(s):** 15

Policy Number: 039.006
Title: Coverage Determination Policy for Intravitreal Implants:

- **Iluvien (Fluocinolone acetonide intravitreal implant); Ozurdex (Dexamethasone intravitreal implant); Retisert (Fluocinolone acetonide intravitreal implant); Yutiq (Fluocinolone acetonide intravitreal implant)**

Regions: ☒ **Texas** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

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Coverage Policy Number: 039.006

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

1. WellMed Medical Management will cover **Iluvien (fluocinolone)** as medically necessary for the treatment of **Diabetic Macular Edema** when **ALL** of the following criteria are met:
   A. Patient has an intolerance, contraindication, or treatment failure to a 3-month series of therapy of first line pharmacologic therapy for DME (e.g. anti-VEGF such as bevacizumab, etc.)
   B. The patient has been treated with a course of corticosteroids without a clinically significant rise in IOP (or a rise in IOP that was/can be medically or surgically managed) **AND** had an improvement or positive response of the inflammation or edema.
   C. No documentation of active ophthalmic infection noted by provider
   D. The patient does not have glaucoma with a cup to disc ratio of greater than 0.8
   E. Must be prescribed by or in consultation with an ophthalmologist

2. WellMed Medical Management will cover **Ozurdex (dexamethasone)** as medically necessary for the treatment of **"Macular Edema" caused by Retinal Vein Occlusion (Branch or Central)** when **ALL** of the following criteria are met:
   A. No documentation of active ophthalmic infection noted by provider
   B. The patient does not have glaucoma with a cup to disc ratio of greater than 0.8
   C. Must be prescribed by or in consultation with an ophthalmologist

3. WellMed Medical Management will cover **Ozurdex (dexamethasone)** as medically necessary for the treatment of **Diabetic Macular Edema (DME)** when **ALL** of the following criteria are met:
   A. No documentation of active ophthalmic infection noted by provider
   B. The patient does not have glaucoma with a cup to disc ratio of greater than 0.8
   C. Must be prescribed by or in consultation with an ophthalmologist

4. WellMed Medical Management will cover **Ozurdex (dexamethasone)** as medically necessary for the treatment of **Non-infectious Posterior Uveitis** when **ALL** of the following criteria are met:
   A. No documentation of active ophthalmic infection noted by provider
   B. The patient does not have glaucoma with a cup to disc ratio of greater than 0.8
   C. Must be prescribed by or in consultation with an ophthalmologist

5. WellMed Medical Management will cover **Retisert (fluocinolone) or Yutiq (fluocinolone)** as medically necessary for the treatment of **Chronic Noninfectious Posterior Uveitis** when **ALL** of the following criteria are met:
   A. Must be prescribed by or in consultation with an ophthalmologist
   B. No documentation of active ophthalmic infection noted by provider

Renewals/Continuation of Therapy

1. Requests for renewed use of **Iluvien (fluocinolone), Ozurdex (dexamethasone), Retisert (fluocinolone) or Yutiq (fluocinolone)** will be approved **only if** in addition to the indication specific data **ALL** of the following are met:

A. No documentation of active ophthalmic infection noted by provider
B. The patient does not have glaucoma with a cup to disc ratio of greater than 0.8 if applicable
C. Documentation of improvement with prior course of treatment

- *WellMed will **NOT** **cover Retisert, Ozurdex, Iluvien or Yutiq** for any other indications as they have not been studied and are not proven safe and/or effective.*
- ***NOTE:** Provider should **NOT** administer Iluvien, Retisert **or Yutiq** bilaterally on the same day.*

General Background

Uveitis (intraocular inflammation) is an important cause of visual impairment. Intermediate, posterior, and panuveitis are the forms of uveitis most likely to cause vision loss. Because of its earlier onset, uveitis results in a longer duration of blindness and more economic cost per case than more common age-related ocular diseases.

