I. POLICY

A fluocinolone acetonide intravitreal implant approved by the U.S. Food and Drug Administration (i.e., Retisert®) may be considered medically necessary for the treatment of chronic noninfectious intermediate, posterior, or panuveitis.

A dexamethasone intravitreal implant approved by the U.S. Food and Drug Administration (i.e., Ozurdex™) may be considered medically necessary for the treatment of:

- Non-infectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye, OR
- Macular edema following branch or central retinal vein occlusion.

All other uses of a corticosteroid intravitreal implant are considered investigational, including but not limited to the treatment of diabetic macular edema. 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-reference

- MP-2.028 Eye Care
- MP-4.008 Ocular Therapy
- MP-2.149 Aqueous Shunts and Devices for Glaucoma
II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[Y] SeniorBlue HMO**
[Y] SeniorBlue PPO**

[N] Indemnity
[N] SpecialCare
[N] POS
[Y] 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

** “FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if determined that the use is medically accepted, taking into consideration the major 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

An intravitreal implant is a drug delivery system, injected or surgically implanted in the vitreous of the eye, for sustained release of drug to the posterior and intermediate segments of the eye. Intravitreal corticosteroid implants are being investigated for a variety of inflammatory eye conditions.

Background

Intravitreal implants are being developed to deliver a constant 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, or by 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 intraocular pressure, and cataract development.

Corticosteroid implants may be either biodegradable or non-biodegradable. Non-biodegradable systems are thought to be preferable for treating chronic, long-term disease, while biodegradable products may be preferred for conditions that require 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® (non-biodegradable 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 0.3–0.4 mcg/day over a period of approximately 2.5 years.
- Iluvien™ (non-biodegradable injectable intravitreal implant with fluocinolone acetonide; Alimera Sciences, Inc.) is a rod-shaped device made of polyimide and polyvinyl alcohol (PVA). 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,
Behcet’s disease, 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 (less than 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 U.S., 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, and tumor necrosis factor [TNF]-inhibitors) may also be utilized 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.

**Diabetic Macular Edema**

Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The two 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. Diabetic macular edema 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 diabetic macular edema and intravitreal steroid implants are being evaluated. Angiostatic agents, which block some stage in the pathway leading to new blood vessel formation (angiogenesis) are also being evaluated for the treatment of diabetic macular edema.

**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 with respect to pathophysiology, clinical course, and therapy. Central retinal vein occlusions are also categorized as ischemic or nonischemic. Ischemic CRVOs are referred to as severe, complete, or total vein obstruction and account for 20-25% 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 commonly than CRVOs. 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 anti-vascular endothelial growth factor (anti-VEGF).

**Regulatory Status**

In April 2005, Retisert® (fluocinolone acetonide intravitreal implant) received fast-track approval by the U.S. Food and Drug Administration (FDA) as an orphan drug for the 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 the FDA as affecting fewer than 200,000 persons in the U.S. Because of the lack of data on the long-term effects of Retisert®, the FDA required that a post marketing analysis be conducted. Outcome analyses will be targeting complications associated with cataract extractions, monitoring for delamination of the implants and assessing the effect of the implant on the corneal endothelium.

A dexamethasone intravitreal implant (Ozurdex™; Allergan, Inc), composed of a biodegradable copolymer of lactic acid and glycolic acid with 0.7 mg micronized...
dexamethasone, received premarket approval by the FDA in 2009 for the treatment of macular edema following branch or central retinal vein occlusion, and in 2010 for the treatment of non-infectious ocular inflammation, or uveitis, affecting the posterior segment of the eye.

The FDA analysis notes that the safety and efficacy effects seen with this product 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 sub capsular cataract formation. The labeling contains the following warnings and precautions “Intravitreal injections 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 sub capsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.”

Data on Iluvien™ (non-biodegradable injectable intravitreal implant with fluocinolone acetonide; Alimera Sciences, Inc.) has been submitted to the FDA for the indication of diabetic macular edema; as of March 2010, this product has not received FDA approval. Other formulations are also being investigated, but are not yet available for the treatment of vitreoretinal disorders in the U.S.

