Effective February 26, 2018
Policy Replaced by Article A54750

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
Intravitreal Implant

Policy #: 451
Category: Pharmacology

Latest Review Date: May 2017
Policy Grade: C

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

An intravitreal implant is a drug delivery system, surgically implanted in the vitreous of the eye, for sustained release of drug to the posterior and intermediate segments of the eye. Three intravitreal corticosteroid implants, i.e., fluocinolone acetonide 0.59 mg (Retisert), fluocinolone acetonide 0.19 mg (Iluvien), and dexamethasone 0.7 mg (Ozurdex) are reviewed herein. Fluocinolone acetonide implants are nonerodible and deliver drug up to 30 to 36 months while dexamethasone implants are bioerodible and last up to 6 months.

Intravitreal implants are being investigated for a variety of inflammatory 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 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 steroid therapies being studied include:

- Retisert® (non-biodegradable fluocinolone acetonide intravitreal implant) 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) 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® (previously known as Posurdex®; biodegradable injectable dexamethasone intravitreal implant); 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. The mean number of Ozurdex injections reported in the literature is 4.2 injections per year, and more than 6 consecutive injections have been reported.

Eye Conditions

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, Bechet'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 three 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. The primary goal of therapy for uveitis is to preserve vision. 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. Alternatives to intravitreal implants include intravitreal injection of triamcinolone acetonide, which is used as an off-label adjunctive therapy for DME. 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.

Macular Edema following 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).

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a degenerative disease of retina that results in loss of central vision with increasing age. Two distinctively different forms of degeneration, known as dry and wet, may be observed. The dry form (also known atrophic or areolar) is more common and is often a precursor to the wet form (also known as exudative neovascular or disciform). The wet form is more devastating and characterized by serous or hemorrhagic detachment of the retinal pigment epithelium and development of choroidal neovascularization (CNV), which greatly increases the risk of developing severe irreversible loss of vision. CNV is categorized as classic or occult. Effective specific therapies for exudative or wet AMD are intravitreous injection of a vascular endothelial growth factor inhibitor, possibly thermal laser photocoagulation (in selected patients), and photodynamic therapy.

Policy:

Effective for dates of service on or after February 26, 2018 refer to Article A54750

Effective for dates of service on or after November 30, 2010 and prior to February 26, 2018:

Blue Advantage will treat **fluocinolone acetonide intravitreal implant** as a **covered benefit for the treatment of diabetic macular edema** for their specific indications:

- **Blue Advantage** will treat **Retisert® (0.59mg)** as a **covered benefit** for the treatment of **chronic noninfectious intermediate, posterior, or panuveitis**, in one or both eyes.

- **Effective for dates of service on or after September 26, 2014 and prior to February 26, 2018:**
  Blue Advantage will treat **Iluvien™ (0.19mg)** as a **covered benefit** for the treatment of **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.

Effective for dates of service on or after November 30, 2010 and prior to February 26, 2018:

Blue Advantage will treat **Dexamethasone intravitreal implant 0.7mg (i.e., Ozurdex®) as a covered benefit** for **treatment** of the following indications:

- Noninfectious uveitis affecting the posterior segment of the eye; **or**
- Macular edema following branch or central retinal vein occlusion
- Diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery **(Effective 06/28/14)**

Blue Advantage will treat all other uses of a corticosteroid intravitreal implant as a non-covered benefit and as **investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent update with literature review was performed through January 29, 2017.

Non-infectious Uveitis

Intravitreal Fluocinolone Acetonide Implant (0.59mg)

Pivotal Trials

Two double-blind, randomized trials were conducted in patients with chronic (≥1-year history) noninfectious uveitis affecting the posterior segment of 1 or both eyes. The primary efficacy end point in both trials was the rate of recurrence of uveitis. These trials randomized patients to a fluocinolone acetonide 0.59-mg or to 2.1-mg implant. In 2004, the Food and Drug Administration (FDA) approved only the 0.59-mg dose and its approval was based on comparison of rates of recurrence of uveitis affecting the posterior segment of the study eye in the 34-week period postimplantation compared to the rates of recurrence in the 34-week period preimplantation. Data from 224 patients were included. Subsequently, FDA reported recurrence rates 1, 2, and 3 years postimplantation. Results are summarized in Table 1.

Table 1: Summary of Results from the FDA Pivotal Trial in Noninfectious Posterior Uveitis

	Uveitis Recurrence Rates, n (%)[a,b]	
Time Point	**Study 1 (n=108)**	**Study 2 (n=116)**
34 weeks preimplant	58 (53.7%)	46 (39.7%)
34 weeks postimplant	2 (1.8%)	15 (12.9%)
1 year postimplant	4 (3.7%)	15 (12.9%)
2 year postimplant	11 (10.2%)	16 (13.8%)
3 year postimplant	22 (20.4%)	20 (17.2%)
3 year postimplant[c]	33 (30.6%)	28 (24.1%)

FDA: Food and Drug Administration.

[a] Recurrence of uveitis for all postimplantation time points was compared to the 34-week preimplantation time point.

[b] P<0.01.

[c] Results presented include imputed recurrences. Recurrences were imputed when a subject was not seen within 10 wk of his or her final scheduled visit.

Results of 1 of the 2 pivotal trials were reported by Jaffe et al (2006). These trials are not discussed in detailed because the comparator was a nonapproved dose of fluocinolone acetonide. Briefly, the 2 trials randomized 278 patients and 239 patients to a fluocinolone acetonide 0.59-mg or 2.1-mg implant, respectively. Pooled data from both doses in the first trial showed a reduction in recurrence rates in implanted eyes compared with an increase in recurrence in nonimplanted eyes. An increase (≈6 mm Hg) in intraocular pressure (IOP) and cataracts were observed in implanted eyes compared to nonimplanted eyes. The second trial was not published and results reported in FDA documents are similar to the first trial.

Additional Randomized Controlled Trials

Pavesio et al (2010) reported results of an industry-sponsored, open-label trial in which 140 patients with chronic noninfectious posterior uveitis were randomized to the fluocinolone acetonide 0.59-mg implant (n=66) or systemic corticosteroid therapy (and immunosuppression when indicated; n=74). To be included in the trial, subjects had to have at least a 1-year history of recurrent uveitis. The primary efficacy outcome was time to first recurrence of uveitis. Patients in whom tapering of adjunctive anti-inflammatory therapy was insufficient despite

receiving the implant were referred to as imputed or inferred failures. Results were therefore presented as both true recurrences and true plus inferred recurrences. When inferred recurrences were censored (11 subjects 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). The relative risk (RR) of recurrence of uveitis was reduced by 71% with implants compared to standard therapy (RR=0.29; 95% confidence interval [CI], 0.14 to 0.59; 132 eyes). Secondary efficacy outcomes included visual acuity improvement. 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. Visual acuity in the systemic corticosteroid group remained consistent over the 2-year study.

