LOUISIANA BLUE

Intravitreal and Suprachoroidal Corticosteroid Products

Policy # 00549
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a fluocinolone acetonide intravitreal implant 0.59 mg (Retisert®)‡ for the treatment of chronic non-infectious intermediate uveitis, posterior uveitis, or panuveitis to be **eligible for coverage.****

Based on review of available data, the Company may consider a fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien®)‡ 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 to be **eligible for coverage.****

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a dexamethasone intravitreal implant 0.7 mg (Ozurdex™)‡ to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for a dexamethasone intravitreal implant 0.7 mg (Ozurdex) will be considered when ONE of the following criteria are met:

- Patient has non-infectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye, OR
- Patient has macular edema following branch or central retinal vein occlusion, OR
- Patient has diabetic macular edema.

Based on review of available data, the Company may consider a triamcinolone suprachoroidal injection 4 mg (Xipere™)‡ to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for a triamcinolone suprachoroidal injection 4 mg (Xipere) will be considered when ALL of the following criteria are met:

- Patient has non-infectious anterior-, intermediate-, posterior-, or pan-uveitis; AND
- Patient has macular edema associated with non-infectious uveitis; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) triamcinolone intravitreal injections 4 mg (Triesence®)‡ unless there is clinical evidence or patient history that suggests the use of this alternative product will be ineffective or cause an adverse reaction to the member; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Dosing does not exceed 4 mg every 12 weeks per impacted eye.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of triamcinolone suprachoroidal injection 4 mg (Xipere) when the patient has NOT tried and failed (e.g., intolerance or inadequate response) triamcinolone intravitreal injections 4 mg (Triesence) to be **not medically necessary**.**

Based on review of available data, the Company may consider a fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq™)‡ and fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien) for the treatment of chronic non-infectious intermediate uveitis, posterior uveitis, or panuveitis to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers a fluocinolone acetonide intravitreal implant 0.59 mg (Retisert) or 0.19 mg (Iluvien) or 0.18 mg (Yutiq) OR dexamethasone intravitreal implant 0.7 mg (Ozurdex) OR triamcinolone suprachoroidal injection 4 mg (Xipere) when treating the following conditions, to be **investigational***

- Age-Related Macular Degeneration
- Birdshot retinochoroidopathy
- Cystoid macular edema related to retinitis pigmentosa
- Idiopathic macular telangiectasia type 1
- Postoperative macular edema
- Circumscribed choroidal hemangiomas
- Proliferative vitreoretinopathy
- Radiation retinopathy

Based on review of available data, the Company considers all other uses of corticosteroid intravitreal implants (except those noted above as **not medically necessary****) to be **investigational.***

Based on review of available data, the Company considers all other uses of triamcinolone suprachoroidal injection 4 mg (Xipere) (except that noted above as **not medically necessary****) to be **investigational.***

Background/Overview

It should be noted that the dosages reflected in this policy for these products are total doses per administration. The HCPCS codes representing the drugs are typically not indicative of the total dose, but are actually a factor of the dose.

INTRAVITREAL IMPLANTS

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

Selection of the route of corticosteroid administration (topical, systemic, periocular, or intraocular injection) is based on the cause, location, and severity of the disease. Each therapeutic approach has 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 are biodegradable or nonbiodegradable. Nonbiodegradable systems are thought to be preferable for treating chronic, long-term disease, while biodegradable products may be preferred for conditions that require short-term therapy. Although the continuous local release of steroid with an implant may reduce or eliminate the need for intravitreal injections and/or long-term systemic therapy, insertion or surgical implantation of the device carries risks, and the device could potentially increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration. With any route of administration, cataracts are a frequent complication of long-term corticosteroid therapy.

Intraocular corticosteroid implants being evaluated include:

- Retisert (nonbiodegradable fluocinolone acetonide intravitreal implant; Bausch & Lomb) is a sterile implant that consists of a tablet containing fluocinolone acetonide 0.59 mg, a synthetic corticosteroid that is less soluble in aqueous solution than dexamethasone. The tablet is encased in a silicone elastomer cup with a release orifice and membrane; the entire

elastomer cup assembly is attached to a suture tab. Following implantation (via pars plana incision and suturing) in the vitreous, the implant releases the active drug at a rate of 0.3 to 0.4 μg/d over 2.5 years.

- Iluvien (nonbiodegradable injectable intravitreal implant with fluocinolone acetonide; Alimera Sciences) is a rod-shaped device made of polyimide and polyvinyl alcohol. It is small enough to be placed using an inserter with a 25-gauge needle. It is expected to provide sustained delivery of fluocinolone acetonide for up to 3 years.
- Ozurdex (previously known as 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. 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.
- Yutiq (non-biodegradable fluocinolone acetonide intravitreal implant, EyePoint Pharmaceuticals) contains 0.18 mg fluocinolone acetonide, designed to release 0.25 μg/d consistently over 36 months.

SUPRACHOROIDAL INJECTIONS

Xipere is the only medication currently approved by FDA for suprachoroidal use. A patented suprachoroidal space (SCS) microinjector syringe and 900 micrometer needle is supplied to access the suprachoroidal space. Injection into the SCS delivers drug to the choroid and retina. An alternative to this product is Triesence, which is a 4 mg triamcinolone intravitreal injection approved for sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. Triesence is also approved for visualization during vitrectomy. These two products have not been studied head-to-head, therefore no superiority claims can be made. Triesence provides an economically sensible option to provide the same corticosteroid product and dosage for the requested condition.

The suprachoroidal corticosteroid injection being evaluated is Xipere (Clearside Biomedical). It is a 4 mg triamcinolone containing injection. Its effects last 12 weeks.