IV. RATIONALE

Noninfectious Uveitis

Fluocinolone Acetonide Implant: There are at least 4 multicenter, randomized controlled clinical trials that address this indication. (1, 2) Two of the studies were double-masked and compared 2 doses (0.59 mg versus 2.1 mg) of the fluocinolone acetonide implant in one eye to no treatment in the control eye. (3, 4) The other 2 trials were open label studies of implants versus standard of care, which generally was systemic steroids. (5, 6)

In the first (Pivotal) Phase III 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. (4) Pooled results from both doses showed a reduction in recurrence rate in the implanted eye compared with an increase in recurrence in the nonimplanted eye over the pre- and post-implant periods. Improvement of 3 or more lines in visual acuity was seen in significantly more implanted eyes compared with the nonimplanted eyes. An increase in intraocular pressure was seen at week 4 with both doses, (approximately 6 mm Hg) compared with no significant change in intraocular pressure (IOP) in the nonimplanted eyes. Over the 34-week course of the study, 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 III 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 recurrence rate was seen in the implanted eye over the 34-week study, 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 compared with the nonimplanted eye. A reduction in cystoid macular edema was also seen in the implanted eye compared with the nonimplanted eye (69% vs. 23%, respectively). The most commonly reported adverse events (50-90%) in the clinical trials included cataracts, increased intraocular pressure, postprocedural complications associated with implant insertion, and ocular pain. Other ocular adverse events included decreased visual acuity, glaucoma, blurred vision, and abnormal sensation in the eye, eye irritation, and a change in tearing (either increased or decreased). Based on data available at this time, 60% of patients will experience an increase in intraocular pressure sufficient to require drug treatment within 34 weeks of implant; 32% of patients will require filtering procedures within 2 years of implant to control intraocular pressure, and nearly all phakic eyes will develop cataracts and require surgery within 2 years of receiving the implant. (1) In addition, 31% of patients in these studies reported headache.

In 2010, Pavesio and colleagues published 2-year results from a manufacturer-sponsored multicenter (10 European countries and 37 centers) randomized open-label controlled trial of the sustained release fluocinolone acetonide implant (0.59 mg) compared to standard of care. (5) To be included in the study, subjects had to have a 1-year or longer 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 longer; “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 standard-of-care 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 prestudy and postoperative anti-inflammatory therapy. The standard-of-care group received prednisolone or an equivalent corticosteroid (less than 15 mg/day 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 standard of care; 6 subjects discontinued before treatment and were excluded from the intention-to-treat population. A total of 131 patients (90%) 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, then every 3 months from 1–3 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 the combination of 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, the time to uveitis recurrence was not statistically different (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 macula edema (CME) was present at baseline, the change in the size of the area of CME on fluorescein angiography. The proportion of subjects with a reduction in the area of cystoid macular edema greater than 1 mm² was 87% (32/37) in the implant group and 74% (29/39) in the standard-of-care 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 standard-of-care group remained consistent over the course of 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 below).
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 standard-of-care group. Implanted eyes also had a greater number of serious ocular adverse events compared with standard-of-care eyes (91% vs. 24%, respectively). The most commonly reported adverse events in the implant group were cataract and elevated intraocular pressure or glaucoma. Of 66 implanted eyes, 49 (74%) were phakic at 2 years, compared to 57 (77%) of 74 eyes that received standard of care. Of the eyes that were phakic, 90% of implanted eyes and 23% of phakic standard-of-care eyes had a change in lens opacity of 2 grades or more; cataracts were extracted in 88% (43/49) of phakic implanted study eyes in comparison with 19% (11/57) of phakic standard-of-care eyes. Thus, development of cataracts of a severity requiring extraction occurred in 65% of the implanted eyes and 15% of eyes receiving standard of care. During the 2-year follow-up, 55% of implanted eyes had an increase in intraocular pressure of 10 mm Hg or more from baseline compared with 11% of standard-of-care study eyes. Medication was required to control elevated intraocular pressure in 62% of implanted eyes compared with 20% of standard-of-care eyes, while intraocular-pressure-lowering surgery was performed in 21% of implanted eyes compared with 3% of standard-of-care eyes. The incidence of hypotony was significantly higher in implanted eyes (20% vs. 1%, respectively). By the 2-year follow-up visit, 8 eyes (12%) had been explanted: 3 because of hypotony, 2 because of elevated intraocular pressure, 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 versus 42% in the standard-of-care eyes. The decrease in visual acuity in implanted eyes was attributed to the implantation procedure at the 1-day post-implantation visit (31% of implanted eyes) and cataract progression (47% of implanted eyes at 18 months). Visual acuity was similar in the two groups following cataract removal. Other serious ocular adverse events in implanted eyes included 3 cases of endophthalmitis (4.5%) compared with none (0%) for standard-of-care eyes. Rates of nonocular adverse events considered to be treatment-related were higher in the standard-of-care group (26% vs. 0%); 3 of the 19 adverse events in the standard-of-care group were considered to be serious (4% of the total standard-of-care group).