The MUST Trial, sponsored by the National Eye Institute, is a partially blind randomized controlled trial (RCT; N=255) designed to compare visual acuity at 2 years with fluocinolone acetonide implants to systemic corticosteroid therapy (and immunosuppression when indicated) in patients with intermediate, posterior, or panuveitis. Assessment of the primary outcome measure of best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart was blinded. After 24 and 54 months of follow-up, the vision improvement from baseline in the implant groups compared to systematic therapy group was not statistically significant (+6.0 and +3.2 letters, p=0.16; +2.4 and 3.1 letters; p=0.073, respectively). Notably, approximately 21% of patients in the systemic group had received an implant by 54 months. At 24 and 54 months, the proportion of patients with a minimally important improvement did not differ significantly for any of the quality of life metrics (results not shown). Patients receiving systemic therapy (in which corticosteroid-sparing immunosuppressive therapy was used to minimize ongoing use of prednisone to <10 mg/d for the large majority of patients) was associated with relatively little additional systemic morbidity compared with implant therapy. Systemic adverse events were infrequent in both groups. At 2 years, the proportion of patients with systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg at any visit was lower in the implant group than in the systemic group (13% vs 27%; hazard ratio [HR], 0.44; p=0.030), but the rate of antihypertensive treatment initiation did not differ substantially between the 2 groups (5% vs 11%; hazard ratio [HR], 0.40; p=0.13), respectively. The incidences of other adverse systemic outcomes, including hyperlipidemia, diabetes, osteoporosis, fractures, and blood count/chemistry abnormalities, were not statistically distinguishable between groups (data not shown). Weight was stable over time in both groups.

Systematic Reviews

Brady et al (2016) reported results of a Cochrane review of RCTs comparing fluocinolone acetonide or dexamethasone intravitreal implants with standard therapy with at least 6 months of follow-up posttreatment. The primary outcome was recurrence of uveitis. Included trials enrolled patients of all ages who had chronic noninfectious posterior uveitis, intermediate uveitis, or panuveitis with vision that was “better than hand motion.” Two trials, Pavesio et al (2010) and Kempen et al (2011), were included and judged to be of moderate quality (both are discussed above). Because the 2 studies were designed to answer different questions (1 measured recurrence, 1 visual acuity), reviewers did not combine efficacy data. However, they

did perform a meta-analysis of common side effects, which showed increased risks of needing cataract surgery (RR=2.98; 95% CI, 2.33 to 3.79; 371 eyes) and surgery to lower IOP (RR=7.48; 95% CI, 3.94 to 14.19; 599 eyes) in the implant group compared with the standard therapy group through 2 years of follow-up. Reviewers were unable to conclude that the implants were superior to traditional systemic therapy for the treatment of noninfectious uveitis.

Harms
As per the prescribing label, nearly all phakic patients who receive implants are expected to develop cataracts and require cataract surgery. Further, 75% of patients may experience elevated IOP and/or glaucoma severe enough to require IOP-lowering medications and 35% filtering surgeries. Separation of implant components is another potential complication and 6-year cumulative risk of a spontaneous dissociation is 4.8% (95% CI, 2.4% to 9.1%).Late-onset endophthalmitis is also a recognized as a surgical complication of intraocular implants.

Subsection Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Noninfectious Uveitis
Four RCTs have established the efficacy of fluocinolone acetonide implants (0.59 mg) for patients with noninfectious intermediate or posterior uveitis. Two of the 4 RCTs compared 2 doses of implants and 2 trials compared implants with systemic steroids (and immunosuppression when indicated). All trials supported the efficacy of fluocinolone acetonide intravitreal implants in preventing recurrence and improving vision over a 4-year follow-up. The head-to-head trial comparing implants with systemic corticosteroids did not show substantial superiority in the overall effectiveness of either approach. The major limitation of these implants is nearly all phakic patients will develop cataracts and will require cataract surgery. Further, most will also develop glaucoma, with 75% patients requiring IOP-lowering medications and 35% requiring filtering surgeries.

<u>Intravitreal Dexamethasone Intravitreal Implant (0.7 mg)</u>
The evidence for dexamethasone intravitreal implants consists of 1 pivotal, double-blind RCT (HURON). In this 8-week, manufacturer-sponsored, multicenter trial (46 study sites in 18 countries), 229 patients with noninfectious intermediate or posterior uveitis were randomized to 0.7-mg implants (n=77), 0.35-mg implants (n=76), or sham procedure (n=76). The primary outcome measure was the proportion of eyes with a vitreous haze score of 0 (0 = no inflammation) at week 8. At baseline, the mean vitreous haze score was approximately +2 (moderate blurring of the optic nerve head). At 8 weeks posttreatment, the proportion of eyes with a vitreous haze score of 0 was 47% with the 0.7-mg implant and 12% with the sham procedure. At 8 weeks, visual acuity, as assessed by gain of 15 or more letters in BCVA from baseline, was achieved by 40% of patients who received implants compared to 10% who received sham control. The incidences of elevated IOP (≥25 mm Hg) and cataracts in phakic eyes were higher in 0.7-mg implant-treated eyes versus sham control eyes (7.1% vs 4.2% and 15% vs 7%, respectively). Unlike the fluocinolone acetonide 0.59-mg implant, the long-term efficacy and safety data for the dexamethasone 0.7-mg implant is not available. Lightman et al (2013) reported 26-week data for vision-related functioning using National Eye Institute-Visual Function Questionnaire (NEI-VFQ) from HURON trial. Using the distribution- and anchor-based methods, the authors reported that a clinically meaningful change for the NEI VFQ-25 composite score was 3.86 and 10 points, respectively. Others have reported that range changes of

2.3 to 3.8 units in the composite score are meaningful. In the HURON trial, the proportion of patients with a 5 or more point improvement in composite score at week 26 was 58% (42/73) in the 0.7-mg implant group versus 32% (24/74) in the sham-controlled arm ($p<0.05$).

Harms
As per the prescribing label, in controlled studies, the most common adverse reactions reported by 20% to 70% of patients were cataract, increased IOP, and conjunctival hemorrhage.

