I. Policy

A fluocinolone acetonide intravitreal implant approved by FDA may be considered medically necessary for the treatment of:

- Chronic noninfectious intermediate, posterior, or panuveitis (Retisert®), OR
- Diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (ILUVIEN®)

A dexamethasone intravitreal implant approved by FDA (i.e., Ozurdex™) may be considered medically necessary for the treatment of:

- Noninfectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye, OR
- Macular edema following branch or central retinal vein occlusion, OR
- Diabetic macular edema

All other uses of a corticosteroid intravitreal implant are considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

An intravitreal implant may be an acceptable alternative in patients who are intolerant or refractory to other therapies or in patients who are judged likely to experience severe adverse events from systemic corticosteroids. Patients should be informed about the potential adverse effects of a corticosteroid intravitreal implant, including cataracts, increased intraocular pressure or hypotony, endophthalmitis, and risk of need for additional surgical procedures. Because of the differing benefits and risks of treatment with intravitreal implants in comparison with systemic corticosteroid therapy or intraocular injections, patients should make an informed choice between treatments.

Cross-references:

MP-2.028 Eye Care
II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

* Refer to FEP Medical Policy Manual MP-9.03.23 Intravitreal Implant. The FEP Medical Policy manual can be found at: www.fepblue.org

Note for Medicare Advantage:
FDA approved drugs used for indications other than what is indicated on the FDA approved product label may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the Medicare recognized national drug compendia, authoritative medical literature and/or accepted standards of medical practice.” Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug). http://www.cms.gov/manuals/Downloads/bp102c15.pdf

III. DESCRIPTION/BACKGROUND

Intravitreal implants are being developed to deliver a continuous concentration of drug over a prolonged period of time. Intravitreal corticosteroid implants are being studied for a variety of eye conditions leading to macular edema, including uveitis, diabetic retinopathy, and retinal venous occlusions. The goal of therapy is to reduce the inflammatory process in the eye while minimizing the adverse effects of the therapeutic regimen.

Selection of the route of corticosteroid administration (topical, systemic, periocular or intraocular injection) is based on the cause, location, and severity of the disease. Each therapeutic approach has its own drawbacks. For example, topical corticosteroids require frequent (e.g., hourly) administration and may not adequately penetrate the posterior segment of the eye due to their poor ability to penetrate ocular tissues. Systemically administered drugs penetrate poorly into the eye because of the blood-retinal barrier, and high-dose or long-term treatments may be necessary. Long-term systemic therapies can be associated with substantial adverse effects such as hypertension and osteoporosis, while repeated (every 4-6 weeks) intraocular corticosteroid injections may result in pain, intraocular infection, globe perforation, fibrosis of the extraocular muscles, reactions to the delivery vehicle, increased IOP, and cataract development.
Corticosteroid implants may be either biodegradable or nonbiodegradable. Nonbiodegradable systems are thought to be preferable for treating chronic, long-term disease, while biodegradable products may be preferred for conditions that require short-term therapy. Although the continuous local release of steroid with an implant may reduce or eliminate the need for intravitreal injections and/or long-term systemic therapy, surgical implantation of the device carries its own risks, and the implant could potentially increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration. With any route of administration, cataracts are a frequent complication of long-term corticosteroid therapy.

Intraocular corticosteroid implants being evaluated include:

Retisert® (nonbiodegradable fluocinolone acetonide intravitreal implant; Bausch & Lomb) sterile implant consists of a tablet containing 0.59 mg fluocinolone acetonide, a synthetic corticosteroid that is less soluble in aqueous solution than dexamethasone. The tablet is encased in a silicone elastomer cup with a release orifice and membrane; the entire elastomer cup assembly is attached to a suture tab. Following implantation (via pars plana incision and suturing) in the vitreous, the implant releases the active drug at a rate of 0.3 to 0.4 µg/day over a period of approximately 2.5 years.

Iluvien® (nonbiodegradable injectable intravitreal implant with fluocinolone acetonide; Alimera Sciences Inc.) is a rod-shaped device made of polyimide and polyvinyl alcohol. It is small enough to be placed using an inserter with a 25-gauge needle and is expected to provide sustained delivery of fluocinolone acetonide for up to 3 years.

Ozurdex® or Posurdex® (biodegradable dexamethasone intravitreal implant; Allergan, Irvine, CA.) is composed of a biodegradable copolymer of lactic acid and glycolic acid with micronized dexamethasone. This implant is placed into the vitreous cavity through the pars plana using a customized, single-use, 22-gauge applicator. The implant provides intravitreal dexamethasone for up to 6 months.

Uveitis
Uveitis encompasses a variety of conditions, of either infectious or noninfectious etiologies, that are characterized by inflammation of any part of the uveal tract of the eye (iris, ciliary body, choroid). Infectious etiologies include syphilis, toxoplasmosis, cytomegalovirus retinitis, and candidiasis. Noninfectious etiologies include sarcoidosis, Behçet syndrome, and “white dot” syndromes such as multifocal choroiditis or “birdshot” chorioretinopathy. Uveitis may also be idiopathic, have a sudden or insidious onset, a duration that is limited (<3 months) or persistent, and a course that may be acute, recurrent, or chronic.

The classification scheme recommended by the Uveitis Study Group and the Standardization of Uveitis Nomenclature (SUN) Working Group is based on anatomic location. Patients with anterior uveitis typically develop symptoms such as light sensitivity, pain, tearing, and redness of the sclera. In posterior uveitis, which comprises approximately 5% to 38% of all uveitis cases in the United States, the primary site of inflammation is the choroid or retina (or both). Patients
with intermediate or posterior uveitis typically experience minimal pain, decreased visual acuity, and the presence of floaters (bits of vitreous debris or cells that cast shadows on the retina). Chronic inflammation associated with posterior segment uveitis can lead to cataracts and glaucoma and to structural damage to the eye, resulting in severe and permanent vision loss. Noninfectious uveitis typically responds well to corticosteroid treatment. Immunosuppressive therapy (e.g., antimetabolites, alkylating agents, T-cell inhibitors, tumor necrosis factor inhibitors) may also be used to control severe uveitis. Immunosuppressive therapy is typically reserved for patients who require chronic high-dose systemic steroids to control their disease. While effective, immunosuppressants may have serious and potentially life-threatening adverse effects, including renal and hepatic failure and bone marrow suppression.

Retinal Vein Occlusion
Retinal vein occlusions are classified by whether the central retinal vein or one of its branches is obstructed. Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) differ in pathophysiology, clinical course, and therapy. CRVOs are categorized as ischemic or nonischemic. Ischemic CRVOs are referred to as severe, complete, or total vein obstruction, and account for 20% to 25% of all CRVOs. Macular edema and permanent macular dysfunction occur in virtually all patients with ischemic CRVO, and in many patients with nonischemic CRVO. Intravitreal injections of triamcinolone are used to treat macular edema associated with CRVO, with a modest beneficial effect on visual acuity. The treatment effect lasts about 6 months, and repeat injections may be necessary. Cataracts are a common side effect, and steroid-related pressure elevation occurs in about one-third of patients, with 1% requiring filtration surgery.