The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group reported a National Eye Institute funded randomized comparison of the fluocinolone acetonide intravitreal implant versus systemic anti-inflammatory therapy for intermediate, posterior, and panuveitis in 2011. (6) 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 was found to improve over 24 months for both groups. Intent-to-treat analysis showed no significant difference between the 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 had macular edema (20% vs. 34%). Over the 24-month period, implant-assigned eyes had a higher risk of cataract surgery (80% vs. 31%, hazard ratio [HR]: 3.3), treatment for elevated intraocular pressure (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 vs. 0.36/person-year) without notable long-term consequences.

A retrospective review of medical records of all patients receiving fluocinolone acetonide intravitreal implants over an 8-year period at one institution revealed a significant risk of increased IOP requiring glaucoma surgery. (7) Nineteen of 42 eyes (45%) that received implants during the 8-year 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.

Conclusions. Taken together, there is strong evidence of efficacy for treatment of noninfectious uveitis. 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 to alternatives. Due to the higher incidence of ocular adverse events, this procedure might be considered a reasonable alternative when patients are intolerant or refractory to systemic therapy, or in patients for whom systemic steroid-related adverse effects are expected to be more frequent and/or severe than the ocular adverse effects.

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 randomized double-masked controlled trial of the dexamethasone intravitreal implant in 229 patients with uveitis. (8) 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; the 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 condition 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 patients (95%) 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 seen in more eyes in the implant groups than the sham group at all study visits (about 40% vs. 10%), although the efficacy of the lower 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 than 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 groups, respectively. The percentage of eyes with intraocular pressure of 25 mm Hg or more peaked at 7.1% for the 0.7 mg implant, 8.7% for the 0.35 mg implant, and 4.2% for the sham group. The incidence of cataract in the phakic eyes was 9 of 62 (15%) with the 0.7 mg implant, 6 of 51 (12%) with the 0.35 mg implant, and 4 of 55 (7%) with the sham procedure.

Macular Edema Following Retinal Vein Occlusion

Fluocinolone Acetonide Implant: No randomized controlled trials were identified with the fluocinolone acetonide implant 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 randomized controlled trials, 2 of which were sham-controlled.

Data presented to the 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. (9, 10) A 6-month open-label extension of these 2 pivotal trials was reported in 2011. (11) A total of 1,267 patients who had clinically detectable macular edema associated with either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) were enrolled. The mean visual acuity at baseline was about 54 letters (20/80) and the mean central retinal thickness was approximately 550 microns. About 75% of the patients had macular edema for a duration of more than 3 months. Patients were randomized to a single treatment with a 0.7 mg dexamethasone implant (n=427), 0.35 mg dexamethasone 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 the placement of study medication. The primary outcome measure for the first trial was the proportion of eyes achieving a 10- to 15-letter improvement from baseline. The primary outcome measure for the second trial, as requested by the 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 equal to or greater than 15 letters from baseline and central subfield retinal thickness measured by optical coherence tomography (OCT).