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Noninfectious Uveitis
One RCT comparing 2 doses of implants with sham-control has supported the efficacy of dexamethasone implants (0.7 mg) for patients with noninfectious intermediate or posterior uveitis. Results of this trial have demonstrated the efficacy of the dexamethasone 0.7-mg implant in reducing inflammation and resulted in clinically meaningful improvements in vision at week 8 compared to sham controls. Further, at week 26, patients treated with implants reported meaningful improvements in vision-related functioning. The major limitation of this trial was its lack of long-term follow-up. Further, as a class effect, use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

Macular Edema Following Retinal Vein Occlusion
In 2015, the American Academy of Ophthalmology (AAO) published a technology assessment on therapies for macular edema associated with central retinal vein occlusion. They identified four clinical trials that provided level I evidence supporting the use of anti-vascular endothelial growth factor (VEGF) pharmacotherapies and two clinical trials providing level I evidence for intravitreal corticosteroid injection with either 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 to anti-VEGF treatments. There was limited information on combination therapy with anti-VEGF and corticosteroid injections compared to monotherapy.

A Bayesian network meta-analysis of the efficacy and safety of treatments for macular edema secondary to branch retinal vein occlusion was published in 2015. A total of 8 RCTs (1743 patients) were included; patients were treated with ranibizumab given as needed, aflibercept monthly, dexamethasone implant, laser photocoagulation, ranizibumab 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% to 54% probability), followed by ranibizumab plus laser, and lowest (0% to 2% probability) for the dexamethasone implant, laser, or sham. Treatment with ranibizumab resulted in an increase of an average eight letters when compared with the dexamethasone implant. Patients treated with the dexamethasone implant had statistically significant higher rates of ocular hypertension compared with anti-VEGF monotherapy (odds ratio [OR] 13.1).

Intravitreal Fluocinolone Acetonide Implant (0.59mg)
No randomized controlled trials were identified with the fluocinolone acetonide implant for the treatment of macular edema following retinal vein occlusion.

Intravitreal Dexamethasone Intravitreal Implant (0.7mg)

Data presented to FDA for the dexamethasone intravitreal implant (Ozurdex) were from two, 6-month, double-masked RCTs called GENEVA (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 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 primary outcome measure was time to achieve a 15-or-more letter improvement in BCVA. A secondary outcome was the proportion of eyes achieving a 15-or-more letter improvement from baseline at 180 days. In individual studies as well as pooled analysis, time to achieve a 15-or-more letter (3-line) improvement in BCVA was significantly faster with implants than with sham ($p<0.01$) (data not shown). As evident from Table 2, the proportion of patients with a 15-or-more letter improvement from baseline in BCVA was higher in the implant with the FDA-approved dose (0.7 mg) compared to sham for the first 3 months. There was no significant difference in the proportion of patients who improved by 15 letters or more at 6-month follow-up. Note that the implant lasts for 6 months.

Table 2. Summary of Results from the FDA Pivotal Trial in Retinal Vein Occlusion

	N (%) of Patients With ≥15 Letters Improvement From Baseline in BCVA					
Time Point	**Study 1**			**Study 2**		
	Implant (0.7 mg)	**Sham**	**p**	**Implant (0.7 mg)**	**Sham**	**p**
Day 30	40 (20%)	15 (7%)	<0.01	51 (23%)	17 (8%)	<0.01
Day 60	58 (29%)	21 (10%)	<0.01	67 (30%)	27 (12%)	<0.01
Day 90	45 (22%)	25 (12%)	<0.01	48 (21%)	31 (14%)	0.039
Day 180	39 (19%)	37 (18%)	0.780	53 (24%)	38 (17%)	0.087

BCVA: best-corrected visual acuity; FDA: Food and Drug Administration.

Additional RCTs

Kuppermann (2007) reported results for an RCT in which 315 patients with persistent macular edema of different etiology (diabetic retinopathy [n=172], BRVO [n=60], CRVO [n=42], uveitis [n=14], or post–cataract surgery macular edema [n=27]) were assigned to the dexamethasone 0.35-mg implant, the dexamethasone 0.7-mg implant, or observation. At 6 months, the proportion of patients meeting the primary outcome of an improvement in visual acuity of 10 letters was 24%, 35% and 13% in 0.35-mg implants, 0.7-mg implants, and observation-only groups, respectively. In a small trial in 50 patients, Pichi et al (2014) found that the combination of dexamethasone 0.7-mg intravitreal implants plus macular grid laser increased both visual acuity and the interval between repeated implants. Gado and Macky (2014; n=60) reported no significant differences in visual acuity outcomes between dexamethasone implants and bevacizumab. Maturi et al (2014) reported results for 30 patients randomized to dexamethasone implants plus bevacizumab or to bevacizumab monotherapy and found no additional benefit for visual acuity with the combination treatment at 6 months.

Harms

As per the prescribing label, in controlled studies, the most common adverse reactions reported by 20% to 70% of patients were cataracts, increased IOP, and conjunctival hemorrhage.

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Macular Edema after Retinal Vein Occlusion
Two identical RCTs have established the efficacy of dexamethasone intravitreal implants (0.7 mg) for patients with macular edema following retinal vein occlusion. The 2 RCTs compared 2 doses of implants with a sham control. Compared to sham, both doses of the dexamethasone implant resulted in clinically meaningful improvements in visual acuity within 1 to 3 months postimplantation. Further, implant-treated patients achieved improvement in vision faster than the sham controls. However, the vision gain was similar at 6 months. Other small RCTs with shorter follow-up have demonstrated that the combination of implants with macular grid laser may increase the interval between repeated implants. Further, as a class effect, use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

Diabetic Macular Edema
A 2008 Cochrane review evaluated the efficacy of intravitreal steroids for macular edema in diabetes. Seven studies, involving 632 eyes with diabetic macular edema (DME) were included. Four trials examined the effectiveness of intravitreal triamcinolone acetate injection, three examined intravitreal steroid implantation with either fluocinolone acetonide (Retisert®) or the dexamethasone drug delivery system (the 2007 trial by Kupperman previously described). 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 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 photocoagulation.