EYE CONDITIONS

Uveitis

Uveitis encompasses various conditions, of infectious and non-infectious 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. Non-infectious etiologies include sarcoidosis, Behçet syndrome, and “white dot” syndromes such as multifocal choroiditis or “birdshot” chorioretinopathy. Uveitis may be idiopathic, have a sudden or insidious onset, a duration that is limited (< 3 months) or persistent, and a course that may be acute, recurrent, or chronic. Uveitis can be associated with a variety of complications, including band keratopathy, posterior synechiae, cataracts, intraocular hypertension, and macular edema.

The classification scheme recommended by the Uveitis Study Group and the Standardization of Uveitis Nomenclature (SUN) Working Group is based on anatomic location. Patients with anterior uveitis typically develop symptoms such as light sensitivity, pain, tearing, and redness of the sclera. In posterior uveitis, which comprises approximately 5% to 38% of all uveitis cases in the United States, the primary site of inflammation is the choroid or retina (or both). Patients with intermediate or posterior uveitis typically experience minimal pain, decreased visual acuity, and the presence of floaters (bits of vitreous debris or cells that cast shadows on the retina). Chronic inflammation associated with posterior segment uveitis can lead to cataracts and glaucoma and to structural damage to the eye, resulting in severe and permanent vision loss.

The primary goal of therapy for uveitis is to preserve vision. Non-infectious uveitis typically responds well to corticosteroid treatment. Immunosuppressive therapy (e.g., antimetabolites, alkylating agents, T-cell inhibitors, tumor necrosis factor inhibitors) may also be used to control severe uveitis. Immunosuppressive therapy is typically reserved for patients who require chronic high-dose systemic steroids to control their disease. While effective, immunosuppressants may have serious and potentially life-threatening adverse effects, including renal and hepatic failure and bone marrow suppression.

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

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

Diabetic Macular Edema
Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The 2 most serious complications for vision are diabetic macular edema (DME) and proliferative diabetic retinopathy. At its earliest stage (non-proliferative retinopathy), microaneurysms occur. As the disease progresses, blood vessels that provide nourishment to the retina are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from leakage of blood into the vitreous. DME is characterized by swelling of the macula due to gradual leakage of fluids from blood vessels and

breakdown of the blood-retinal barrier. Moderate vision loss can arise from the fluid accumulating in the center of the macula (macular edema) during the proliferative or non-proliferative 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 inhibitors, which block stages in the pathway leading to new blood vessel formation (angiogenesis), have demonstrated efficacy in DME.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In June 2009, Ozurdex (dexamethasone 0.7 mg intravitreal implant; Allergan) was approved by 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 non-infectious 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 March 2025, the indication was expanded to include treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

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

In October 2018, Yutiq (fluocinolone acetonide 0.18 mg intravitreal implant; EyePoint Pharmaceuticals) was approved by FDA for the treatment of chronic non-infectious uveitis affecting the posterior segment (intermediate, posterior, and panuveitis) of the eye.

In October 2021, Xipere (triamcinolone acetonide 0.4 mg suprachoroidal injection; Clearside Biomedical) was approved by FDA for the treatment of macular edema associated with uveitis.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

INTRAVITREAL IMPLANTS

NON-INFECTIOUS UVEITIS

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)-Retisert

Pivotal Trials

Two double-blind, randomized trials were conducted in patients with chronic (≥ 1-year history) non-infectious 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 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 post-implantation compared to the rates of recurrence in the 34-week period pre-implantation. Data from 224 patients were included. Subsequently, FDA reported recurrence rates 1, 2, and 3 years post-implantation. Results are summarized in Table 1.

Table 1. Summary of Results From FDA Pivotal Trial in Non-infectious Posterior Uveitis

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

FDA: Food and Drug Administration.

[a] Recurrence of uveitis for all post-implantation time points was compared to the 34-week pre-implantation 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 (RCTs)
Pavesio et al (2010) reported results of an industry-sponsored, open-label trial in which 140 patients with chronic non-infectious 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 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 non-infectious 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 non-infectious uveitis.

Subsection Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Non-infectious Uveitis
Four RCTs have established the efficacy of fluocinolone acetonide implants (0.59 mg) for patients with non-infectious 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.

Intravitreal Dexamethasone Implant (0.7 mg)-Ozurdex
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 non-infectious 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 ($p < 0.05$).

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Non-infectious Uveitis
One RCT comparing 2 doses of implants with sham-control has supported the efficacy of dexamethasone implants (0.7 mg) for patients with non-infectious 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.

Intravitreal Fluocinolone Implant (0.18 or 0.19) mg- Yutiq, Iluvien
For individuals with chronic (≥ 1-year history) noninfectious uveitis affecting the posterior segment of one or both eyes who receive fluocinolone acetonide (0.18 or 0.19 mg), the pivotal evidence includes 2 double-blind, randomized trials of 282 patients (range, 129 to 153): A Phase III, Multi-National, Multi-Center, Randomized, Masked, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal Insert in Subjects With Chronic Non-Infectious Uveitis Affecting the Posterior Segment of the Eye (study #PSV-FAI-001) and A Multi-center, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects With Chronic Non-infectious Uveitis Affecting the Posterior Segment of the Eye (study #PSV-FAI-005). Results of 1 of the pivotal trials (study #PSV-FAI-001) were reported by Jaffe et al (2019). The second trial was reported only in FDA documents. The primary efficacy endpoint in both trials was the proportion of recurrence of uveitis within 6 months. Secondary outcomes at 12 months have also been reported.