Uveitis is a term used to describe a heterogeneous group of intraocular inflammatory diseases of the anterior, intermediate, and posterior uveal tract (iris, ciliary body, choroid). Uveitis is the fifth most common cause of vision loss in high-income countries, accounting for 5% to 20% of legal blindness, with the highest incidence of disease in the working-age population. Posterior uveitis alone accounts for approximately 15% to 22% of uveitis cases in the United States, and leads to approximately 10% of legal blindness in the United States.

Diabetic Macular Edema (DME) is the leading cause of vision impairment in patients with diabetes. Given the association between DME and vision loss, early and effective treatment is critical. Without treatment, nearly half of all patients who develop DME will lose 2 or more lines of visual acuity (VA) within 2 years. Improved understanding of the pathophysiologic mechanisms leading to DME has led to the development of a range of treatments, including laser therapy, intravitreal antivascular endothelial growth factor (VEGF) injections, and corticosteroid treatments.

DME is the consequence of retinal microvascular changes from poorly controlled diabetes and diabetic retinopathy (DR). DR is a deterioration of the retinal blood vessels. The condition leads to abnormally-permeable retinal capillaries and the proliferation of retinal vessels, which in turn lead to the accumulation of fluid in the retina. When DR causes fluid accumulation and swelling in the macula, the disease is considered to have progressed to DME.

DME is classified into two types:

- Focal macular edema: caused by vascular abnormalities (primarily microaneurysms), which tend to leak fluid.
- Diffuse macular edema: caused by dilated capillaries in the retina.

Corticosteroids inhibit inflammatory responses to many different inciting agents, such as inflammatory cytokines to inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. Corticosteroids can produce a rise in intraocular pressure. Corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins. These proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Intravitreal corticosteroid implants are drug delivery systems resulting in sustained release of corticosteroid when surgically implanted into the eye:
Retisert® (fluocinolone acetonide intravitreal implant, 0.59mg) is a single-indication orphan drug, which is FDA-approved for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.
Retisert® is surgically implanted into the posterior segment of the affected eye through a pars plana incision. The implant contains one tablet of 0.59 mg of fluocinolone acetonide. Retisert® is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 µg/day, decreasing over the first month to a steady state between 0.3-0.4 µg/day over approximately 30 months (2.5 years). Following depletion of fluocinolone acetonide from Retisert® as evidenced by recurrence of uveitis, Retisert® may be replaced. The intended implantation regimen for Retisert® 0.59mg is once every 2.5 years by intravitreal insertion through an aseptic surgical sclerotomy into the eye to be treated.
Retisert® is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex, keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infections of the eye and fungal diseases of ocular structures. Retisert® is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of its preparation and to other corticosteroids. Generally, it would be expected that a short course of peri-ocular injections (6-8 weeks) or a short course of systemic corticosteroid therapy (less than 3 months) would be tried to see if the inflammation completely subsides before moving to Retisert. Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation should not be carried out, in order to limit the potential for bilateral post-operative infection.
Ozurdex® (dexamethasone intravitreal implant, 0.7mg) is indicated for macular edema following branch retinal vein occlusion or central retinal vein occlusion, noninfectious uveitis affecting the posterior segment of the eye and diabetic macular edema. Ozurdex® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the NOVADUR® solid polymer sustained-release drug delivery system. Ozurdex® is preloaded into a single-use, DDS® applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The NOVADUR® system contains poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative which slowly degrades to lactic acid and glycolic acid.

Ozurdex® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Ozurdex® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8. Ozurdex® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for Ozurdex® use.