BRVO is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more often than CRVO. Macular photocoagulation with grid laser improves vision in BRVO but is not recommended for CRVO. Although intravitreal injections of triamcinolone have also been used for BRVO, the serious adverse effects have stimulated the evaluation of new treatments, including intravitreal steroid implants or the intravitreal injection of antivascular endothelial growth factor.

Diabetic Macular Edema
Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The 2 most serious complications for vision are diabetic macular edema and proliferative diabetic retinopathy. At its earliest stage (nonproliferative retinopathy), microaneurysms occur. 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 leakage of blood into the vitreous. DME is characterized by swelling of the macula due to gradual leakage of fluids from blood vessels and breakdown of the blood-retinal barrier. Moderate vision loss can arise from the fluid accumulating in the center of the macula (macular edema) 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.
Tight glycemic and blood pressure control is the first line of treatment to control diabetic retinopathy, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss, it does not restore lost vision. Intravitreal injection of triamcinolone acetonide is used as an off-label adjunctive therapy for DME, and intravitreal steroid implants are being evaluated. Angiostatic agents such as injectable vascular endothelial growth factor (VEGF) inhibitors, which block some stage in the pathway leading to new blood vessel formation (angiogenesis), have demonstrated efficacy in DME.

**Regulatory Status**

In 2005, Retisert® (Bausch & Lomb), a fluocinolone acetonide intravitreal implant, was approved by the U.S. Food and Drug Administration (FDA) through fast-track approval as an orphan drug for treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. Drugs granted orphan drug status are used to treat rare conditions, defined by FDA as affecting fewer than 200,000 persons in the United States. Because of the lack of data on the long-term effects of Retisert®, FDA required that postmarketing analysis be conducted.

In 2014, Iluvien™ (Alimera Sciences), a nonbiodegradable injectable intravitreal implant with fluocinolone acetonide, was approved by FDA through the premarket approval process for treatment of diabetic macular edema (DME) in patients who were previously treated with corticosteroids and did not have a clinically significant rise in intraocular pressure.

Ozurdex® (Allergan), a dexamethasone intravitreal implant composed of a biodegradable copolymer of lactic acid and glycolic acid with 0.7-mg micronized dexamethasone, was approved by FDA through the premarket approval process in 2009 for treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion and, in 2010, for the treatment of non-infectious uveitis affecting the posterior segment of the eye. In 2014, FDA approved Ozurdex® for the treatment of DME.

FDA analysis has noted that the safety and efficacy effects seen with Ozurdex are class effects related to steroids. Among other effects, prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. The labeling contains the following warnings and precautions:

“**Intravitreal injections, including those with Ozurdex® have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.**”

Other formulations are also being investigated but are not yet available for the treatment of vitreoretinal disorders in the United States.
IV. RATIONALE

The most recent literature update was performed through January 29, 2016.

Noninfectious Uveitis

Fluocinolone Acetonide Implant
There are at least 4 multicenter, randomized controlled trials (RCTs) that address use of the fluocinolone acetonide implant for noninfectious uveitis. Two were double-masked and compared 2 doses (0.59 mg vs 2.1 mg) of the fluocinolone acetonide implant in 1 eye to no treatment in the control eye. The other 2 trials were open-label studies of implants versus standard of care (SOC), which generally was systemic steroids.

In the first (pivotal) phase 3 trial, reported in 2006, 278 patients with noninfectious posterior uveitis were randomly assigned in a 2:3 ratio to receive the 0.59 mg (n=110) or 2.1 mg (n=168) fluocinolone acetonide implant. Pooled results from both doses showed a reduction in noninfectious uveitis recurrence rates in the implanted eye compared with an increase in recurrence in the nonimplanted eye over the pre- and postimplant periods. Improvement of 3 or more lines in visual acuity was seen in significantly more implanted eyes than in nonimplanted eyes. An increase in intraocular pressure (IOP) was seen at week 4 with both doses (≈6 mm Hg) compared with no significant change in IOP in the nonimplanted eyes. Over the 34-week trial, increases of 10 mm Hg or more in IOP were seen in 59% of the implanted eyes compared with only 11% of the nonimplanted eyes. Cataracts severe enough to require surgery were more commonly seen in implanted eyes versus nonimplanted eyes (9.9% vs 2.7%, respectively).

In the second phase 3 trial, 239 patients with noninfectious posterior uveitis were randomly assigned to receive fluocinolone acetonide 0.59 mg or 2.1 mg in a 1:1 ratio. A reduction in uveitis recurrence rates was seen in the implanted eye over the 34-week trial, while an increase in recurrence rate was seen in the nonimplanted eye. There was a greater improvement in visual acuity from baseline in the implanted eye than in the nonimplanted eye. A reduction in cystoid macular edema was also seen in the implanted eye (69%) compared with the nonimplanted eye (23%). The most commonly reported adverse events (50%-90%) in the clinical trial included cataracts, increased IOP, postprocedural complications associated with implant insertion, and ocular pain. Other ocular adverse events included decreased visual acuity, glaucoma, blurred vision, abnormal sensation in the eye, eye irritation, and a change in tearing (either increased or decreased). Based on data available, 60% of patients would experience an increase in IOP sufficient to require drug treatment within 34 weeks of implant; 32% of patients will require filtering procedures within 2 years of implant to control IOP, and nearly all phakic eyes will develop cataracts and require surgery within 2 years of receiving the implant. In addition, 31% of patients in these studies reported headache.

In 2010, Pavesio et al published 2-year results from a manufacturer-sponsored multicenter (10 European countries and 37 centers), open-label RCT of the sustained release fluocinolone acetonide implant (0.59 mg) compared with SOC. To be included in the study, subjects had to
have at least a 1-year history of recurrent or recrudescent unilateral or asymmetric noninfectious posterior uveitis not associated with significant systemic activity of any underlying disease, with the last episode occurring within 8 months of enrollment; systemic therapy for 1 month or more; and “quiet eyes” at the time of treatment, with either 0.2 mg/kg or more daily prednisolone, or the equivalent of 0.1 mg/kg or more daily prednisolone plus immunosuppressant at the time of randomization. At baseline, more subjects in the SOC group were on tritherapy (8 vs 4, respectively), indicating greater severity in the control group following randomization. Subjects in the implant group received the implant in 1 eye, followed by tapering of the steroids or other agents over a period of 12 weeks; this 12-week period was excluded from the analysis of implant efficacy to allow tapering of pre- and postoperative anti-inflammatory therapy. The SOC group received prednisolone or an equivalent corticosteroid (<15 mg/d for the average weight), or an immunosuppressive agent combined with a reduced dose of corticosteroid. After 6 months, if the disease was controlled, the treatment doses were tapered according to the standard guideline of each investigational site.

A total of 146 subjects were enrolled and randomly assigned to implants or SOC; 6 subjects discontinued before treatment and were excluded from the intention-to-treat population. A total of 131 (90%) patients completed the 2-year visit. Reasons for discontinuation before the 2-year visit included adverse events (n=4), withdrawal of consent (n=1), and loss to follow-up (n=3). Subjects returned to the study site on weeks 1, 4, 8, 12, 18, 24, 30, and 34, and then every 3 months from 1 to 3 years for safety and efficacy assessments. Assessments made at 34 weeks and yearly thereafter included physical examination, medical history, clinical laboratory tests, complete ophthalmic examination, visual field tests, and fluorescein angiography, and bilateral fundus photography (masked assessments). In the event of a clinical recurrence, subjects were treated, as appropriate, with corticosteroid injections as the preferred first-line therapy.