For the primary outcome of recurrence at 6 months, both trials consistently found significantly lower rates in the fluocinolone groups but the effect size was much smaller in the unpublished trial. Similarly, at 12 months, both trials found significantly lower recurrence rates in the fluocinolone groups, but the odds ratio had more than doubled in the published trial and decreased in the unpublished trial. Results were inconsistent between trials for the remainder of the key outcomes, appearing more favorable in the published trial. Most notable were the differences between trials in mean change in best-corrected visual acuity at 12 months (higher in the published trial, lower in the unpublished trials) and risk of increased intraocular pressure within 12 months (increased risk in the unpublished trial, but not in the published trial).

The most important limitation of these studies is the higher rate of "imputed" recurrences in the sham groups compared to the fluocinolone group (16% vs. 57% at 6 months in study PSV-FAI-001 and 12% vs. 39% in study PSV-FAI-005). Overall, the majority of the recurrences were not directly observed, but were "imputed" based on either the study eye being treated with a prohibited local or systemic medication (oral, systemic, injectable, or topical corticosteroids or systemic immunosuppressants) or the participant had a missing ophthalmic assessment at the 6- or 12-month visit. This means that the between-groups difference in the recurrence rates was mostly driven by imputed outcomes. Although the use of prohibited medications may be a reasonable surrogate for the occurrence of uveitis-related symptoms, it is unclear whether such symptoms would meet the rigorous threshold for a clinical diagnosis of recurrence (e.g., a 2-step or more increase in the number of cells in the anterior chamber per high-powered field [1.6 using a 1-mm]; a 2-step or more increase in vitreous haze; or a deterioration in visual acuity of 15 letters or more of best-corrected visual acuity). Therefore, it cannot be ruled out that the imputation led to an overestimation of the number of recurrences. With more imputed recurrences in the sham group than the treatment group, then it also cannot be ruled out that this led to an overestimation of the treatment effect. For example, in the published RCT by Jaffe et al (2019), when the results of observed recurrences were separately reported, the absolute between-group differences were numerically lower than in the imputed subgroups both at 6 months (sham rate – fluocinolone rate difference of 27.5% in observed group [n = 13] vs. 35.5% [n = 49]) and at 12 months (25.2% for observed group [n = 15] vs. 34.5% [n = 59]). In the unpublished trial PSV-FAI-005, the discrepancy was even larger. For example, at 6 months the absolute between-group difference in the observed recurrence subgroup was 5% (15% in sham and 10% in the fluocinolone group) versus 27% in the imputed group (39% in sham and 12 in the fluocinolone group). Further, it cannot be ruled out that visibility of the injected fluocinolone acetonide insert – or lack thereof - may have influenced the perceived need for use of prohibited medications. In the publication by Jaffe et al (2019), they noted that "The injected insert typically remains in a peripheral location within the vitreous base and is not detected easily on routine ophthalmologic examination. Regardless, we cannot exclude the possibility that the insert could have been visible in some study participants." Therefore, because of the inconsistency in key findings between the pivotal studies and the questions raised by the use of the imputed recurrence rates, the evidence is not sufficient to draw strong conclusions on the effect on health outcomes.

In 2020, the 3-year results from the pivotal study PSV-FAI-001 study were published. Over 36 months of treatment, cumulative uveitis recurrences were significantly reduced with fluocinolone acetonide (0.18 mg) compared with sham (65.5% vs. 97.6%, respectively). The time to the first recurrence in the fluocinolone acetonide (0.18 mg) group was significantly longer compared to sham-treatment (median 657 days; 95% CI, 395 to 105 vs. median 70.5 days; 95% CI, 57 to 91). The number of recurrences per eye occurring over 36 months was significantly lower in the treatment group compared to sham and a higher proportion of eyes in the fluocinolone acetonide (0.18 mg) group had no uveitis recurrence compared to sham (34.5% vs. 2.4%). Additionally, a greater proportion of eyes in the treatment group compared to sham had uveitis recur only once in 3 years (33.3% vs. 11.9%, respectively). Of note, the 36-month results included imputed recurrences, as in the initial results. However, observed protocol-defined uveitis recurrences occurred in a greater percentage of the sham-treated eyes, whereas the percentage of eyes with an imputed recurrence was more similar in the 2 groups (59.8% and 69.0%, respectively). At 36 months, more eyes in the treatment group had a 15-letter or greater increase in best-corrected visual acuity from baseline

compared to the sham-treated group (33.3% vs. 14.7%). There was also a significantly greater mean change in best-corrected visual acuity over 36 months in the treatment group compared to sham. Intraocular pressure was well-controlled in both groups and similar for both groups at month 36. The proportion of eyes in the fluocinolone acetonide (0.18 mg) group that underwent intraocular pressure-lowering surgery was approximately half that in the sham-treated group. Cataract surgery was required more frequently over 36 months in the treatment group compared with the sham-treated group.

The 3-year results of the PVS-FAI-005 study were reported by Biswas et al (2023). Over 36 months, uveitis recurrence was lower in the fluocinolone acetonide (0.18 mg) group (46.5%) than with sham (75.0%). Observed recurrences were lower with fluocinolone acetonide (0.18 mg; 18.8%) than with sham (28.8%), and suspected recurrences were also lower with active treatment (27.7% vs. 46.2%, respectively). The time to first recurrence was longer in the fluocinolone acetonide (0.18 mg) group than with sham (1116 days vs. 190.5 days, respectively), and the mean number of recurrences was lower with active versus sham treatment (2.9 vs. 4.2, respectively). At 36 months, a similar proportion of eyes in the treatment group had a 15-letter or greater increase in best-corrected visual acuity from baseline compared to the sham-treated group (26.7% vs. 27.3%). Over 36 months, a similar percentage of eyes in both groups required intraocular pressure-lowering surgery (2% vs. 0%, respectively). Among patients with phakic eyes at baseline, 70.5% in the fluocinolone acetonide (0.18 mg) group underwent cataract surgery compared to 26.5% of the sham group.