<u>Intravitreal Fluocinolone Acetonide Implant (0.59mg)</u>
In 2011, Pearson et al reported 3-year efficacy and safety results from an industry-sponsored single blind (evaluator) RCT in which 196 patients with persistent or recurrent unilateral or bilateral diabetic macular edema were randomized to implants (n=127) or standard of care, defined as additional laser as needed after 6 months or observation (n=69). All patients had received focal/grid laser photocoagulation prior to randomization. At 6 months, the proportions of patients who received laser retreatment in implant and standard of care groups were 4% and 13%, respectively; the percentages after 3 years of follow-up were 15% and 41%, respectively. The primary efficacy outcome (≥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 standard of care eyes ($p<0.05$). Between 6 and 24 months, visual acuity was statistically significant in favor of the implant group but not beyond 30 months. At 3 years, there were no significant differences between the groups (e.g., 31.1% of implanted eyes vs 20.0% of standard of care eyes improved ≥15 letters at 3 years). As expected, there were higher incidences of elevated IOP (≥30 mm Hg; 61.4% vs 5.8%), need for surgery to treat glaucoma (33.8% vs 2.4%), and cataracts extraction in phakic eyes (91% vs 20%), respectively, for eyes treated with implants compared to standard of care. The incidence of vitreous hemorrhage (40.2% vs 18.8%), pruritus (38.6% vs 21.7%), and abnormal sensation in the eye (37.0% vs 11.6%), respectively, were also higher in the eyes treated with implants versus standard of care.

Subsection Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Diabetic Macular Edema

One RCT comparing fluocinolone acetonide implants (0.59 mg) with standard of care (as needed laser or observation) has supported the efficacy of implants for patients with DME. The primary efficacy outcome, at least a 15-letter improvement in BCVA was significantly improved in a greater proportion of patients given implants versus laser at all time points assessed, except at or beyond 30 months. Note that this implant is active for 30 months. As a class effect, in patients with phakic eyes, use of implants resulted in 90% requiring cataract surgery and 60% developing elevated IOP. Due to the substantial increase in adverse events and availability of agents with safer tolerability profiles (e.g., VEGF inhibitors), this implant is not indicated for DME.

Intravitreal Fluocinolone Acetonide Implant (0.19mg)

Two double-blind, randomized trials (FAME) has assessed patients with DME previously treated with laser photocoagulation. The primary efficacy end point of both trials was the proportion of subjects in whom vision had improved by 15 letters or more at 2 years from baseline. These trials randomized patients to fluocinolone acetonide 0.19-mg or 0.5-mg implants or to sham. Results of these trials were published by Campochiaro et al (2011). In 2014, FDA approved the 0.19-mg dose only based on similar efficacy at 2 years between the low and high dose in improving vision by 15 letters or more from baseline (data not shown). Relevant results with FDA-approved dosing are summarized in Table 3. Subsequently, 3-year results were reported in 2012. The percentage of patients who gained 15 letters or more using the last observation carried forward was 28.7% in the implant group and 18.9% in the sham group. Results of sensitivity analysis without imputation for missing data (~70% follow-up) showed similar results; the percentages of patients who gained 15 letters or more in the 2 groups were 33.0% and 21.4%, respectively. Subgroup analysis showed greater improvement in visual acuity in patients who were pseudophakic compared to those who were phakic (difference in mean change in number of letters at 2 years from baseline was 5.6 in pseudophakic patients vs 1 letter in phakic patients). This was due to loss of vision as a result of cataracts in phakic eyes that was observed more frequently in eyes with implants versus sham controls. Subgroup analysis also showed greater efficacy in patients with chronic (≥3 years) compared with nonchronic (<3 years) DME. The difference in the proportion of patients who gained 15 or more letters in the implant group versus the sham control group with chronic DME patients was 21% and -5.5 % among nonchronic DME patients.

Table 3: Summary of Results (2 Years) From the FDA Pivotal Trials in Diabetic Macular Edema

Outcome	Study 1 (N=285)			Study 2 (N=276)		
	Implant (n=190)	**Sham (n=95))**	**Difference (95% CI)**	**Implant (n=186)**	**Sham (n=90)**	**Difference (95% CI)**
↑ 15 letters	51 (27%)	14 (15%)	12.1% (2.6% to 21.6%)	57 (31%)	16 (18%)	13.0% (2.7% to 23.4%)
↓ 15 letters	26 (14%)	5 (5%)	8.4% (1.8% to 15.1%)	22 (12%)	9 (10%)	1.8% (-5.9% to 9.6%)

CI: confidence interval; FDA: Food and Drug Administration.

Massin et al (2016) reported the results of a small prospective noncomparative study in 16 patients with DME insufficiently responsive to laser and anti-VEGF who received fluocinolone acetonide 0.19-mg implants. Two groups of patients were evaluated: group 1 (n=6) included

patients ineligible anti-VEGF therapy who received previous treatment with laser photocoagulation while group 2 (n=10) included patients previously treated with laser photocoagulation and at least 3 monthly anti-VEGF treatments. Central subfield thickness was reduced by -299 μm in group 1 and -251 μm in group 2 at 12 months. Mean change in area under the curve from baseline to last value for all eyes was +4.2 letters in group 1 and +3.9 letters in group 2. The benefit in BCVA letter score was more limited and heterogeneous (the effect was more pronounced in pseudophakic eyes) with some patients achieving high improvements of visual acuity, whereas others did not improve. Small number of patients and lack of a control arm limit the interpretation of these findings.

Harms

As per the prescribing label, at the end of the 3-year follow-up, 82% (192/235) of phakic eyes with implants underwent cataract surgery compared to 50% (61/121) receiving the sham control. Among these patients, 80% of implant patients versus 27% of sham-controlled had cataract surgery, generally within the first 18 months of the trials. The proportion of patients with IOP elevation of 10 mm Hg or more from baseline was 3 times higher in the implant group (34%) versus the sham group (10). Respective proportions of patients with IOP of 30 mm Hg or more were 20% and 4%, respectively. As a consequence, a higher proportion of patients in the implant group required surgery for glaucoma (5% vs 1%).

Subsection Summary: Intravitreal Fluocinolone Acetonide Implant (0.19 mg) for Diabetic Macular Edema

Two RCTs have established the efficacy of fluocinolone acetonide implants (0.19 mg) for patients with DME. Both trials demonstrated the superiority of implants over sham controls. Implant-treated eyes showed clinically meaningful improvement in vision at 2 and 3 years postimplant. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic. The major limitation of these implants is that nearly 80% all phakic patients will develop cataracts and will require cataract surgery. Further, IOP was elevated in 34% of patients who received this implant compared with 10% of controls, leading to the restricted indication for patients previously treated with corticosteroids that do not have a clinically significant rise in IOP.