The primary efficacy outcome was time to first recurrence of uveitis (recurrent inflammation or inferred by use of adjunctive therapy at a level sufficient to reduce the potential for ocular inflammation). In a number of implant subjects, the tapering of anti-inflammatory therapy was insufficient. This led to early imputed or inferred failures and, in some subjects, uveitis medications were increased before the study eye experienced protocol-defined uveitis recurrence. Results were therefore presented as both true recurrences and as combination true plus inferred recurrences. When recurrences inferred for reasons not related to protocol-defined ocular inflammation were censored (11 subjects were removed from the at-risk population), Kaplan-Meier analysis showed a significant decrease in the time to uveitis recurrence (6.3 months for 12 failures vs 7.0 months for 44 failures). When all subjects were included in the analysis, time to uveitis recurrence did not differ statistically (p=0.07).

Secondary efficacy outcomes included the percentage of subjects who had at least 1 recurrence, the number of recurrences per subject, the proportion of subjects with a visual acuity improvement greater than 15 letters from baseline, and, in a subset of the subjects, whether cystoid macular edema (CME) was present at baseline, and the change in the size of the area of CME on fluorescein angiography. The proportion of subjects with a reduction in the area of CME greater than 1 mm² was 87% (32/37) in the implant group and 74% (29/39) in the SOC.
MEDICAL POLICY

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group. The proportion of subjects experiencing at least 1 recurrence was lower in the implant group when measured either by true plus inferred recurrence (35% vs 65%, respectively) or by true recurrences of inflammation (18% vs 64%, respectively). This indicates that patients in the implant group were more likely to be treated with an increase in medication in the absence of protocol-defined uveitis recurrence. Visual acuity in the SOC group remained consistent over the 2-year study. Visual acuity in the implant group decreased after the surgery and again in the 15-to 18-month interval as a result of cataracts, then returned to baseline levels at 24 months, following extraction of the cataracts (safety outcomes follow).

Ocular adverse events considered to be related to treatment were reported in 96% of subjects in the implant group compared with 40% of subjects in the SOC group. Implanted eyes also had a greater number of serious ocular adverse events compared with SOC eyes (91% vs 24%, respectively). The most commonly reported adverse events in the implant group were cataract and elevated IOP or glaucoma. Of 66 implanted eyes, 49 (74%) were phakic at 2 years, compared with 57 (77%) of 74 eyes that received SOC. Of phakic eyes, 90% of implanted eyes and 23% of SOC eyes had a change in lens opacity of 2 grades or more; cataracts were extracted in 88% (43/49) of phakic implanted study eyes compared with 19% (11/57) of phakic SOC eyes. Thus, development of cataracts of a severity requiring extraction occurred in 65% of the implanted eyes and 15% of eyes receiving SOC. During the 2-year follow-up, 55% of implanted eyes had an increase in IOP of 10 mm Hg or more from baseline compared with 11% of SOC study eyes. Medication was required to control elevated IOP in 62% of implanted eyes compared with 20% of SOC eyes, while IOP-lowering surgery was performed in 21% of implanted eyes compared with 3% of SOC eyes. The incidence of hypotony was significantly higher in implanted eyes (20% vs 1%, respectively). By the 2-year follow-up visit, 8 (12%) eyes had been explanted: 3 because of hypotony, 2 because of elevated IOP, and 1 eye each because of scleral thinning, implant extrusion, and postoperative complications. A greater proportion of patients in the implant group had a decrease in visual acuity of 3 lines or more during the 2-year follow-up (79% in the implanted eyes vs 42% in the SOC eyes). The decrease in visual acuity in implanted eyes was attributed to the implantation procedure at the 1-day postimplantation visit (31% of implanted eyes) and cataract progression (47% of implanted eyes at 18 months). Visual acuity was similar in the 2 groups following cataract removal. Other serious ocular adverse events included 3 (4.5%) cases of endophthalmitis only in implanted eyes. Rates of nonocular adverse events considered to be treatment-related were higher in the SOC group (26% vs 0%); 3 of the 19 adverse events in the SOC group were considered to be serious (4% of the total SOC group).

The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group reported a National Eye Institute–funded randomized comparison of the fluocinolone acetonide intravitreal implant and systemic anti-inflammatory therapy for intermediate, posterior, and panuveitis in 2011.5,7,8 Included were 255 patients (479 eyes) randomized to implant or systemic therapy (corticosteroids and corticosteroid-sparing immunosuppressive drugs). Groups were comparable at baseline except for more osteopenia/osteoporosis and poorer visual field sensitivity in the implant group. Over 95% of patients received their assigned therapies. Visual acuity measured by masked examiners improved over 24 months for both groups. Intention-to-treat analysis showed no significant difference between implant and systemic groups for improvement in
visual acuity (+6.0 and +3.2 letters), improvement in vision-related quality of life (+11.4 and +6.8), change in EuroQol-EQ5D health utility (+0.02 and -0.02), or residual active uveitis (12% and 29%), respectively. Control of uveitis was more frequent in the implant group (88% vs 71%) and fewer patients in the implant group had macular edema (20% vs 34%), respectively. Over the 24-month trial, implant-assigned eyes had a higher risk of cataract surgery (80% vs 31%; hazard ratio [HR], 3.3), treatment for elevated IOP (61% vs 20%; HR=4.2), and glaucoma (17% vs 4%; HR=4.2). Patients assigned to systemic therapy had more prescription-requiring infections than patients assigned to implant therapy (0.60/person-year vs 0.36/person-year, respectively) without notable long-term consequences.

Fifty-four month results from the MUST trial were reported in 2015. Both groups had an approximate mean improvement of 0.5 lines of vision, which was not statistically significant. By 54 months, approximately 21% of patients in the systemic group had received an implant, typically as rescue therapy. Throughout follow-up, control of inflammation was superior in the implant group (p<0.05), although most eyes in the systemic therapy arm achieved complete control or low levels of inflammation. The proportion of patients who had active uveitis in the implant group ranged from 9% to 16%. For the systemic group, active uveitis was observed in 31% of patients at 24 months and 21% of patients at 54 months. Macular edema was present in about half of the patients in both groups. Cataract and cataract surgery occurred significantly more often in the implant group. IOP elevation also occurred more frequently in the implant group, and that group had more cases of glaucoma (26.3% vs 10.2%) and IOP-lowering surgery (HR=14.4, p<0.001). Potential complications of systemic therapy did not differ between groups. Quality of life and 36-Item Short-Form Health Survey Physical Component Summary scores were modestly superior in the implant group, with a 3.17-point difference on a scale of 100 (p=0.01).