Iluvien® (fluocinolone acetonide intravitreal implant, 0.19mg) is a non-bioerodable intravitreal implant. It is the first DME treatment to deliver 36 months of continuous, low-dose corticosteroid with a single injection. Fluocinolone acetonide is a corticosteroid, which may play an important role in addressing the inflammatory process associated with DME. Corticosteroids have been shown to inhibit inflammatory responses to a variety of inciting agents. They inhibit edema, fibrin

deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

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

Adverse reactions associated with Iluvien® include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Yutiq (fluocinolone acetonide intravitreal implant) is a low to medium-potency corticosteroid agent designed for intravitreal implantation. Fluocinolone acetonide is a synthetic corticosteroid that has anti-inflammatory, antipruritic, and vasoconstrictive properties. Its anti-inflammatory action is thought to be due to its ability to control biosynthesis of potent mediators of inflammation. It stimulates phospholipase A(2) inhibitory proteins (lipocortins) and subsequently blocks the release of arachidonic acid, which is a common precursor to prostaglandins and leukotrienes.

Yutiq (fluocinolone acetonide intravitreal implant) is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

Yutiq is available as a sterile 0.18 mg fluocinolone acetonide intravitreal implant designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day and lasting 36 months.

Yutiq is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex, keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infections of the eye and fungal diseases of ocular structures. Yutiq is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of its preparation and to other corticosteroids. Generally, it would be expected that a short course of peri-ocular injections (6-8 weeks) or a short course of systemic corticosteroid therapy (less than 3 months) would be tried to see if the inflammation completely subsides before moving to Yutiq. Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation should not be carried out, in order to limit the potential for bilateral post-operative infection.

There are no relevant NCDs, LCDs or LCAs for Retisert, Ozurdex or Iluvien or Yutiq available for Texas or New Mexico at the time of this policy revision.

FDA Approved Dose and Indication

FDA Approved Indications:	Retisert	Ozurdex	Iluvien	Yutiq
Diabetic Macular Edema		1 implant (0.7 mg) via intravitreal injection; may repeat in contralateral eye	0.19-mg intravitreal implant via intravitreal injection	
Macular Edema caused by Branch (BRVO) or Central (CRVO) Retinal Vein Occlusion		1 implant (0.7 mg) via intravitreal injection into eye; may repeat in contralateral eye		
Chronic Noninfectious Uveitis of the posterior segment	0.59 mg (1 intravitreal implant) via intravitreal implant; provides initial drug release rate of 0.6 mcg/day, decreasing over the first month to 0.3 to 0.4 mcg/day and lasting for approximately 30 months. May be replaced following depletion of drug	1 implant (0.7 mg) via intravitreal injection into eye; may repeat in contralateral eye		0.18 mg (1 intravitreal implant) via intravitreal injection; provides initial drug release rate of 0.25 mcg/day and lasts for 36 months

Clinical Evidence

Ozurdex

Retinal Vein Occlusion

The efficacy of OZURDEX® for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) was assessed in two, multicenter, double-masked, randomized, parallel studies.

Following a single injection, OZURDEX® demonstrated the following clinical results for the percent of patients with ≥ 15 letters of improvement from baseline in best-corrected visual acuity (BCVA):

In each individual study and in a pooled analysis, time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with OZURDEX® compared to sham ($p < 0.01$), with OZURDEX® treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a ≥ 15 letter (3-line) improvement in BCVA with OZURDEX® occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately one to three months after onset of this effect.

Posterior Segment Uveitis

The efficacy of OZURDEX® was assessed in a single, multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye.

After a single injection, the percent of patients reaching a vitreous haze score of 0 (where a score of 0 represents no inflammation) was statistically significantly greater for patients receiving OZURDEX® versus sham at week 8 (primary time point) (47% versus 12%). The percent of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving OZURDEX® versus 7% for sham at week 8.

Diabetic Macular Edema

The efficacy of OZURDEX® for the treatment of diabetic macular edema was assessed in two, multicenter, masked, randomized, sham-controlled studies. Subjects were to be evaluated for retreatment eligibility every three months starting from Month 6 but could only receive successive treatments at least 6 months apart. Retreatment was based on physician's discretion after examination including Optical Coherence Tomography. Patients in the OZURDEX® arm received an average of 4 treatments during the 36 months.