Dexamethasone Intravitreal Implant (0.7mg)

Two double-blind, randomized trials have assessed patients with DME. These trials randomized patients to a 0.7-mg or to a 0.35-mg implant or to a sham procedure. Retreatment was allowed if it was at least 6 months since the prior treatment and there was evidence of residual edema. The primary efficacy end point in both trials was the proportion of subjects in whom visual acuity had improved by 15 or more letters at 39 months from baseline or at the final visit for patients who exited the study at or prior to month 36. The month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for patients who received retreatment at month 36. Results of these trials were published by Boyer et al (2014). In 2014, FDA approved the 0.7-mg dose. Relevant results with FDA-approved dosing are summarized in Table 4. Only 14% of study patients completed the month 39 visit (16.8% from implant, 12.2% from sham). The visual acuity improvement from baseline increased during a treatment cycle, peaked at 3 months posttreatment and diminished thereafter (data not shown). This was due to loss of vision related to development of cataracts. Subgroup analysis showed greater

improvements in visual acuity in patients who were pseudophakic than in those who were phakic (difference in mean change in number of letters at 39 months from baseline was 4.2 letters in pseudophakic patients vs 0.3 letters in phakic patients).

Table 4: Summary of 39-Month Results From the FDA Pivotal Trials in Diabetic Macular Edema

Outcome	Study 1 (N=328)			Study 2 (N=328)		
	Implant (n=163)	Sham (n=165)	Difference (95% CI)	Implant (n=165)	Sham (n=163)	Difference (95% CI)
↑ 15 letters	34 (21%)	19 (12%)	9.3% (1.4% to 17.3%)	30 (18%)	16 (10%)	13.0% (2.7% to 23.4%)
↓ 15 letters	15 (9%)	17 (10%)	-1.1% (-7.5% to 5.3%)	30 (18%)	18 (11%)	7.1% (-0.5% to 14.7%)

CI: confidence interval; FDA: Food and Drug Administration.

The BEVORDEX trial compared bevacizumab with dexamethasone implants in a randomized trial of 86 patients with DME. Forty-six received bevacizumab every four weeks and 46 eyes received a dexamethasone implant every 16 weeks as needed. Results after 12 months of follow-up were reported. Although the primary end point of improvement in BCVA of 10 letters or more was similar for the two groups (40% of the bevacizumab-treated eyes and 41% of the dexamethasone-treated eyes), the proportion of patients with vision loss of more than 10 letters was higher in the eyes treated with dexamethasone (10.9%) than in the eyes treated with bevacizumab (0%). The dexamethasone implant reduced central macular thickness to a greater extent than bevacizumab (187 vs 122 microns; p=0.015), but led to a greater number of adverse events including IOP elevation of 10 mmHg 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. Other studies have shown an increase in cataracts predominantly in the second year of treatment with the dexamethasone implant.

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Diabetic Macular Edema

Two identical RCTs have established the efficacy of dexamethasone intravitreal implants (0.7 mg) for patients with DME. The 2 RCTs compared 2 doses of implants with a sham control. Compared to sham, both doses of the dexamethasone implant resulted in clinically meaningful improvements in visual acuity at 39 months postimplantation. The visual acuity improvement peaked at 3 months posttreatment but diminished thereafter, possibly due to development of cataracts. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic than in those who were phakic. One small RCT with 1-year follow-up has demonstrated similar rates of success on the primary end point; however, more implant-treated patients experienced vision loss of at least 10 letters and greater frequency of side effects (e.g., cataracts, elevated IOP) compared to bevacizumab.

Intravitreal Dexamethasone Implant (0.7mg) plus anti-Vascular Endothelial Growth Factor

Maturi et al reported a small (n=40 eyes) single masked randomized trial of dexamethasone plus bevacizumab compared with bevacizumab alone. 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 nine injections of bevacizumab, which was similar to a mean of six injections of

bevacizumab plus 2.1 injections with dexamethasone for the combined treatment group. Treatment with dexamethasone implants led to a greater mean reduction in central subfield thickness (difference 69 microns; p=0.03). Drug-related adverse events were higher in the combined treatment group, with IOP elevation (>21 mm Hg) in six eyes and worsening of cataracts in nine eyes. This compared with one instance of IOP elevation in the bevacizumab monotherapy group.

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) plus Anti-VEGF Therapy for Diabetic Macular Edema

One small RCT with 1-year follow-up has demonstrated that combined treatment with implants plus bevacizumab compared to bevacizumab alone resulted in similar gains in visual acuity but a greater frequency of side effects with combined treatment. Use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

Intravitreal Dexamethasone Implant (0.7mg) plus Laser Photocoagulation

The PLACID study group reported a multicenter double masked RCT (n=253) that compared dexamethasone implant 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 one month (31.7% vs 11.0%; p<0.001) and nine months (31.7% vs 17.3%; p=0.007), than at 12 months (27.8% vs 23.6%), respectively. More patients in the sham group discontinued the study due to lack of efficacy (8.7% vs 0.8%), which may bias results. An increase in IOP of at least 10 mm Hg was observed in 15.2% of eyes treated with dexamethasone implants. In addition, cataract-related adverse events were more common following treatment with dexamethasone implants (22.2% vs 9.5%, p=0.017).

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) plus Laser Photocoagulation for Diabetic Macular Edema

One RCT with 1-year follow-up comparing combination implants plus laser photocoagulation to laser photocoagulation alone found better visual acuity (as measured by gain of ≥10 letters) at 9 months but not at 12 months. But a differential lost to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis limit interpretation of results. Use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

Age-related Macular Degeneration

Dexamethasone Intravitreal Implant

Kuppermann et al (2015), reported the results of industry-sponsored, single-masked, sham-controlled randomized trial in which 243 patients with choroidal neovascularization secondary to age related macular degeneration were allocated to dexamethasone implants (n=123) or a sham procedure (n=120). All patients received 2 protocol-mandated intravitreal 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 at 6 months. The median injection-free survival was 34 days in the implant group and 29 days in the sham control group. Though this difference was statistically significant (p=0.016), the effect size was small and clinically insignificant. The proportions of patients who did not require rescue ranibizumab over the 6-month study period were 8.3% the implant group and 2.5% in the sham group (p=0.048). There were no significant differences between groups in mean change from baseline BCVA. More

patients in the dexamethasone implant group had increased IOP (13.2% vs 4.2%; p=0.014), but there were no differences between groups in cataracts-related events. Notably, the trial had a short follow-up (6 months).

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) plus Anti-VEGF Therapy for Age-Related Macular Degeneration

One RCT evaluated the impact of adding implants to a standard VEGF inhibitor for patients with AMD. Results of this trial failed to demonstrate clinically meaningful reductions in the ranibizumab injection-free interval. Further, there was an IOP elevation in greater proportion of patients receiving implants without any additional clinical benefit.