A retrospective review of medical records of 47 eyes in 35 patients receiving fluocinolone acetonide intravitreal implants over an 8-year period at 1 institution revealed a significant risk of increased IOP requiring glaucoma surgery. Nineteen (45%) of 42 eyes that received implants during the study period required surgical intervention for glaucoma, with a mean time to IOP-lowering surgery of 14 months after implantation. At 24 months postoperatively, success of IOP-lowering surgery was achieved in 92% of eyes, and patients who underwent IOP-lowering surgery had an average 2-line gain in visual acuity measured 3 years after receiving a fluocinolone acetonide intravitreal implant.

Dexamethasone Intravitreal Implant
In 2011, investigators from the manufacturer-sponsored multicenter Ozurdex HURON study group (46 study sites in 18 countries) reported safety and efficacy outcomes of a double-masked RCT of the dexamethasone intravitreal implant in 229 patients with uveitis. Eyes with noninfectious intermediate or posterior uveitis were stratified by baseline vitreous haze and randomized to a single treatment with a 0.7-mg implant (n=77), 0.35-mg implant (n=76), or sham procedure (n=76). Key exclusion criteria were active ocular disease or infection; uveitis unresponsive to prior corticosteroid treatment; use of IOP-lowering medications within the last month and a history of glaucoma, ocular hypertension, or clinically significant IOP elevation in
response to corticosteroid treatment; IOP more than 21 mm Hg at baseline; best-corrected visual acuity (BCVA) less than 34 letters in the nonstudy eye; or any uncontrolled systemic disease. Outcomes were measured by an investigator masked to treatment conditions at 2, 6, 8, 12, 16, 20, and 26 weeks. At baseline, the mean vitreous haze score was approximately +2 (moderate blurring of the optic nerve head). At 8 weeks after treatment, the proportion of eyes with a vitreous haze score of 0 (no inflammation; primary outcome measure) was 47% with the 0.7-mg implant, 36% with the 0.35-mg implant, and 12% with the sham procedure. The benefit of treatment lasted through the 6-month trial, with 217 (95%) patients included in follow-up. Two patients had discontinued due to adverse events, and 1 patient discontinued because of lack of efficacy. A gain of 15 or more letters from baseline BCVA was achieved in more eyes in the implant groups (≥40) than in the sham group at all study visits (10%), although the efficacy of the 0.35-mg dexamethasone dose began to decline at 4 months after implantation. Use of rescue therapy with systemic immunosuppressive therapy or corticosteroids was based on set criteria and occurred more frequently in the sham group than in the implant groups. For example, at week 26, rescue medication was used in 38% of the sham group and 25% and 22% of the 0.35- and 0.7-mg implant groups, respectively. The percentage of eyes with IOP of 25 mm Hg or more peaked at 7.1% for the 0.7-mg implant group, 8.7% for the 0.35-mg implant group, and 4.2% for the sham group. The incidence of cataracts in the phakic eyes was 9 (15%) of 62 in the 0.7-mg implant, 6 (12%) of 51 in the 0.35-mg implant, and 4 (7%) of 55 with the sham procedure. Vision-related functioning, assessed with the National Eye Institute Visual Function Questionnaire–25 (NEI VFQ-25) showed significant improvement with the 0.7-mg implant compared with sham procedure at both 8 weeks (p=0.007) and 26 weeks (p=0.001). The 0.35-mg implant group showed significant improvement compared with sham procedure at 8 weeks (p=0.012) but not at 26 weeks. Interpretation of these results is limited by the higher baseline scores for the sham group.

Section Summary: Noninfectious Uveitis
Retisert has been approved by the Food and Drug Administration (FDA) as an orphan drug for the treatment of chronic noninfectious posterior uveitis. There is strong evidence of efficacy for treatment of noninfectious uveitis with the fluocinolone acetonide implant (Retisert). There are at least 4 multicenter RCTs that have examined the fluocinolone acetonide intravitreal implant. Sham-controlled RCTs support greater efficacy over placebo for posterior uveitis. Open-label RCTs support similar outcomes between systemic therapy and fluocinolone acetonide intravitreal implants for intermediate, posterior, and panuveitis. In all studies, there is a higher risk of cataracts and glaucoma with the implants compared with alternatives.

Ozurdex is approved for the treatment of noninfectious uveitis affecting the posterior segment of the eye. This dexamethasone implant has been studied in a single multicenter, double-masked RCT in patients with intermediate or posterior uveitis, which showed a significant increase in the percentage of patients who gained 15 or more letters compared with sham treatment.

Macular Edema Following Retinal Vein Occlusion
In 2015, the American Academy of Ophthalmology published a technology assessment of therapies for macular edema associated with central retinal vein occlusion (CRVO). They
identified 4 clinical trials that provided level I evidence supporting the use of antivascular endothelial growth factor (anti-VEGF) pharmacotherapies and 2 clinical trials providing level I evidence for intravitreal corticosteroid injection with the dexamethasone intravitreal implant or triamcinolone. Evidence on the safety and efficacy of other reported interventions was of lesser strength. The assessment noted that evidence on long-term efficacy of corticosteroid treatments is limited and that intravitreal corticosteroids led to a higher frequency of adverse events, including cataract and IOP elevation compared with anti-VEGF treatments. There was limited information on combination therapy with anti-VEGF and corticosteroid injections compared with monotherapy.

A Bayesian network meta-analysis of the efficacy and safety of treatments for macular edema secondary to branch retinal vein occlusion (BRVO) was published in 2015. A total of 8 RCTs (1743 patients) were included, treated with ranibizumab given as needed, aflibercept monthly, dexamethasone implant, laser photocoagulation, ranibizumab plus laser, or sham intervention. The probability of being the most efficacious treatment, based on letters gained, or for a gain 15 letters or more, was highest for monotherapy of anti-VEGF treatments (30%-54% probability), followed by ranibizumab plus laser, and lowest (0%-2% probability) for the dexamethasone implant, laser, or sham treatment. Treatment with ranibizumab resulted in an increase of an average 8 letters compared with the dexamethasone implant. Patients treated with the dexamethasone implant had statistically significant higher rates of ocular hypertension than patients given anti-VEGF monotherapy (odds ratio, 13.1).

**Fluocinolone Acetonide Implant**

No RCTs were identified with fluocinolone acetonide implants for the treatment of macular edema following retinal vein occlusion.

**Dexamethasone Intravitreal Implant**

Evidence on the dexamethasone intravitreal implant for the treatment of macular edema following retinal vein occlusion includes 3 RCTs, 2 of which were sham-controlled.

Data presented to FDA for the dexamethasone intravitreal implant (Ozurdex) were from two 6-month double-masked, multicenter studies that took place at 167 clinical sites in 24 countries. A 6-month open-label extension of these 2 pivotal trials was reported in 2011. A total of 1267 patients who had clinically detectable macular edema associated with either CRVO or BRVO were enrolled. Mean visual acuity at baseline was about 54 letters (20/80) and mean central retinal thickness was approximately 550 μm. About 75% of the patients had macular edema for more than 3 months. Patients were randomized to a single treatment with a dexamethasone 0.7-mg implant (n=427), dexamethasone 0.35-mg implant (n=414), or sham control (n=426). The sham procedure included anesthetic and surgical preparation, with a needleless applicator placed against the conjunctiva to simulate medication placement. The primary outcome measure for the first trial was the proportion of eyes achieving a 15-or-more letter improvement from baseline at 180 days. The primary outcome measure for the second trial, as requested by FDA, was the time to reach a 15-letter improvement (3 lines) from baseline BCVA. Secondary outcome measures included the proportion of eyes exhibiting loss of 15 or
more letters from baseline and central subfield retinal thickness measured by optical coherence tomography.