Table 2. Summary of Key RCT Results

Study	6-mo Recurrence	12-mo Recurrence	Mean change in BCVA at 12 mo	Increased intraocular pressure within 12 mo	Cataract within 12 mo
Jaffe et al (2019)	129	129	124	129	129
Fluocinolone acetonide (0.18 mg)	24 (27.6%)	33 (37.9%)	+5.8	23 (26.4%)	24 (27.6%)
Sham	38 (90.5%)[1]	41 (97.6%)	+3.3	11 (26.2%)	2 (4.8%)
OR (95% CI)	24.94 (8.04 to 77.39)	67.09 (8.81 to 511.06)	NR	NR	NR
PSV-FAI-005	153	153	142	153	153
Fluocinolone acetonide (0.18 mg)	22 (22%)[1]	33 (33%)[2]	+3.0	29 (28.7%)	12 (11.9%)
Sham	28 (54%)[1]	31 (60%)	+7.4	1 (1.9%)	7 (13.5%)
OR (95% CI)	4.2 (2.0 to 8.6)	3.04 (1.52 to 6.08)	NR	NR	NR

	36-mo Recurrence	Mean number of recurrences per eye at 36-mo (SD)	Mean change in BCVA at 36 mo (SD)	Increased intraocular pressure within 36 mo	Cataract surgery over 36 mos
Jaffe et al (2020) 3-year results	129	129	129	129	129
Fluocinolone acetonide (0.18 mg)	57 (65.5%)[1]	1.7 (2.4)	+9.1 (13)	14.5 (16.6%)	73.8%
Sham	41 (97.6%)[1]	5.3 (3.8)	+2.5 (14.2)	14.8 (35.2%)	23.8%
OR (95% CI)	21.58 (2.83 to 164.7)	NR	NR	NR	NR
p-value	<.001	<.001	.020	NR	NR

BCVA: best-corrected visual acuity; CI: confidence interval; NR: Not Reported; OR: odds ratio; PSV-FAI-005: A Multi-center, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects With Chronic Non-infectious Uveitis Affecting the Posterior Segment of the Eye; SD: standard deviation; RCT: randomized controlled trial.
[1] Primarily imputed, not observed recurrence
[2] From FDA statistical review

Subsection Summary: Intravitreal Fluocinolone Implant (0.18 or 0.19 mg) for Non-Infectious Uveitis
For individuals with chronic noninfectious posterior uveitis affecting the posterior segment of the eye and who receive intravitreal fluocinolone acetonide implant (0.18 or 0.19 mg), the evidence includes 2 pivotal RCTs. Relevant outcomes are symptom improvement, change in disease status, functional status, and quality of life. Harmful outcomes of interest are treatment-related morbidity. Both RCTs consistently found statistically significantly lower uveitis recurrence rates for intravitreal fluocinolone acetonide implant (0.18 mg) at both 6 and 12 months. The 3-year follow-up for Jaffe et al also found statistically significant lower uveitis recurrence rates at 36 months. However, serious limitations of these findings include inconsistency in the magnitude of the benefit at 12 months (odds ratio [OR]=67.09; 95% CI, 8.81 to 511.06 in published RCT and OR 3.04; 95% CI, 1.52 to 6.08 in the unpublished RCT) and, with more imputed recurrences in the sham groups than the treatment groups, we also cannot rule out an overestimation of the treatment effect. For the remainder of key outcomes, results were inconsistent between RCTs, appearing more favorable in the published trial. Most notable were the differences between RCTs in mean change in best-corrected visual acuity at 12 months (higher for fluocinolone acetonide in the published trial, lower in the unpublished trials) and risk of increased intraocular pressure within 12 months (increased risk in the unpublished trial, but not in the published trial).

MACULAR EDEMA AFTER RETINAL VEIN OCCLUSION
In 2015, the American Academy of Ophthalmology (AAO) published a technology assessment on therapies for macular edema associated with CRVO. AAO identified 4 clinical trials that provided level I evidence supporting the use of anti-vascular endothelial growth factor (anti-VEGF) pharmacotherapies and 2 clinical trials providing level I evidence for intravitreal corticosteroid

injection with the dexamethasone intravitreal implants 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 cataracts and IOP elevation compared with anti-VEGF treatments. There was limited information on combination therapy with anti-VEGF and corticosteroid injections compared with monotherapy.

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

Intravitreal Dexamethasone Implant (0.7 mg)-Ozurdex

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 3. Summary of Results From 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.

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)-Retisert

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

Additional RCTs

Several additional RCTs have evaluated the comparative effects of dexamethasone intravitreal implants to other therapies and found mixed results. 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. Compared to anti-VEGF for the treatment of macular edema after branch retinal vein occlusion, a meta-analysis by Ji et al (2019) of 6 studies (1 RCT, 4 retrospective studies, 1 prospective study; N = 452 eyes) found similar best-corrected visual acuity change at 3 or 6 months with dexamethasone intravitreal implants (0.7 mg), but a higher risk of intraocular pressure elevation for dexamethasone treatment. Another meta-analysis by Tang et al (2024) also compared anti-VEGF agents to dexamethasone 0.7 mg intravitreal implants for the treatment of macular edema after branch retinal vein occlusion and included 8 RCTs (N = 336 eyes). In this analysis, dexamethasone resulted in superior best corrected visual acuity (mean difference, -3.68; 95% CI, -6.11 to -1.25; p=.003) and significantly reduced central macular thickness (mean difference, 31.32; 95% CI, -57.92 to -4.72; p = 0.02). However, dexamethasone also increased the risk of elevated intraocular pressure (relative risk, 6.98; 95% CI, 2.16 to 22.50; p = 0.001). The risk of cataract progression did not significantly differ between treatments (relative risk, 1.83; 95% CI, 0.63 to 5.27; p = 0.31). In another 60 patients with macular edema following branch retinal vein occlusion from a single-center in New Delhi, a randomized, open-label trial by Kumar et al (2019) found that best-corrected visual acuity gains at 6 months for 0.7 mg dexamethasone intravitreal implants, with or without laser photocoagulation (+ 9.50 and + 10.50, respectively), were similar to intravitreal ranibizumab (1 injection of 0.5 mg) with laser photocoagulation (+ 10.00), but lower than for 3 injections of 0.5 mg ranibizumab without laser photocoagulation (+ 18.00).