Other Conditions

Birdshot Retinochoroidopathy

Birdshot retinochoroidopathy, also known as birdshot chorioretinopathy or vitiliginous chorioretinitis, is a chronic, bilateral rare form of posterior uveitis with characteristic hypopigmented lesions. No RCTs were identified for the treatment of this indication for any corticosteroids intravitreal implants. Bajwa et al (2014) published a retrospective case series involving 11 patients (11 eyes) refractory or intolerant to conventional immunomodulatory therapy who received fluocinolone acetonide implants (0.59 mg). Reported outcomes were disease activity markers. The proportion of patients with intraocular inflammation was 55% at baseline, which decreased to 10%, 11%, and 0% at year 1, 2, and 3, respectively. Active vasculitis was noted in 36.3% patients at baseline and 0% at 3-year follow-up. More than 20% reduction in central retinal thickness was noted in all patients with cystoid macular edema at 6 months, 1 year, 2 years, and 3 years postimplant. Another retrospective cohort study (2015) that included 11 eyes with birdshot chorioretinitis reported improved control of inflammation and decreased reliance on adjunctive therapy with fluocinolone acetonide implants (0.59 mg). Authors observed a more robust increase in IOP compared to the observed elevation in patients with other types of posterior uveitis and panuveitis. Results of another retrospective study by Rush et al (2011) (which included 32 eyes with birdshot chorioretinopathy) who received fluocinolone acetonide implant (0.59 mg) with 12-month follow-up, also reported decrease in vitreous haze from 26% at baseline to 100% at 12 months. In 2 small retrospective studies with 6 eyes in 3 patients38 and 6 eyes in 4 patients, respectively, reported the favorable effects of dexamethasone implants on ocular inflammation and macular edema during treatment. All eyes exhibited control of ocular inflammation and macular edema. In the first study, all 3 patients achieved BCVA of at least 20/25 during treatment. In the second, there was a mean improvement of 70 letters on BCVA using the EDTRS chart.

Section Summary: Birdshot Retinochoroidopathy

No RCTs were identified on the treatment of birdshot retinochoroidopathy with any corticosteroids intravitreal implants. Available evidence includes multiple observational studies that noted improvements in anatomic and visual acuity outcomes in patients refractory or intolerant to current standard of treatment. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in refractory or intolerant patients with birdshot retinopathy.

Cystoid Macular Edema Related to Retinitis Pigmentosa

Retinitis pigmentosa is a degenerative process of the retina affecting primarily the rod photoreceptors and retinal pigment epithelium. Many studies have shown a prevalence of cystoid macular edema in 10% to 15% of patients with retinitis pigmentosa. No RCTs were identified on the treatment of this indication for any corticosteroids intravitreal implants. Multiple case reports40-45 describing the use of dexamethasone implants in 8 patients with macular edema as a consequence of retinitis pigmentosa have been published. All case reports have short follow-up (<1 year) and a few lacked complete description of benefit. Overall, these reports found mix improvements on various anatomic and functional outcomes with transient benefits to complete recovery of cystoid macular edema.

Section Summary: Cystoid Macular Edema Related to Retinitis Pigmentosa

No RCTs were identified on the treatment of cystoid macular edema with any corticosteroids intravitreal implants. Available evidence includes multiple case reports that have noted mix results for anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. Larger RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with cystoid macular edema related to retinitis pigmentosa.

Idiopathic Macular Telangiectasia Type 1

Type 1 macular telangiectasia is a rare congenital and unilateral condition of the eye in which a focal expansion or outpouching and dilation of capillaries in the parafoveal region leads to vascular incompetence, atrophy, and central loss of vision. It is also considered a variant of Coats disease. No RCTs were identified on the treatment of macular telangiectasia with any corticosteroids intravitreal implants. Three case reports with a total 9 patients with type 1 idiopathic macular telangiectasia treated with dexamethasone implants have described mixed results on improvements in visual acuity and reduction in inflammation.

Section Summary: Idiopathic Macular Telangiectasia Type 1

No RCTs were identified on the treatment of idiopathic macular telangiectasia type 1with any corticosteroids intravitreal implants. Available evidence includes multiple case reports, which have noted mix results for visual acuity and inflammation-related outcomes. Long-term follow-up on efficacy and safety is limited. Better quality studies with long-term follow-up are needed to permit conclusions on the efficacy of corticosteroid implants in patients with this indication.

Postoperative Chronic Macular Edema

Postoperative chronic macular edema, also called as pseudophakic cystoid macular edema or Irvine-Gass syndrome, is one of the most common causes of visual loss after cataract surgery. It is thought to occur as a consequence of inflammatory mediators that are upregulated in the aqueous and vitreous humors after surgical manipulation; it can lead to permanent visual loss. No RCTs were identified on the treatment of this indication with any corticosteroids intravitreal implants. Multiple case series have assessed improvements in visual acuity and anatomic changes. However, these studies have included only small numbers of patients and reported mean pre-post changes in visual acuity and eye anatomy that lack responder analysis using clinically meaningful changes in outcomes. EPISODIC, a 2016 observational retrospective study conducted in France included 100 patients with postsurgical macular edema who received dexamethasone implants between April 2011 and June 2014 and who had a minimum of 1-year

follow-up. Mean improvement in BCVA was 9.6 EDTRS letters at month 6 and 10.3 at month 12. The proportion of eyes with gains in BCVA of 15 or more letters was 32.5% and 37.5% at months 6 and 12, respectively. Average reduction in central subfield macular thickness was 135.2 and 160.9 μm at months 6 and 12.

Section Summary: Postoperative Chronic Macular Edema

No RCTs were identified on the treatment of postoperative chronic macular edema with any corticosteroids intravitreal implants. Available evidence includes multiple observational studies. Of these, 1 large retrospective analysis of 100 patients showed that 2 of every 5 patients experienced clinically meaningful improvements in visual acuity after 1 year of follow-up. An RCT is needed to confirm the efficacy of corticosteroid implants in patients with this indication.

Circumscribed Choroidal Hemangioma

Circumscribed choroidal hemangiomas are benign vascular hamartomas without systemic associations. No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroids intravitreal implants. A single case report has described the use of photodynamic therapy combined with dexamethasone implants. Authors concluded that implants potentiated the effect of photodynamic therapy with less risk of local side effects than triamcinolone acetonide.