For the combined trial data, the time to achieve a treatment response of equal to or greater than 15 letters improvement was faster with the intravitreal implant, meeting the prespecified outcome. There was no significant difference in the proportion of patients who had improved by equal to or greater than 15 letters at 6-month follow-up. The proportion of sham-treated patients who achieved equal to or greater than 15 letters improvement was 7.5% at day 30, 11.3% at day 60, and 17.6% at day 180. The proportion of patients who achieved equal to or greater than 15 letters improvement with the 0.7 mg dexamethasone 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 to sham (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-treated patients who achieved equal to or greater than 15 letters 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 microns vs. 85 microns, respectively) but not at day 180 (119 microns vs. 119 microns, respectively) compared to sham-treated eyes. There was a small, but statistically significant decrease in the percentage of eyes with loss of equal to or greater than 15 letters throughout the study. For example, at 180 days, the percentage of eyes with a loss of equal to or greater than 15 letters was 6% for the dexamethasone 0.7 mg group and 11% for the sham-treated group. Although retinal neovascularization was decreased (0.7% vs. 2.6%, respectively), the overall incidence of ocular adverse events was higher with the dexamethasone implant (62%) than the sham 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 0.7 mg dexamethasone implant after the initial 180-day study, 25% of patients had an increase in intraocular pressure.

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 0.7 mg dexamethasone implant if BCVA was less than 84 letters or retinal thickness was greater than 250 microns. (11) At day 180, 997 patients received a dexamethasone implant, of which 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 according to the treatment received. Cataract progression over the 12 months occurred in 90 of 302 phakic eyes (29.8%) that received 2 implants in comparison with 31 of 296 eyes (10.5%) that received a single implant and 5 of 88 sham-treated phakic eyes (5.7%). Increases in IOP tended to be transient but increased to 35 mm Hg or more in about 15% of eyes at 60 days after implantation. A 15-letter or more improvement in BCVA was found in 30% of patients at
MEDICAL POLICY

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<th>POLICY TITLE</th>
<th>INTRAVITREAL CORTICOSTEROID IMPLANTS</th>
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<td>POLICY NUMBER</td>
<td>MP-2.159</td>
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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 was 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 patients with diabetic retinopathy, BRVO and CRVO, uveitis, or Irvine-Gass Syndrome (postcataract surgery macular edema) in a U.S. Phase II multicenter trial. (12) The primary inclusion criteria was that the patient had persistent macular edema that had persisted for 90 days or more 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 0.35 mg and 0.7 mg dexamethasone implants increased the proportion of patients meeting the primary outcome of an improvement in visual acuity of equal to or greater than 10 letters at 90 days (24.3% and 35.2%, respectively) versus 13.3% of patients in the observation group. As in the FDA trial described above, the effect was reduced at 180 days (24.3% and 32.4% with the 0.35 mg and 0.7 mg dexamethasone implants vs. 21% for observation, respectively; p=0.06). Anterior chamber flare and increased intraocular pressure were more frequent in the dexamethasone implant group. Subgroup analysis indicated that the efficacy results were similar across the different diseases. Additional subgroup analysis from the 2007 trial was reported in 2009 and 2010. (13, 14)

Diabetic Macular Edema

A 2008 Cochrane review evaluated the efficacy of intravitreal steroids for macular edema in diabetes. (15) Seven studies, involving 632 eyes with diabetic macular edema were included. Four trials examined the effectiveness of intravitreal triamcinolone acetate injection, 3 examined intravitreal steroid implantation with either fluocinolone acetonide (Retisert®) or the dexamethasone drug delivery system (the 2007 trial by Kupperman described above). The authors concluded that steroids placed inside the eye by either intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory diabetic macular edema. However, questions remained about whether intravitreal steroids could be of value in other (earlier) stages of diabetic macular edema or in combination with other therapies, such as laser photoocoagulation.