For the comparison to triamcinolone, the evidence includes the open-label multicenter PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) trial by Thorne et al (2019), in which 192 patients with macular edema, defined as a central subfield thickness 2 standard deviations greater than the population normative mean, were randomized to receive periocular triamcinolone acetonide 40 mg, intravitreal triamcinolone acetonide 4 mg, or the 0.7 mg intravitreal dexamethasone implant. Retreatment was permitted for the triamcinolone treatments at 8 weeks and at 12 weeks for dexamethasone. The proportion of eyes with macular edema resolution varied between treatments

at 8 weeks (61% for dexamethasone, 47% for intravitreal triamcinolone, 20% for periocular triamcinolone) but not at 24 weeks (41%, 36%, and 35%, respectively). Change in best-corrected visual acuity was similar for intravitreal dexamethasone, intravitreal triamcinolone, and periocular triamcinolone at 8 weeks (+9.53 vs. +9.70 vs. +4.37 letters) and 24 weeks (+9.21 vs. +9.60 vs. +4.07). The main limitation was that, at 24 weeks, follow-up was relatively short-term. Longer-term data will be needed to confirm these findings.

An open-label, prospective, real-world study evaluated the effectiveness of dexamethasone intravitreal implant (0.7 mg) in a subgroup of patients with treatment-naive diabetic macular edema (Fraser-Bell et al 2021). Of the 200 eyes enrolled in the original AUSSIEDEX study, 57 were treatment-naive. Changes in mean best-corrected visual acuity and central subfield retinal thickness from baseline to 52 weeks in this subgroup were + 3.4 letters ($p = 0.042$) and -89.6 micrometers ($p < 0.001$), respectively, with a mean of 2.5 injections of dexamethasone intravitreal implant 0.7 mg. The most common adverse event was increased intraocular pressure, with 20% of eyes requiring intraocular-pressure lowering medications.

An open-label, retrospective, 5-year real world study evaluated the effectiveness of dexamethasone intravitreal implant (0.7 mg) compared to anti-VEGF treatment in patients with diabetic macular edema secondary to retinal vein occlusion (Zhang et al 2022). There were 16 patients included, with 8 patients in each group. At the end of the 5-year evaluation period, changes in the best-corrected visual acuity (0.69 ± 0.36 LogMAR vs. 0.57 ± 0.30 LogMar; $p = 0.574$) and central macular thickness (183.25 ± 97.31 μm vs. 195.38 ± 40.92 μm; $p = 0.442$) were not significantly different between the dexamethasone and anti-VEGF groups, respectively. The dexamethasone group had a higher foveal avascular zone circularity index and higher retinal perfusion density than the anti-VEGF group.

Garay-Aramburu et al (2024) conducted a multicenter, retrospective study comparing dexamethasone intravitreal implants (0.7 mg) and anti-VEGF agents for branch (n = 407 eyes) and central (n = 318 eyes) retinal vein occlusion using data from the European Fight Retinal Blindness! Registry. At 12 months, changes in visual acuity were not significantly different between groups (branch retinal vein occlusion: dexamethasone, + 6.7 vs. anti-VEGF, + 10.6 letters; central retinal vein occlusion: dexamethasone, + 2.8 vs. anti-VEGF, + 6.8 letters). Dexamethasone therapy required fewer injections and visits but had higher rates of intraocular pressure elevation in patients with branch retinal vein occlusion (dexamethasone, 5 of 47 [11%] vs. anti-VEFG, 9 of 360 [2%] patients; $p = 0.015$).

Subsection Summary: Intravitreal Dexamethasone Implant (0.7 mg) or Intravitreal Fluocinolone Acetonide Implant (0.59 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 post-implantation. Further, implant-treated patients achieved improvement in vision faster than the sham controls. However, the vision gain was similar at 6 months. Several additional RCTs, systematic reviews, and observational studies have evaluated the comparative effects of dexamethasone intravitreal implants

versus other therapies and found mixed results. A few notable findings include that the combination of implants with macular grid laser may increase the interval between repeated implants and dexamethasone intravitreal implants may have similar efficacy to other types of treatments. Further, as a class effect, use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

DIABETIC MACULAR EDEMA

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)-Retisert

Rittiphairoj et al (2020) published a Cochrane review that evaluated the efficacy of intravitreal steroids for macular edema in diabetes. It is an update of the previously published Cochrane review by Grover et al (2008). Ten trials were included, involving 4505 eyes with diabetic macular edema. Among those, 4 trials examined the effectiveness of intravitreal steroid implantation with fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system compared with sham or an anti-VEGF agent (all discussed below) and 6 examined triamcinolone. Cochrane reviewers concluded that, compared to sham or control, intravitreal steroids may improve visual outcomes in people with diabetic macular edema, but that these benefits should be weighed against the risk of intraocular pressure elevation.

In 2011, Pearson et al reported on the 3-year efficacy and safety results of an industry-sponsored, single-blind (evaluator) RCT in which 196 patients with persistent or recurrent unilateral or bilateral DME (referred to as refractory DME) 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 was no significant differences between the groups (eg, 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 (eg, VEGF inhibitors), this implant is not indicated for DME.