Section Summary: Circumscribed Choroidal Hemangiomas

No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroids intravitreal implants. Available evidence includes a single case report that does not permit conclusion on the efficacy and safety of adding dexamethasone implants to photodynamic therapy for treatment of circumscribed choroidal hemangiomas. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with this indication.

Proliferative Vitreoretinopathy

Proliferative vitreoretinopathy develops as a complication of rhegmatogenous retinal detachment. Proliferative vitreoretinopathy occurs in 8% to 10% of patients undergoing primary retinal detachment surgery and prevents the successful surgical repair of rhegmatogenous retinal detachment. No RCTs were identified on the treatment of proliferative vitreoretinopathy with any corticosteroids intravitreal implants. A case series (2017) of 5 patients with proliferative vitreoretinopathy has described combined use of surgery, endolaser, and dexamethasone implants. A case report (2013) found a benefit of dexamethasone implants in preventing proliferative vitreoretinopathy in a patient with a rhegmatogenous retinal detachment, who experienced improvements in visual acuity and retinal attachment 9 months postsurgery.

Section Summary: Proliferative Vitreoretinopathy

No RCTs were identified on the treatment of proliferative vitreoretinopathy with any corticosteroids intravitreal implants. Available evidence includes 1 case series and 1 case report. These studies reported multiple interventions, including dexamethasone implants in conjunction with surgery and laser, for preventing proliferative retinopathy after retinal

detachment surgery. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with proliferative retinopathy.

Radiation Retinopathy

Radiation retinopathy is delayed-onset damage to the retina due to exposure to ionizing radiation, typically after months and is slowly progressive. No RCTs were identified on the treatment of radiation retinopathy with any corticosteroids intravitreal implants. In a retrospective study (2015), 12 eyes diagnosed with radiation maculopathy secondary to plaque brachytherapy were treated with dexamethasone implants. Anatomic improvements in foveal thickness were reported, with nonsignificant improvements in visual acuity. In a 2014 retrospective case series, 2 patients who developed radiation maculopathy after radiotherapy for uveal melanoma were treated with dexamethasone implants. They had limited responses to bevacizumab and intravitreal triamcinolone. Dexamethasone implants provided a prolonged period of anatomic stabilization. In another retrospective chart review (2013) of 5 patients with choroidal melanoma treated with dexamethasone implants for radiation macular edema, mix improvements in visual acuity were reported. The mean improvement in EDTRS letters was 5. Visual acuity improved for 3 patients (+4, +9, and +15 letters) and remained unchanged for 2.

Section Summary: Radiation Retinopathy

No RCTs were identified on the treatment of radiation retinopathy with any corticosteroids intravitreal implants. Available evidence includes multiple observational studies that noted improvements in anatomic stability and visual acuity. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with radiation retinopathy.

Summary of Evidence

Uveitis

For individuals with chronic noninfectious intermediate or posterior uveitis who receive an intravitreal fluocinolone acetonide implant (0.59 mg), the evidence includes 4 randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Two of the 4 RCTs compared 2 doses of implants and 2 trials compared implants with systemic steroids (and immunosuppression when indicated). All trials supported the efficacy of intravitreal fluocinolone acetonide implants in preventing recurrence and improving visual acuity over 4-year follow-up. The head-to-head trial comparing implants with systemic corticosteroids did not show substantial superiority in the overall effectiveness of either approach. After 24 and 54 months of follow-up, visual acuity improved from baseline in the implant groups compared to the systematic therapy groups by +6.0 and +3.2 letters (p=0.16) and +2.4 and 3.1 letters (p=0.073), respectively. However, nearly all phakic patients receiving implants developed cataracts and required cataract surgery. Further, most also developed glaucoma, with 75% of patients requiring intraocular pressure (IOP) - lowering medications and 35% requiring filtering surgeries. Systemic adverse events such as hyperlipidemia, diabetes, osteoporosis, fractures, and blood count/chemistry abnormalities were infrequent and not statistically distinguishable between groups. The incidence of hypertension was greater in the systemic therapy group (27%) compared to the implant group (13%), but rates of antihypertensive treatment initiation did not differ. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with noninfectious intermediate or posterior uveitis who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of this trial at 8 weeks showed that the implant was effective in reducing inflammation (the proportion of eyes with no inflammation was 47% and 12% with implant and sham, respectively) and resulted in clinically meaningful improvement in vision at week 8 compared to sham controls (the proportion of patients with a gain of ≥15 letters in best-corrected visual acuity [BCVA] from baseline was ~40% with implants and 10% with sham). Further, at week 26, patients treated with implants reported meaningful increases in vision-related functioning. The major limitation of this trial was its lack of long-term follow-up. Use of implants resulted in higher incidences of cataracts and elevated IOP. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Macular Edema

For individuals with macular edema after retinal vein occlusion who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared to sham controls, implants resulted in clinically meaningful improvements in visual acuity within 1 to 3 months postimplant and improvement in vision occurred faster. The difference in the proportion of patients with gain of 15 or more letters in BCVA from baseline was more than 10% in favor implants versus sham in both studies at 30, 60 and 90 days, but not at 180 days postimplant. Use of implants resulted in higher incidences of cataracts and elevated IOP. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with macular edema after retinal vein occlusion who receive an intravitreal fluocinolone acetonide implant (0.59 mg), no studies were identified. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Diabetic Macular Edema