For the combined trial data, the time to achieve a 15-or-more letter improvement was faster with the intravitreal implant, meeting the prespecified outcome. There was no significant difference in the proportion of patients who improved by 15 letters or more at 6-month follow-up. The proportion of sham-treated patients who achieved a 15-or-more letter improvement was 7.5% at day 30, 11.3% at day 60, and 17.6% at day 180. The proportion of patients who achieved a 15-or-more letter improvement with the dexamethasone 0.7-mg implant was 21.3% at day 30, 29.3% at day 60, and 21.5% at day 180. Thus, the maximal improvement in visual acuity gain compared with sham procedure (e.g., 29.3% vs 11.3% at day 60) was observed in the first months of treatment. By day 180, the proportion of sham procedure-treated patients who achieved 15-or-more letter improvement approached that of the dexamethasone-treated group (17.6% for sham vs 21.5% for dexamethasone 0.7-mg). The dexamethasone implant also resulted in a decrease in central subfield retinal thickness at day 90 (208 μm vs 85 μm, respectively), but not at day 180 (119 μm vs 119 μm, respectively) compared with sham procedure-treated eyes. There was a small, but statistically significant decrease in the percentage of eyes with loss of 15 letters or more throughout the study. For example, at 180 days, the percentage of eyes with such a loss was 6% for the dexamethasone 0.7-mg group and 11% for the sham procedure-treated group. Although retinal neovascularization decreased (0.7% vs 2.6%, respectively), the overall incidence of ocular adverse events was higher with the dexamethasone implant (62%) than with the sham procedure group (43%). There were significant increases in eye pain (7.4% vs 3.8%), ocular hypertension (4% vs 0.7%), and anterior chamber cells (1.2% vs 0%), all respectively. In patients who were retreated with the dexamethasone 0.7-mg implant after the initial 180-day study, 25% of patients had an increase in IOP.

In the open-label extension phase, patients in both the implant and sham-control groups who completed the 6-month, double-masked phase could receive a dexamethasone 0.7-mg implant if BCVA was less than 84 letters or retinal thickness was more than 250 μm. At day 180, 997 patients received a dexamethasone implant, of whom 341 received a second implant. Another 199 patients entered into the open-label phase of the study for follow-up without receiving further treatment. The primary outcome at 12 months was safety, and results were analyzed for all patients by treatment received. Cataract progression over the 12 months occurred in 90 (30%) of 302 phakic eyes that received 2 implants compared with 31 (11%) of 296 eyes that received a single implant and 5 (6%) of 88 sham procedure-treated phakic eyes. Increases in IOP tended to be transient but increased to 35 mm Hg or more in 15% of eyes at 60 days after implantation. A 15-or-more letter improvement in BCVA was found in 30% of patients at 60 days after the first implant and 32% of patients at 60 days after the second dexamethasone implant. With the exception of cataract progression, the efficacy and safety of receiving 2 implants were similar to the efficacy and safety of 1 dexamethasone implant.

The dexamethasone intravitreal implant (0.35 or 0.7 mg) has been compared with observation for the treatment of persistent macular edema in 315 patients with diabetic retinopathy, BRVO and CRVO, uveitis, or Irvine-Gass syndrome (post–cataract surgery macular edema) in a U.S. phase
2 multicenter trial. The primary inclusion criterion was that the patient had macular edema that persisted for at least 90 days after laser treatment or medical therapy; randomization was stratified by the underlying cause of the macular edema. The study included 172 patients with diabetic retinopathy, 60 patients with BRVO, 42 patients with CRVO, 14 patients with uveitis, and 27 patients with Irvine-Gass syndrome. Both the dexamethasone 0.35-mg and 0.7-mg implants increased the proportion of patients meeting the primary outcome of an improvement in visual acuity of 10 letters or more at 90 days (24% and 35%, respectively) versus 13% of patients in the observation group. As in the FDA trial previously described, the effect was reduced at 180 days (24% and 32% with the dexamethasone 0.35-mg and 0.7-mg implants vs 21% for observation, respectively; p=0.06). Anterior chamber flare and increased IOP were more frequent in the dexamethasone implant group. Subgroup analysis indicated that the efficacy results were similar across the different diseases. Additional subgroup analyses from the 2007 trial were reported in 2009 and 2010.

In a 2014 randomized trial, Pichi et al found that the combination of an Ozurdex implant plus macular grid laser increased both visual acuity and the time interval between repeated Ozurdex injections. In other small trials, Maturi et al found no additional benefit for visual acuity with a combination of dexamethasone plus bevacizumab, while Gado and Macky found similar visual acuity outcomes when comparing Ozurdex to bevacizumab.

Section Summary: Macular Edema Following Retinal Vein Occlusion
No RCTs were identified with fluocinolone acetonide implants. Ozurdex is approved for the treatment of macular edema following BRVO and CRVO. Evidence for these indications includes 3 RCTs, 2 of which were sham-controlled. The time to improved vision was faster with the implant, which met the prespecified outcome, but there were no differences between treatment groups at the 6-month time point.

Diabetic Macular Edema
A 2008 Cochrane review evaluated the efficacy of intravitreal steroids for macular edema in diabetes. Seven studies, involving 632 eyes with DME, were included. Four trials examined the effectiveness of intravitreal triamcinolone acetate injection, and 3 examined intravitreal steroid implantation with fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system (the 2007 trial by Kuppermann previously described). The Cochrane review concluded that steroids placed inside the eye by intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DME. However, questions remained about whether intravitreal steroids could be of value in other (earlier) stages of DME or in combination with other therapies, such as laser photoagulation.

Fluocinolone Acetonide Implant

Retisert
In 2011, Pearson et al reported 3-year efficacy and safety results from an industry-sponsored study of a fluocinolone acetonide intravitreal implant (Retisert) in 196 eyes with persistent or recurrent DME. All affected eyes had undergone focal/grid laser photoagulation at least 12
weeks before enrollment. Patients were randomized 2:1 to receive the Retisert 0.59-mg implant (n=127) or SOC (additional laser as needed after 6 months, n=69). Follow-up by masked examiners was performed on day 2 and then in weeks 1, 3, 6, 12, 26, 39, and 52, and then every 13 weeks for 3 years. The primary efficacy outcome, at least a 15-letter improvement in BCVA at 6 months (before any additional laser treatment), was achieved in 16.8% of implanted eyes versus 1.4% of SOC eyes. Between 6 and 24 months, there was a trend toward a higher proportion improved in the implant group (not statistically significant at some follow-up visits), and, at 3 years, there was no significant difference between the groups (e.g., 31.1% of implanted eyes vs 20.0% of SOC eyes improved ≥15 letters at 3 years). The proportion of eyes with no evidence of retinal thickening was greater in the implant group through 2 years, but not at 3 years postimplantation (≥40% in both groups at 3 years). More patients in the implant group showed improvement of 1 grade on the 12-grade Diabetic Retinopathy Severity Scale (≥30% vs 20% for SOC), but there were no significant differences in the proportion of patients who improved by more than 1 grade (≥10% in both groups). There was a higher rate of treatment-related ocular adverse events in the implant group (100% vs 88.4%). The most frequent adverse events in implanted eyes were elevated IOP (69.3% vs 11.6%), worsening cataracts (55.9% vs 21.7%), vitreous hemorrhage (40.2% vs 18.8%), pruritus (38.6% vs 21.7%), and abnormal sensation in the eye (37.0% vs 11.6%) between the implanted and the SOC groups. IOP of 30 mmHg or more at any time during follow-up was recorded in 61.4% of implanted eyes versus 5.8% of SOC eyes, and 33.8% of implanted eyes required surgery for ocular hypertension. In 3 (2.4%) eyes, the implant was removed to relieve IOP. Of phakic eyes, 20% of SOC eyes had cataract extraction compared with 91% with a fluocinolone acetonide implant.