Fluocinolone Acetonide Implant: In 2011, Pearson et al. reported 3-year efficacy and safety results from an industry-sponsored study of the fluocinolone acetonide intravitreal implant in 196 eyes with persistent or recurrent diabetic macular edema. (16) All affected eyes had undergone focal/grid laser photocoagulation at least 12 weeks before enrollment. Patients were randomized 2:1 to receive the 0.59-mg Retisert implant or standard of care (SOC; additional laser as needed after 6 months, n=69). Follow-up by masked examiners was
performed on day 2 and then on weeks 1, 3, 6, 12, 26, 39, and 52 and then every 13 weeks for 3 years. The primary efficacy outcome, a 15 letter or greater improvement in BCVA at 6 months (prior to 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 (did not attain statistical significance on some of the follow-up visits), and during the third year, there was no significant difference between the groups (e.g., 31.1% of implanted eyes versus 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 post-implantation (about 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 (roughly 30% vs. 20% for SOC), but there were no significant differences in the proportion of patients who improved by more than 1 grade (about 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 cataract (55.9% vs. 21.7%), vitreous hemorrhage (40.2% vs. 18.8%), pruritis (38.6% vs. 21.7%), and abnormal sensation in the eye (37.0% vs. 11.6%). IOP of 30 mm Hg 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 eyes (2.4%), the implant was removed to relieve IOP. Of phakic eyes, 20% of SOC eyes had cataract extraction compared to 91% with a fluocinolone acetonide implant.

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. (17) A total of 956 patients with persistent diabetic macular edema (at least 1 previous macular laser treatment) were randomized 1:2:2 to sham injection (n=185), low-dose insert (0.2 microgram/day, n=375), or high-dose insert (0.5 microgram/day, 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- and high-dose insert groups (28.7% and 28.6%, respectively) compared with the sham group (16.2%). The mean improvement in BCVA between baseline and month 24 was modestly greater in the low- and high-dose groups (4.4 and 5.4 letters, respectively) compared with the sham group (1.7 letters), while a final BCVA of 20/40 was achieved in 31% to 33% of patients in the insert groups compared to 22% in the sham group. Foveal thickness less than 250 microns was attained by a greater percentage of patients in the low- and high-dose groups (51% and 47%, respectively) compared to 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%). An increase in IOP (not defined) occurred in 3.25% of the implant groups and 0% of the sham group. Surgery for glaucoma was performed in 3.7% and 7.6% of the low- and high-dose
inserts, respectively, compared to 0.5% of the sham groups. More patients in the insert groups required cataract surgery. Of phakic eyes, 23.1% had cataract surgery compared to 74.9% and 84.5% in the low- and high-dose groups, respectively.

Three-year results from the FAME study were reported in 2012. (18) 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 the patients who remained in the trial at 36 months were included (about 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 microns) 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.

Conclusions. The marginal improvement in visual outcomes compared to laser photocoagulation, combined with the high adverse event rate, does not currently support use of fluocinolone acetonide implants (Retisert) or inserts (Iluvien) for diabetic macular edema. (For comparison, see policy # 9.03.27 on intravitreal angiogenesis inhibitors as an alternative treatment for diabetic macular edema.) In addition, Iluvien has not been approved by the FDA.

Dexamethasone Intravitreal Implant: The dexamethasone intravitreal implant has been investigated for the treatment of persistent macular edema in 172 patients with diabetic retinopathy, along with other etiologies of macular edema. (12) This U.S. Phase II multicenter trial compared the dexamethasone implant (0.35 or 0.7 mg) with observation. Both the 0.35 mg and 0.7 mg dexamethasone implants increased the proportion of patients meeting the primary outcome of an improvement in visual acuity of equal to or greater than 10 letters at 90 days (24.3% and 35.2%, respectively) versus 13.3% of patients in the observation group, with a reduced effect at 180 days (24.3% and 32.4% for the 0.35 mg and 0.7 mg dexamethasone implants vs. 21% for observation, respectively; p=0.06). Subgroup analysis indicated that the efficacy results were similar across the different diseases.
Clinical Input Received Through 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.