Intravitreal Fluocinolone Acetonide Implant (0.19 mg)-ILUVIEN

Two double-blind, randomized trials (FAME) have 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 4. Summary of Results (2 Years) From 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.

Morozova et al (2024) reported on a retrospective study that evaluated fluocinolone acetonide 0.19-mg intravitreal implants in 115 patients (148 eyes) with diabetic macular edema over an average follow-up of 29.4 months. Results demonstrated that the fluocinolone implant stabilized visual acuity, with a 0.8 letter decrease in the mean best-corrected visual acuity, and an increase in eyes achieving ≥ 70 letters (20/40 Snellen equivalent) from 20.6% at baseline to 23.7% at 24 months. Furthermore, the central subfield thickness was reduced from 379.9 μm to 323.7 μm, with 58.7% of eyes achieving central subfield thickness ≤ 300 μm at month 24 ($p < 0.001$). Lastly, the frequency of treatment for diabetic macular edema (intravitreal antivascular endothelial growth factor injections or laser photocoagulation) decreased from 4.9 to 1.5 treatments per year ($p < 0.001$).

Capone et al (2024) reported on a retrospective study evaluating fluocinolone acetonide 0.19-mg intravitreal implants in 178 patients (241 pseudophakic eyes). In a subset of 111 eyes with 24 months of follow-up, mean best-corrected visual acuity improved by 5.1 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (95% CI, 2.6 to 7.5; $p < 0.001$), and central macular thickness decreased by 189 μm (95% CI, 151 to 227; $p < 0.001$). Additional intravitreal treatments were required in 38 (34.2%) eyes. Safety outcomes, based on the full cohort of 241 eyes, revealed that 66 (27.4%) eyes required intraocular pressure-lowering medications (primarily within the first year of follow-up), and 14 (5.8%) eyes underwent trabeculectomy (predominantly during the second year).

Subsection Summary: Intravitreal Fluocinolone Acetonide Implant (0.19 mg) for Diabetic Macular Edema
Two RCTs and several observational studies have established the efficacy of fluocinolone acetonide implants (0.19 mg) for patients with DME. Both RCTs demonstrated the superiority of implants over sham controls. Implant-treated eyes showed clinically meaningful improvement in vision at 2 and 3 years post-implant. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic. Similar results were seen in observational studies with follow up to 2 years. 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 who do not have a clinically significant rise in IOP.

Intravitreal Dexamethasone Implant (0.7 mg)-Ozurdex
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 5. 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.

Subsequent to the 2014 pivotal trials and FDA approval, several small and/or short-term trials have been published that evaluate the comparative effects of intravitreal dexamethasone implant (0.7 mg) versus other treatments – primarily anti-VEGF in various subgroups of patients with diabetic macular edema. In general, compared with primarily anti-VEGF treatments, intravitreal dexamethasone implant (0.7 mg) was consistently associated with larger reductions in retinal thickness, but visual acuity changes were similar between treatment groups. While promising, as these findings are based on single small studies, several of which are nonrandomized, adequately powered and longer-term randomized trials are still needed to confirm these findings.

Table 6. Summary of Additional Studies of Intravitreal Dexamethasone Implant (0.7 mg) in Diabetic Macular Edema

Author, Year, study design, sample size	Population	Comparator	Summary of findings
Gillies et al (2014) , BEVORDEX RCT, N=88	Patients with DME	Bevacizumab	Dexamethasone had greater reduction in 12-mo retinal thickness and similar for BCVA improvement of ≥ 10 letters. But, dexamethasone resulted in greater risk of vision loss > 10 letters and more adverse events.
Callanan et al (2017), RCT, N=363	Patients with DME	Ranibizumab 0.5 mg	Dexamethasone was noninferior to ranibizumab in mean average BCVA change based on the prespecified noninferiority margin of 5 letters, similar in retinal thickness reduction, but ocular adverse events were more frequent for dexamethasone.

Sharma et al (2019), RCT, N=40	Centre involved DME	Bevacizumab 1.25 mg or ranibizumab 0.5 mg	Dexamethasone had greater improvements in 3-mo retinal thickness, but similar visual acuity
Unpublished RCT, NCT02471651, N=40	Persistent DME following anti-VEGF therapy	Continue on various anti-VEGF therapy	Treatments similar in 9-mo retinal thickness and visual acuity improvements

BCVA: best-corrected visual acuity; DME: Diabetic Macular Edema; NCT02471651: Dexamethasone Intravitreal Implant (0.7mg) for the Treatment of Persistent Diabetic Macular Edema Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor.

Cornish et al (2023) reported on 5-year outcomes of the BEVORDEX trial in patients with diabetic macular edema. Patients were randomized to receive either intravitreal dexamethasone implant (0.7 mg) or intravitreal bevacizumab. Data was available for 82% (n = 72) of eyes 3 years after enrollment, 72% (n = 63) at 4 years, and 59% (n = 52) at 5 or more years of follow-up. Baseline characteristics of the eyes from both study arms were similar. Table 7 summarizes the trial's results.