For individuals with refractory (persistent or recurrent) diabetic macular edema (DME) who receive an intravitreal fluocinolone acetonide implant (0.59 mg), the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared to standard of care (as needed laser or observation), a greater proportion of patients with implants reported clinically significant improvement in vision at 6 months (1.4% vs 16.8% respectively) and subsequent time points assessed but not at or beyond 30 months of follow-up. Ninety percent of patients with phakic eyes who received implants required cataract surgery and 60% developed elevated IOP. Due to the substantial increase in adverse events and availability of agents with safer tolerability profiles (e.g., anti-vascular endothelial growth factor [anti-VEGF] inhibitors), implant use in DME is questionable. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with DME who receive an intravitreal fluocinolone acetonide implant (0.19 mg), the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Implant-treated eyes showed in clinically meaningful improvements in vision at 2 and 3 years postimplant. The percentage of patients who gained 15 letters or more was 28.7% in the implant group versus 18.9% in the sham group at 3 years. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic (difference in mean change in number of letters at 2 years from baseline was 5.6 letters in pseudophakic patients vs 1 letter in phakic patients). A major limitation of these implants is that nearly 80% all phakic patients will develop cataracts and will require cataract surgery. Further, IOP was elevated in 34% of patients who received this implant compared with 10% of controls. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with DME who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 3 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared to sham control, 2 identically designed RCTs showed clinically meaningful improvements in vision with dexamethasone implants that peaked at 3 months and maintained 39 months (with retreatment). The difference in proportion of patients with a gain of 15 or more letters in BCVA from baseline was 9.3% and 13.0% in the 2 trials, respectively, favoring implant versus sham at 39 months postimplant. Subgroup analysis of these trials showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic. Results of 1 small RCT showed that, compared to bevacizumab, implant-treated patients at 1 year had similar improvement rates on the primary end point, but experienced greater rates of vision loss (0% vs 10.9%), greater frequency of side effects such as cataracts (4.8% vs 13%), and elevated IOP (0% vs 19.6%), all respectively. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with DME who receive an intravitreal dexamethasone implant (0.7 mg) plus anti-VEGF therapy, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. One small RCTs with a 1-year follow-up demonstrated that combination implants plus bevacizumab compared to bevacizumab alone resulted in similar gain in visual acuity (5.4 letters vs 4.9 letters), but greater frequency of side effects with combined treatment. Use of dexamethasone implants resulted in higher incidence of cataracts and elevated IOP. A larger RCT with adequate power is needed to confirm these findings. The use of dexamethasone implant resulted in higher incidence of cataract and elevated IOP. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with DME who receive an intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 1-year follow-up demonstrated that combination implants plus laser photocoagulation compared to laser photocoagulation alone resulted in better visual acuity (as

measured by gain of ≥10 letters) at 9 months but not at 12 months. However, the generally acceptable standard outcome measure for change is 15 or more letters and it was not used in this trial. The use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP Further, a differential loss to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis preclude interpretation of results. A larger RCT with adequate power is needed to confirm these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

Age-Related Macular Degeneration

For individuals with age-related macular degeneration who receive an intravitreal dexamethasone implant (0.7 mg) plus anti-VEGF inhibitor, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of this trial did not demonstrate clinically meaningful reductions in the ranibizumab injection-free interval between combined treatments (34 days) and anti-VEGF alone (29 days; p=0.016). Further, IOP was elevated in a greater proportion of patients receiving implants without any additional clinical benefit. More patients in the dexamethasone implant group had increased IOP, but there were no between-group differences in cataracts-related events. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other Conditions

For individuals with birdshot retinochoroidopathy refractory or intolerant to standard therapy who receive an intravitreal fluocinolone acetonide implant (0.59 mg) or intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Multiple observational studies have noted improvements in anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in refractory or intolerant patients with birdshot retinopathy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cystoid macular edema related to retinitis pigmentosa who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Case reports have noted mix results for anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. Larger RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with cystoid macular edema related to retinitis pigmentosa. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with idiopathic macular telangiectasia type 1 who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Case reports have noted mix results for visual acuity and inflammation-related outcomes. Long-term follow-up for efficacy and safety is limited. Better quality studies with long-term follow-up are needed to permit conclusions on the efficacy of

corticosteroid implants in patients with idiopathic macular telangiectasia type 1. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with postoperative chronic macular edema who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Of multiple observational studies, 1 large retrospective analysis of 100 patients showed that 2 of every 5 patients experienced clinically meaningful improvements in vision at 1-year follow-up. An RCT is needed to confirm the efficacy of corticosteroid implants in patients with postoperative chronic macular edema. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with circumscribed choroidal hemangiomas who receive an intravitreal dexamethasone implant (0.7 mg) plus photodynamic therapy, the evidence includes a 1 case report. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of the case report do not permit conclusions about the efficacy and safety of adding dexamethasone implants for circumscribed choroidal hemangiomas to photodynamic therapy. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with circumscribed choroidal hemangiomas. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with proliferative vitreoretinopathy who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 1 case series and 1 case report. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. These studies have reported multiple interventions, including dexamethasone implants in conjunction with surgery and laser for preventing proliferative retinopathy after retinal detachment surgery. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with proliferative retinopathy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with radiation retinopathy who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Multiple observational studies have noted improvements in anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with radiation retinopathy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Academy of Ophthalmology

In 2015, the American Academy of Ophthalmology published it preferred practice guidelines for retinal vein occlusions. These guidelines stated: “The safest treatment for the associated macular edema is the use of anti-VEGFs [anti-vascular endothelial growth factors]. Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation in BRVO [branch retinal vein occlusion] has a potential

role in treatment." The pivotal GENEVA trials were not rated for quality. The guidelines rate multiple RCTs that have demonstrated the efficacy of anti-VEGF agents as I++ (high-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias), good quality (further research is very unlikely to change our confidence in the estimate of effect), strong recommendation (used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not).

National Institute for Health and Care Excellence

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. 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 November 2013, NICE replaced technology appraisal (TA) guidance 271 (January 2013) with TA 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:

- 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.

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

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force has not addressed the use of intravitreal corticosteroid implants.

Key Words:

Intravitreal implant, fluocinolone acetonide, Retisert®, Ozurdex®, dexamethasone intravitreal implant, Iluvien™

Approved by Governing Bodies:

In June 2009, Ozurdex® (dexamethasone 0.7 mg intravitreal implant; Allergan) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion. Subsequently, in September 2010, the indication was expanded to include treatment of noninfectious uveitis affecting the

posterior segment of the eye. In June 2014, the indication was again expanded to include treatment of diabetic macular edema.

In September 2014, Iluvien® (fluocinolone acetonide 0.19 mg intravitreal implant; Alimera Sciences) was approved by FDA for the treatment of diabetic macular edema in patients previously treated with a course of corticosteroids and without a clinically significant rise in intraocular pressure.

In November 2014, Retisert™ (fluocinolone acetonide 0.59 mg intravitreal implant; Bausch & Lomb) was approved by FDA for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

For Retisert implantation:

J7311	Fluocinolone acetonide, intravitreal implant
67027	Implantation of intravitreal drug delivery system (e.g., ganciclovir implant), includes concomitant removal of vitreous

For Iluvien implantation:

J7313	Injection, fluocinolone acetonide, intravitreal implant, 0.01mg **(Effective 01/01/2016)**
67028	Intravitreal injection of a pharmacologic agent (separate procedure)

For Ozurdex implantation:

J7312	Injection, dexamethasone, intravitreal implant, 0.1 mg
67028	Intravitreal injection of a pharmacologic agent (separate procedure)

Previous Coding:

For Iluvien implantation:

J3490	Unclassified drugs **(Effective 12/31/2015)**

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