Summary

Due to the increase in ocular adverse events requiring additional surgical procedures, results from multicenter randomized controlled trials do not support an overall health benefit with the 0.59 mg fluocinolone acetonide intravitreal implant compared with the standard of care (systemic therapy) for all patients with recurrent noninfectious intermediate, posterior or panuveitis. However, this procedure might be considered a reasonable alternative (medically necessary) when patients are intolerant or refractory to systemic or topical therapy. In addition, this therapy may be considered in patients for whom systemic steroid-related adverse effects are expected to be more frequent and/or severe than the ocular adverse effects.

Informed decision making is a key part of this process. Patients should be informed about the potential adverse effects of intravitreal implants 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 therapy, patients should make an informed choice between the treatments.

FDA approval of the dexamethasone intravitreal implant for BRVO and CRVO was based on two 6-month multicenter studies showing that the time to achieve a treatment response of equal to or greater than 15 letters improvement was faster with the intravitreal implant than sham treatment. Improvement in vision was similar at 6-month follow-up for the 2 groups, suggesting that retreatment may be needed. Use of the dexamethasone intravitreal implant for noninfectious posterior uveitis has also been approved by the FDA, based on positive results from a multicenter randomized controlled trial.
A systematic review indicates that corticosteroids placed inside the eye by either intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory diabetic macular edema, but recent trials with fluocinolone acetonide intravitreal implants/inserts show a modest beneficial effect and a high rate of adverse effects. As a result, it is uncertain whether the overall risk/benefit ratio is favorable when compared to the current standard of laser photocoagulation. Therefore, intravitreal corticosteroid implants for diabetic macular edema are considered investigational.

**Practice Guidelines and Position Statements**

In 2011, the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) provided guidance on the use of the dexamethasone intravitreal implant for macular edema secondary to retinal vein occlusion. (19) The dexamethasone implant is recommended as an option for the treatment of macular edema following 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 2013, NICE concluded that the fluocinolone acetonide intravitreal implant (Iluvien) is not recommended for the treatment of chronic diabetic macular edema considered insufficiently responsive to available therapies. (20) Although the advisory committee concluded that the fluocinolone intravitreal acetonide implant showed greater efficacy compared with sham injection in people with chronic diabetic macular edema, the implant had not been shown to be a cost-effective use of the National Health Service resources. The committee also noted that the significant side effects associated with steroid injections in the eye, especially the acceleration of cataract and increased rates of raised intraocular pressure, still occur with the fluocinolone acetonide intravitreal implant.

**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. REFERENCES


Other:
IX. 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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<table>
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<tr>
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<th>Description</th>
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<td>Fluocinolone acetonide, intravitreal implant</td>
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<tr>
<td>J7312</td>
<td>Injection, dexamethasone, intravitreal implant, 0.1 mg</td>
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<td>Sympathetic uveitis</td>
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<td>362.35 – 362.36</td>
<td>Central retinal occlusion</td>
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<td>362.83</td>
<td>Retinal edema</td>
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<tr>
<td>363.00 – 363.08</td>
<td>Focal chorioretinitis, unspecified</td>
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<tr>
<td>363.20 – 363.22</td>
<td>Chorioretinitis, unspecified</td>
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<tr>
<td>364.21 – 364.24</td>
<td>Fuchs’ heterochromic cyclitis</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
The following ICD-10 diagnosis codes will be effective October 1, 2015

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<td>H44.131 – H44.139</td>
<td>Sympathetic uveitis, code range</td>
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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 Implants.” |
| CAC 8/28/12 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 klr |
| CAC 7/30/13 Consensus review. References updated. No changes to the policy statements. Policy guidelines added. No coding changes. |