**ILUVIEN**

The FAME study group reported the efficacy and safety of 2 doses of fluocinolone acetonide intravitreal inserts (ILUVIEN) in 2 pivotal industry-sponsored multicenter, double-masked, randomized sham-controlled trials. A total of 956 patients with persistent DME (at least 1 previous macular laser treatment) were randomized 1:2:2 to sham injection (n=185), low-dose insert (0.2 mg/d, n=375), or high-dose insert (0.5 mg/d, n=393). Patients were eligible for rescue laser after 6 weeks and could be given additional study drug or sham injections after 1 year. Follow-up visits were performed at 1 week, 6 weeks, and 3 months, and then every 3 months thereafter. The primary outcome, the percentage of patients with improvement from baseline BCVA of 15 letters or more at 24 months, was significantly greater in the low- (28.7%) and high-dose insert groups (28.6%) than in the sham group (16.2%). A final BCVA of 20/40 was achieved in 31% to 33% of patients in the insert groups compared with 22% in the sham group. Foveal thickness less than 250 μm was attained by a greater percentage of patients in the low- (51%) and high-dose groups (47%) than in the sham group (40%), while more patients in the sham group received focal/grid laser therapy after study entry (58.9% vs 36.7% and 35.2%). The authors reported an increase in IOP (not defined) in 3.25% of the implant groups and 0% of the sham group. However, the package insert indicated that there was an IOP elevation of 10 mm Hg or more from baseline in 34% of patients who received an ILUVIEN insert compared with 10% of controls. Surgery for glaucoma was performed in 3.7% and 7.6% of the low- and high-dose inserts, respectively, compared with 0.5% of the sham groups. More patients in the insert groups...
required cataract surgery. Of phakic eyes, 23.1% had cataract surgery compared with 74.9% and 84.5% in the low- and high-dose groups, respectively. The low-dose insert has FDA approval for the treatment of DME.

Three-year results from the FAME study were reported in 2012. The percentage of patients who gained 15 letters or more using the last observation carried forward was 28.7% (low dose) and 27.8% (high dose) compared with 18.9% in the sham group. When only patients who remained in the trial at 36 months were included (≈70% follow-up), the percentage of patients who gained 15 letters or more was 33.0% and 31.9% (low and high dose, respectively) compared with 21.4% for controls. Masked grading of diabetic retinopathy showed improvement of 2 steps or more in the Early Treatment Diabetic Retinopathy Study Retinopathy Scale in a similar percentage of patients in the high-dose group compared with the sham group (8.9% vs 10.1%, respectively), with a slightly higher percentage (13.7%) in the low-dose group. At 36 months, there was no significant difference in mean foveal thickness between the high-dose and sham groups, and a statistically significant difference between the low-dose and sham patients (29 μm) of uncertain clinical significance. Cataract surgery was performed in 80.0% of phakic patients in the low-dose group and 87.2% of the high-dose group compared with 27.3% of the sham group. The occurrence of laser or incisional glaucoma surgery by 36 months was 6.1% in the low-dose group and 10.6% in the high-dose group compared with 0.5% of the sham group. Masked grading of diabetic retinopathy showed improvement of 2 steps or more in a similar percentage of patients in the high-dose group compared with the sham group (8.9% vs 10.1%, respectively), with a slightly higher percentage (13.7%) in the low-dose group. At 36 months, there was no significant difference in mean foveal thickness between the high-dose and sham groups, and a statistically significant difference between the low-dose and sham patients (29 μm) of uncertain clinical significance. Cataract surgery was performed in 80.0% of phakic patients in the low-dose group and 87.2% of the high-dose group compared with 27.3% of the sham group. The occurrence of laser or incisional glaucoma surgery by 36 months was 6.1% in the low-dose group and 10.6% in the high-dose group compared with 0.5% of the sham group. Planned subgroup analysis showed greater efficacy in patients with chronic (≥3 years) compared with nonchronic (<3 years) DME. Specifically, the percentage of patients who gained 15 letters or more was significantly greater in patients with chronic DME compared with sham (34.0% vs 13.4%, p<0.001), but not in patients with nonchronic DME (22.3% vs 27.8%). Improvement in visual acuity was not associated with an improvement in anatomic measures in the chronic DME group. Adverse event rates did not differ between the chronic and the subchronic groups.

Dexamethasone Intravitreal Implant

Dexamethasone Intravitreal Implant Compared With Sham Procedure
Three-year results from 2 pivotal industry-sponsored, multicenter, double-masked phase 3 trials (NCT00168389, NCT00168337) with Ozurdex were published in 2014. A total of 1048 patients with DME were randomized to treatment with a Ozurdex 0.7-mg or 0.35-mg implant or a sham procedure. Retreatment was allowed if it was at least 6 months since the prior treatment and there was evidence of residual edema. Patients with a loss of 15 letters or more in BCVA discontinued, with the last observation carried forward for the primary outcome measure of the percentage of patients with a 15-or-more letter improvement in BCVA. The 3-year completion rate was 57.9% of patients, with only 43.4% of patients in the sham group completing the study. Completion rates for the dexamethasone groups were 64.1% and 66.3% for 0.7 mg and 0.35 mg, respectively.

Compared with sham treatment, the dexamethasone 0.7-mg and 0.35-mg implants led to improved visual acuity in a significantly higher percentage of patients, and a greater mean decrease in central retinal thickness (see Table 1). Notably, the difference in the percentage of Ozurdex- and sham procedure-treated patients who achieved greater than 15-letter improvement...
in BCVA ranged from about 6% to 10%, with a number needed to treat (NNT) of 9.8 patients to provide 1 patient with at least a 15-letter improvement with the 0.7-mg implant. IOP increased by 10 mm Hg or more in one-quarter of patients treated with the corticosteroid implant. The occurrence of cataract was more than 3-fold higher for Ozurdex than sham procedure, with two-thirds of patients requiring cataract surgery.