Table 7. Summary of Key Nonrandomized Trials Study Results

Study	Mean VA at 5 years, letters (95% CI)	Proportion of eyes who gained ≥ 10 letters from baseline to 5 years, n (%)	Mean change in CMT, µm	Proportion of eyes that had cataract surgery by 5 years (%)
Cornish et al (2023)			**From baseline to 5 years (95% CI)**	
Dexamethasone	58.5 (95% CI, 55.1 to 61.9)	14 (30.4%)	−150 (95% CI, −199 to −100)	84%
Bevacizumab	59.5 (95% CI, 57.4 to 63.6)	14 (33.3%)	−173 (95% CI, −232 to −121)	68%
Chakraborty et al (2024	**Mean BCVA at 12 months**		**CMT (µm) at 12 months**	**Need for IOP lowering surgery, n (%)**
Dexamethasone	0.50 + 0.07 logMAR		293 + 15.9	5 (13)
Aflibercept	0.47 + 0.12 logMAR		292 + 10.8	0
P-value	0.58		0.95	0.02
Bolukbasi et al (2019)	**Mean BCVA at 3 months**		**Mean change in CMT (+/- SD), µm**	

Dexamethasone	0.4 ± 0.2 LogMAR	NR	228.6 ± 109.8	NR
Aflibercept	0.3 ± 0.2 LogMAR	NR	168.5 ± 106.4	NR
Cakir et al (2019)	**Mean BCVA at 4 months**	**Mean change in CMT (+/- SD), µm at 1 month**	**Mean change in CMT (+/- SD), µm at 4 months**	**Proportion of eyes that had cataract surgery by end of study**
Dexamethasone	1.0 ± 0.5 LogMAR	188.2 ± 142.7	−63 ± 67.3	0
Ranibizumab	0.7 ± 0.5 LogMAR	95.7 ± 110.7	−5.8 ± 43.9	0
Coelho et al (2019)		**Letter improvement on ETDRS chart**	**CFT reduction, µm**	
Dexamethasone	NR	> 5-letter improvement on the ETDRS chart at months 1 and 3	> 100 µm CFT reduction at month 1	NR
Fluocinolone acetonide	NR	> 10-letter improvement on the ETDRS chart over months 3 to 24	Sustained ~200 µm over 1 to 24 months	NR

BCVA, best corrected visual acuity; CI: confidence interval; CFT: central foveal thickness; CMT, central macular thickness; CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; NR: not reported; SD, standard deviation; VA: visual acuity.

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 post-implantation. 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. Evidence from various small and/or short-term trials have found that, compared with primarily anti-VEGF treatments, intravitreal dexamethasone implant (0.7 mg) was consistently associated with larger reductions in retinal thickness, but visual acuity changes were similar between treatment groups.

Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus anti-VEGF therapy, the evidence includes 2 small RCTs of 169 patients (N range, 40 to 129). The first RCT, published by Maturi et al (2015), was single-blinded and used bevacizumab as the anti-VEGF treatment. The second RCT, published by Maturi et al (2018) was double-blinded, used ranibizumab as the anti-VEGF treatment, and focused on a ranibizumab-resistant population with persistent diabetic macular edema despite previous treatment. Findings from both trials were consistent in demonstrating that although adding dexamethasone to an anti-VEGF treatment can lead to a greater mean reduction in central subfield thickness, it does not improve visual acuity and can lead to a higher risk of intraocular pressure elevation. The main limitations of both RCTs were their small sample size and the relatively short-term follow-up in the 2018 RCT.

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy for Diabetic Macular Edema

Two small RCTs have consistently demonstrated that although combined treatment with dexamethasone implants plus an anti-VEGF treatment can lead to a greater mean reduction in central subfield thickness compared to the anti-VEGF treatment alone, it does not improve visual acuity and can lead to a higher risk of intraocular pressure elevation. Therefore, these RCTs provide insufficient evidence to determine that the technology results in a meaningful improvement in the net health outcome.

Intravitreal Dexamethasone Implant (0.7 mg) Plus Laser Photocoagulation

In 2013, Callanan et al reported on a multicenter, double-masked, RCT (N = 253) that compared dexamethasone implant plus combination laser photocoagulation with sham treatment plus laser photocoagulation for the treatment of diabetic macular edema. Of the patients included in the study, 61.3% were White, 21% were Hispanic/Latinx, 9.8% were Black, 2.7% were Asian, and 5.2% did not have their race or ethnicity reported. The percentage of patients in the combination group versus the sham group who gained 10 or more letters was greater at 1 month (31.7% vs. 11.0%; < 0.001) and 9 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 might have biased results. An increase in intraocular pressure of at least 10 mm Hg was observed in 15.2% of eyes treated with dexamethasone implants. Also, cataracts-related adverse events were more common after treatment with dexamethasone implants (22.2% vs. 9.5% ; p = 0.017).

Section 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 with laser photocoagulation alone found better visual acuity (as measured by a gain of ≥ 10 letters) at 9 months but not at 12 months. A differential loss to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis limit the interpretation of results. Use of dexamethasone implants resulted in higher incidences of cataracts and elevated intraocular pressure.

AGE-RELATED MACULAR DEGENERATION

Intravitreal Dexamethasone Implant (0.7 mg) Plus Anti-VEGF Therapy- Ozurdex

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 AMD 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 post-implant. 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 patients 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
Cystoid macular edema results from cystic accumulation of fluid in multiple layers of the retina following the breakdown of the blood-retinal barriers. It is a sub-type of macular edema which can be caused by many underlying conditions, including uveitis, retinal vein occlusion, diabetic macular edema, retinitis pigmentosa, as well as following procedures such as cataract extraction.

No large, multi-center, sham-controlled RCTs were identified on the treatment of this indication for any corticosteroids intravitreal implants.

The only RCT identified for this indication is for individuals who have cystoid macular edema related to retinitis pigmentosa. Park et al (2019) published a small (N = 14), single-center, observation-controlled RCT from South Korea. In this RCT, 14 patients with bilateral cystoid macular edema related to retinitis pigmentosa with macular cystic changes as shown by spectral domain optical coherence tomography with central macular thickness of.250 mm in both eyes had 1 eye randomized to intravitreal dexamethasone implant 0.7 mg and the other eye was observed. At 2 months, compared to the control eyes, the intravitreal dexamethasone implant eyes resulted in improved central macular thickness (-147.5 μm vs. -14 μm, $p < 0.001$) and median change of best-corrected visual acuity (+6 vs. +1; $p < 0.001$). But, at month 6, the central macular thickness of the study eyes returned to baseline level and there were no longer any significant differences between the eyes. At month 12, 40% of study eyes and 12.5% control eyes experienced cataract formation or progression. But none required cataract surgery.