The primary endpoint was the proportion of patients with 15 or more letters improvement in BCVA from baseline at Month 39 or final visit for subjects who exited the study at or prior to Month 36. The Month 39

extension was included to accommodate the evaluation of safety and efficacy outcomes for subjects who received re-treatment at Month 36. Only fourteen percent of the study patients completed the Month 39 visit (16.8% from Ozurdex and 12.2% from Sham).

Iluvien

Iluvien® was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema (DME) were treated with either Iluvien® (n=375) or sham

(n=185). Table 1 summarizes safety data available when the last subject completed the last 36 month follow up visit for the two primary Iluvien® trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three year follow up period, approximately 75% of the Iluvien® treated subjects received only one implant. The most common ocular (study eye) adverse reactions were cataracts, myodesopsia, eye pain, and conjunctival hemorrhage.

Retisert, Yutiq

In the Multicenter Uveitis Steroid Treatment trial patients with active or recently active uveitis were randomized to systemic or implant therapy. Masked examiners measured the primary outcome: change in best-corrected visual acuity from baseline. Secondary outcomes included patient-reported quality of life, ophthalmologist-graded uveitis activity, and local and systemic complications of uveitis or therapy. Reading Center graders and glaucoma specialists assessing ocular complications were masked. Participants, ophthalmologists, and coordinators were unmasked.

On evaluation of changes from baseline to 24 months among 255 patients randomized to implant and systemic therapy (479 eyes with uveitis), the implant and systemic therapy groups had an improvement in visual acuity of +6.0 and +3.2 letters (P = 0.16, 95% confidence interval on difference in improvement between groups, -1.2 to +6.7 letters, positive values favoring implant), an improvement in vision-related quality of life of +11.4 and +6.8 units (P = 0.043), a change in EuroQol-EQ5D health utility of +0.02 and -0.02 (P = 0.060), and residual active uveitis in 12% and 29% (P=0.001), respectively. Over the 24 month period, implant-assigned eyes had a higher risk of cataract surgery (80%, hazard ratio [HR] = 3.3, P < 0.0001), treatment for elevated intraocular pressure (61%, HR=4.2, P < 0.0001), and glaucoma (17%, HR=4.2, P = 0.0008). Patients assigned to systemic therapy had more prescription-requiring infections than patients assigned to implant therapy (0.60 vs 0.36/person-year, P=0.034), without notable long-term consequences; systemic adverse outcomes otherwise were unusual in both groups, with minimal differences between groups.

In each treatment group, mean visual acuity improved over 24 months, with neither approach superior to a degree detectable with the study's power. Therefore, the specific advantages and disadvantages identified should dictate selection between the alternative treatments in consideration of individual patients' particular circumstances.

Visual outcomes of fluocinolone acetonide implant and systemic treatment for intermediate uveitis, posterior uveitis, and panuveitis were similarly favorable through 54 months. The implant maintained a clear advantage in controlling inflammation through 54 months. Nevertheless, with systemic therapy, most patients also experienced greatly improved inflammatory status. Macular edema improved equally with longer follow-up. Based on cost effectiveness and side-effect considerations, systemic therapy may be indicated as the initial treatment for many bilateral uveitis cases. However, implant therapy is a reasonable alternative, especially for unilateral cases and when systemic therapy is not feasible or is not successful.

HCPCS Code

HCPCS codes	Available Dosage Form	Route of Administration
J7311: Retisert (Fluocinolone acetonide)	Intraocular Implant: 0.59 MG	Intravitreal injection
J7312: Ozurdex (Dexamethasone)	Intraocular Implant: 0.7 MG	Intravitreal injection
J7313: Iluvien (fluocinolone acetonide)	Intraocular Implant: 0.19 MG	Intravitreal injection
J7314: Yutiq (Fluocinolone Acetonide)	Intraocular Implant: 0.18 MG	Intravitreal injection

Acronyms

IOP = Intraocular pressure

DME = Diabetic Macular Edema

VA = Visual Acuity

ME = Macular Edema

anti-VEGF = anti-vascular endothelial growth factors

anti-TNF = anti-tumor necrosis factor

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