**Table 1. Results from Boyer et al (2014)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ozurdex 0.7 mg</th>
<th>Ozurdex 0.35 mg</th>
<th>Sham</th>
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<tbody>
<tr>
<td>Treatments received over 3 y, n</td>
<td>4.1</td>
<td>4.4</td>
<td>3.3</td>
</tr>
<tr>
<td>≥15-letter improvement, % of patients</td>
<td>22.2%</td>
<td>13.4%</td>
<td>12%</td>
</tr>
<tr>
<td>Baseline CRT, μm</td>
<td>463.0</td>
<td>465.8</td>
<td>463.9</td>
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<tr>
<td>Mean reduction in CRT, μm</td>
<td>111.6</td>
<td>-107.9</td>
<td>-41.9</td>
</tr>
<tr>
<td>Increase in IOP ≥10 mm Hg, % of patients</td>
<td>27.7%</td>
<td>24.8%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Cataract adverse events in phakic eyes, %</td>
<td>67.9%</td>
<td>64.1%</td>
<td>20.4%</td>
</tr>
</tbody>
</table>

CRT: central retinal thickness; IOP: intracocular pressure.

\( ^a p<0.001 \)

\( ^b p=0.018 \)

**Dexamethasone Intravitreal Implant Compared With Anti-VEGF**

The BEVORDEX study was a phase 2, randomized comparison of bevacizumab and dexamethasone implant for the treatment of DME.\(^{29}\) Forty-two eyes were randomized to bevacizumab every 4 weeks and 46 eyes were randomized to a dexamethasone implant every 16 weeks as needed. After 12 months of treatment, the improvement in BCVA of 10 letters or more was similar for both groups (40% of the bevacizumab-treated eyes vs 41% of the dexamethasone-treated eyes). The dexamethasone implant reduced mean central macular thickness more than bevacizumab (187 μm vs 122 μm; \( p=0.015 \)), but led to a greater number of adverse events, including IOP elevation of 10 mm Hg or more (19.6% vs 0%), cataracts (13% vs 4.8%), and vision decrease of more than 10 letters (10.9% vs 0%) at 12 months, respectively. Other studies have shown an increase in cataracts predominantly in the second year of treatment with the dexamethasone implant.\(^{28}\)

**Dexamethasone Intravitreal Implant Plus Anti-VEGF**

Maturi et al reported a small (N=40 eyes) single-masked, randomized trial of Ozurdex plus bevacizumab compared to bevacizumab alone.\(^{30}\) At 12 months, there was no significant difference between the groups in visual acuity, with an improvement of 5.4 letters for the combined group and 4.9 letters for the monotherapy group. The monotherapy group received a mean of 9 injections of bevacizumab, which was similar to a mean of 6 injections of bevacizumab plus 2.1 injections with Ozurdex for the combined treatment group. Treatment with Ozurdex led to a greater mean reduction in central subfield thickness (difference, 69 μm; \( p=0.03 \)). Drug-related adverse events were higher in the combined treatment group, with IOP elevation (>21 mm Hg) in 6 eyes and worsening of cataracts in 9 eyes. This compared with 1 instance of IOP elevation in the bevacizumab monotherapy group.
Dexamethasone Intravitreal Implant Plus Laser Photocoagulation

The PLACID study group reported a multicenter, double-masked, RCT (N=253) that compared Ozurdex plus combination laser photocoagulation to sham treatment plus laser photocoagulation for the treatment of diabetic macular edema. The percentage of patients who gained 10 letters or more was greater at 1 month (31.7% vs 11.0%, p<0.001) and 9 months (31.7% vs 17.3%, p=0.007) than at 12 months (27.8% vs 23.6%). More patients in the laser-alone group discontinued the study due to lack of efficacy (8.7% vs 0.8%), which may have biased results. An increase in IOP of at least 10 mm Hg was observed in 15.2% of eyes treated with Ozurdex. In addition, cataract-related adverse events were more common after treatment with Ozurdex (22.2% vs 9.5%, p=0.017).

Section Summary: Diabetic Macular Edema

Retisert is not approved by FDA for this indication. This fluocinolone acetonide implant was compared with focal/grid laser photocoagulation in a single (investigator)-masked RCT. The primary efficacy outcome, at least a 15-letter improvement in BCVA at 6 months, was significantly improved, but there was no significant difference between the groups at 3 years. An IOP of 30 mm Hg or more was observed in 61.4% of implanted eyes versus 5.8% of eyes treated with SOC, and 33.8% of implanted eyes required surgery for ocular hypertension. Due to the marginal benefit and substantial increase in adverse events with this fluocinolone acetonide 0.59-mg implant, it is not indicated for DME.

ILUVIEN has been approved for DME in patients previously treated with corticosteroids who did not have a clinically significant rise in IOP. Approval of the ILUVIEN 0.19-mg implant was based on 2 multicenter, double-masked, RCTs with 2 doses of fluocinolone acetonide. As with the other indications, the benefit for vision was modest. The lower dose had similar efficacy to the high-dose implant, with a reduction in adverse events. There was an IOP elevation in 34% of patients who received this implant compared with 10% of controls, leading to the restricted indication.

Ozurdex has been approved for DME. Results from the pivotal FDA-regulated trials that evaluated the dexamethasone implant for DME showed modest benefit compared with sham treatment (number needed to treat, 9.8) with a significant increase in adverse events. There was at least a 10 mm Hg increase in IOP in about 25% of study participants and a 3-fold increase in cataracts. Smaller trials comparing the dexamethasone implant to laser photocoagulation or bevacizumab also reported modest benefits for visual acuity, with an increase in adverse events.

Age-Related Macular Degeneration

Dexamethasone Intravitreal Implant

In 2015, the ERIE Study Group published a single-masked, sham-controlled, multicenter trial on the use of a dexamethasone intravitreal implant as adjunctive therapy to treat age-related macular edema. All patients (n=243) in this industry-sponsored study received 2 ranibizumab injections, with the next injection given as needed based on established study criteria. The primary efficacy end point was the ranibizumab injection-free interval. Ozurdex increased the injection interval...
based on Kaplan-Meier survival analysis (p=0.016). A small, but statistically significant percentage of patients did not require rescue ranibizumab over the 6-month study period (8.3% vs 2.5%, p=0.048). There was a very small reduction in the mean number of as-needed ranibizumab injections over the 6 months of the study (3.15 vs. 3.37), but patients in the Ozurdex group received an additional injection of the implant. There were no significant differences between the groups in mean change from baseline BCVA. More patients in the Ozurdex group had increased IOP (13.2% vs 4.2%; p=0.014), but there were no differences between the groups in cataract-related events.

Other
There are reports of corticosteroid implants being investigated for other disorders of the eye, including radiation retinopathy, macular edema related to retinitis pigmentosa, vasoproliferative retinal tumors, idiopathic macular telangiectasia type 1, postoperative macular edema, Irvine-Gass syndrome, Coat disease, circumscribed choroidal hemangioma, age-related macular degeneration, proliferative vitreoretinopathy, rhegmatogenous retinal detachment, and anterior scleritis.33

Adverse Events
In 2013, Kiddee et al conducted a systematic review of IOP following intravitreal corticosteroid administration.34 The review included 7 studies on the fluocinolone intravitreal implant and 6 studies on the dexamethasone implant. Meta-analysis of ocular hypertension with intravitreal corticosteroid implants was conducted using a threshold of a 10 mm Hg rise from baseline or an IOP greater than 21 mm Hg for fluocinolone or 25 mm Hg or more for dexamethasone. Pooled analysis found a rise in IOP in 65.9% of patients with a fluocinolone 0.59-mg implant and 10.9% of patients with a dexamethasone 0.7-mg implant. Most cases of ocular hypertension can be controlled medically.