Section Summary: Cystoid Macular Edema
Evidence for this indication includes 1 observation controlled RCT (N = 14), 3 comparative observational studies, and numerous case series. The RCT found improved mean visual acuity and eye anatomy outcomes with intravitreal dexamethasone compared to the control eyes, but these differences were not sustained at 6 months. The comparative observational studies included 269 patients (range, 60 to 135) and lacked responder analysis of the proportion of patients with a 15-or-more letter improvement. One case series evaluated the proportion of patients with a 3-line improvement in best-corrected visual acuity. Although 88% of patients achieved this outcome at 2 months, the proportion with improvement was not sustained at 6 months (27.8%). Additional

blinded, multicenter RCTs are needed that compare intravitreal dexamethasone to another established treatment. The trials should be adequately powered for measuring the proportion of patients in whom vision had improved by 15 letters or more.

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 1 with 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 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.

Mylonas et al (2017) published an RCT that compared dexamethasone intravitreal implant to triamcinolone intravitreal injection in 29 patients with refractory postoperative cystoid macular edema. Participants were mostly female (72%) and the mean age was 73 years in the dexamethasone group and 71 years in the triamcinolone group. No primary outcome was specified. There were no significant differences between the groups in improvement in mean best corrected visual acuity, but central millimeter retinal thickness reduction was significantly greater for triamcinolone at 1 week and 6 months. Minimal information on adverse events was reported. Key results are reported in Table 8.

Table 8. Summary of Key RCT Results

Study	Best-Corrected Visual Acuity	Central Millimeter thickness	Intraocular pressure
Mylonas et al (2017)	Mean (SD) at baseline, 1mo, 3mo, and 6mo	Mean (SD) at baseline, 1w, 1m, 3mo, and 6mo	Data not provided; "All cases of IOP elevation were managed readily by observation or
Dexamethasone	60 (10), 72 (10), 72 (11) and 66 (13)	548 (110), 406 (72), 357 (69), 391 (102), and 504 (159)	

Triamcinolone	63 (13), 73 (11), 73 (11), and 71 (13)	516 (121), 350 (54) 355 (59), 389 (89), and 365 (74)	topical pressure lowering medications and no glaucoma surgery was necessary"
p-value	>.05	≤.05 at 1w and 6m	

IOP: intraocular pressure; RCT: randomized controlled trial; SD: standard deviation.

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 2017 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
Evidence for this indication includes 1 RCT (N = 29) that compared dexamethasone intravitreal implant, 0.7 mg to triamcinolone intravitreal injection 4 mg, 2 comparative observational studies, and numerous case series. The RCT found no statistically significant difference between treatments in mean visual acuity improvement at 3 or 6 months. The proportion of patients in whom vision had improved by 15 letters or more was not reported. The comparative observational studies included only small numbers of patients and also lack responder analysis of the proportion of patients with a 15-or-more letter improvement. In the largest case series (N = 100), 2 of every 5 patients experienced clinically meaningful improvements in visual acuity after 1 year of follow-up. Additional RCTs are needed that have clearly defined and representative populations (ie, for chronic and refractory patients, documentation of intensity and duration of the first-line therapy regimens) and are adequately powered for measuring the proportion of patients in whom vision had improved by 15 letters or more.

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.

SUPRACHOROIDAL INJECTIONS

MACULAR EDEMA ASSOCIATED WITH UVEITIS

Suprachoroidal triamcinolone injection (4 mg) - Xipere

The efficacy of Xipere was assessed in a 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with anterior-, intermediate-, posterior-, or pan-uveitis. Patients were treated at baseline and week 12. The primary efficacy endpoint was the proportion of patients in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up. A statistically significantly greater proportion of patients treated with Xipere achieved a ≥ 15-letter improvement in BCVA than control patients ($p < 0.01$) at week 24 (47% vs. 16%, respectively).

Section Summary: Macular Edema Associated With Uveitis

One RCT demonstrated that a triamcinolone suprachoroidal 4 mg injection (Xipere) was better than placebo for the treatment of macular edema associated with uveitis.

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Policy History

Original Effective Date: 04/19/2017
Current Effective Date: 08/01/2026

04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. New Policy.
04/05/2018	Medical Policy Committee review
04/18/2018	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Added a new drug, Yutiq, to the policy. Updated background and rationale information. Removed summary section at the end of the policy.

Policy # 00549
Original Effective Date: 04/19/2017
Current Effective Date: 08/01/2026

04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/16/2021	Coding update
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Changed policy title from "Intravitreal Corticosteroid Implants" to "Intravitreal and Suprachoroidal Corticosteroid Products". Added a new product, Xipere, to the policy. Added information to the policy about suprachoroidal injections.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated Rationale section with most recent literature.
06/20/2023	Coding Update
12/12/2023	Coding Update
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2025	Medical Policy Committee review
05/13/2025	Medical Policy Implementation Committee approval. Updated literature review. Coverage eligibility unchanged.
05/07/2026	Medical Policy Committee review
05/13/2026	Medical Policy Implementation Committee approval. Updated criteria for Yutiq and Iluvien, stating that the use of both drugs for the treatment of chronic non-infectious intermediate uveitis, posterior uveitis, or panuveitis is considered not medically necessary. Updated literature.

Next Scheduled Review Date: 05/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines.

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Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	67027, 67028, 67516
HCPCS	J7311, J7312, J7313, J7314, J3299
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.