In addition to the common occurrence of an increase in IOP and development of cataracts, several rarer adverse events have been reported. They include fracture and/or desegmentation of the implant, implant migration into the anterior chamber, and inadvertent injection of the implant into the crystalline lens. Anterior chamber migration may be particularly problematic in vitrectomized eyes without an intact lens capsule, and has led to corneal edema necessitating corneal transplantation.33

Ongoing and Unpublished Clinical Trials
An online search of ClinicalTrials.gov in March 2016 identified a large number of small trials with intravitreal corticosteroid implants.

Summary of Evidence
The evidence for intravitreal corticosteroid implants in individuals who have inflammation or edema of the eye (e.g., noninfectious uveitis, edema following retinal vein occlusion, diabetic macular edema) includes a number of high-quality trials submitted to U.S. Food and Drug Administration (FDA) in support of new technologies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Overall,
results have shown a modest improvement in visual outcomes in a relatively small number of patients, with a significantly higher rate of cataracts and increased intraocular pressure (IOP) compared with controls. As a result, one FDA-approved indication for a fluocinolone implant limits treatment to patients who have previously shown an improvement with corticosteroid treatment without an increase in IOP. Overall, intravitreal implants might be considered a reasonable alternative when patients are intolerant or refractory to topical or systemic therapy, in patients for whom systemic steroid-related adverse effects are expected to be more frequent and/or severe than ocular adverse effects, or in patients who have failed to respond to other intravitreal therapies. Given the modest improvement in vision and the potential for adverse events, patients should be informed about the potential for cataracts, increased IOP or hypotony, endophthalmitis, and risk of additional surgical procedures. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 1 academic medical center while this policy was under review in 2011. Input supported use of intravitreal corticosteroid implants, confined to the FDA-labeled indications. It was noted that Ozurdex is used for short-term uveitis control while the Retisert implant is used for more long-term control of uveitis.

Practice Guidelines and Position Statements
In 2011, the U.K.’s National Institute for Health and Care Excellence (NICE) provided guidance on the use of the dexamethasone intravitreal implant for macular edema secondary to retinal vein occlusion.55 The dexamethasone implant is recommended as an option for the treatment of macular edema following either central retinal vein occlusion. It is recommended as an option for the treatment of macular edema following branch retinal vein occlusion when treatment with laser photocoagulation has not been beneficial, or if laser photocoagulation is not considered suitable because of the extent of macular hemorrhage.

In 2015, NICE provided guidance on the dexamethasone intravitreal implant for treating diabetic macular edema.36 Ozurdex is recommended as a possible treatment for diabetic macular edema if there is an artificial lens and the edema either has not improved with non-corticosteroid treatment or non-corticosteroid treatment is not considered suitable.

In November 2013, NICE replaced technology appraisal guidance 271 (January 2013) with guidance 301, concluding that the fluocinolone acetonide intravitreal implant (ILUVIEN) is recommended as an option for treating chronic diabetic macular edema that is insufficiently responsive to available therapies only if:
**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
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<td>POLICY NUMBER</td>
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- The implant is to be used in an eye with an intraocular (pseudophakic) lens and
- The manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme.\(^{37}\)

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD).

**V. DEFINITIONS**

**INTRAVITREAL** - refers to that which is injected into the eye's vitreous humor between the lens and the retina.

**UVEITIS** - An inflammation of part or all of the uvea, the middle (vascular) tunic of the eye and commonly involving the other tunics (the sclera and cornea and the retina).

**VI. BENEFIT VARIATIONS**

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

**VII. DISCLAIMER**

*Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*
VIII. CODING INFORMATION

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Covered when medically necessary:**

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**HCPCS Code**  **Description**

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**ICD-10-CM Diagnosis Codes**  **Description**

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<td>E08.331</td>
<td>Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema</td>
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<td>Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema</td>
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<td>E08.351</td>
<td>Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema</td>
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<td>E09.321</td>
<td>Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema</td>
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<td>E09.331</td>
<td>Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema</td>
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<tr>
<td>E09.341</td>
<td>Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema</td>
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<td>E09.351</td>
<td>Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema</td>
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<td>E10.321</td>
<td>Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema</td>
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<td>E10.331</td>
<td>Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema</td>
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<td>ICD-10-CM Diagnosis Codes</td>
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<td>Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema</td>
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<td>Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema</td>
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<td>Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema</td>
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<td>E13.321</td>
<td>Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema</td>
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<td>H30.011</td>
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<td>H30.013</td>
<td>Focal chorioretinal inflammation, juxtapapillary, bilateral</td>
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<td>H30.021</td>
<td>Focal chorioretinal inflammation of posterior pole, right eye</td>
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<td>H30.043</td>
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<td>H30.21</td>
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<td>H34.811</td>
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<td>Central retinal vein occlusion, bilateral</td>
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IX. REFERENCES


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<tr>
<th>Policy Title</th>
<th>Intravitreal Corticosteroid Implants</th>
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<tr>
<td>Policy Number</td>
<td>MP-2.159</td>
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Other:

X. POLICY HISTORY

| MP-2.159 | CAC 4/26/10. New policy. Adopted BCBSA- Policy addresses the fluocinolone acetonide intravitreal implant (e.g., Retisert®) which may be considered medically necessary for the treatment of chronic noninfectious posterior uveitis, in one or both eyes. All other indications are considered investigational. |
| CAC 10/25/11. For this review, Ozurdex (dexamethasone implant) was added to the policy, previously these FDA-approved criteria were in MP-4.008 Ocular Therapy; corticosteroid implants may be medically necessary for FDA-approved indications. Background/description was revised. Policy title changed to “Intravitreal Corticosteroid

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<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>CAC 8/28/12</td>
<td>Medically necessary policy statement on use of fluocinolone acetonide intravitreal implant expanded to include intermediate, posterior, and panuveitis. Medically necessary policy statement on use of dexamethasone intravitreal implant expanded to include non-infectious ocular inflammation or uveitis, affecting the intermediate or the posterior segment of the eye. Changed FEP variation from standard to reference FEP Medical Policy Manual MP-9.03.23 Intravitreal Corticosteroid Implants. Codes reviewed 8/13/12</td>
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<tr>
<td>CAC 7/30/13</td>
<td>Consensus review. References updated. No changes to the policy statements. Policy guidelines added. No coding changes.</td>
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<tr>
<td>CAC 11/25/14</td>
<td>Minor revision. Policy being revised to add new medically necessary indications for flucinolone and dexamethasone inserts considered medically necessary for the treatment of diabetic macular edema. Background, rationale and references revised. Added 362.07 to medically necessary diagnosis.</td>
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<tr>
<td>CAC 9/27/16</td>
<td>Consensus review. No change to the policy statements. Background, references and rationale updated. Variations reformatted. Coding reviewed.</td>
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