Intravitreal and Punctum Corticosteroid Implants

Policy Number: 9.03.23
Origination: 07/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Intravitreal Corticosteroid Implants when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

A fluocinolone acetonide intravitreal implant 0.59 mg (Retisert®) may be considered medically necessary for the treatment of:
- Chronic noninfectious intermediate, posterior, or panuveitis

A fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien®) may be considered medically necessary 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.

A dexamethasone intravitreal implant 0.7 mg (ie, Ozurdex™) may be considered medically necessary for the treatment of:
- Noninfectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye, OR
- Macular edema following branch or central retinal vein occlusion, OR
- Diabetic macular edema.

A punctum dexamethasone insert 0.4 mg (Dextenza®) may be considered medically necessary for the treatment of:
- With ocular inflammation and pain following ophthalmic surgery

When Policy Topic is not covered

A fluocinolone acetonide intravitreal implant 0.59 mg (Retisert®) or 0.19 mg (Iluvien®) or dexamethasone intravitreal implant 0.7 mg (Ozurdex™) is considered investigational for the treatment of:
- Birdshot retinochoroidopathy
- Cystoid macular edema related to retinitis pigmentosa
- Idiopathic macular telangiectasia type 1
- Postoperative macular edema
- Circumscribed choroidal hemangiomas
- Proliferative vitreoretinopathy
- Radiation retinopathy.
- A punctum dexamethasone insert 0.4 mg (Dextenza®) may be considered medically necessary for the treatment of ocular inflammation and pain following ophthalmic surgery

A fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq®) is considered investigational for the treatment of chronic noninfectious posterior uveitis affecting the posterior segment of the eye.

All other uses of a corticosteroid intravitreal implant are considered investigational.

**Considerations**

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

Insertion of intravitreal implants for drug delivery is usually reported with CPT code 67027 – Implantation of intravitreal drug delivery system (eg, ganciclovir implant), includes concomitant removal of vitreous. Insertion of the Ozurdex or Iluvien implant is done by injection and is reported with CPT code 67028 – Intravitreal injection of a pharmacologic agent (separate procedure).

The following HCPCS codes are available for the implants:
- J7311 Fluocinolone acetonide, intravitreal implant.
- J7312: Injection, dexamethasone, intravitreal implant, 0.1 mg
- J7313 Injection, fluocinolone acetonide, intravitreal implant, 0.01 mg
- J7314: Injection, fluocinolone acetonide, intravitreal implant (Yutiq), 0.01 mg

**Description of Procedure or Service**

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| • Noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery | • Prophylactic intravitreal dexamethasone 0.7 mg (Ozurdex) | • Standard of care | • Symptoms  
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An intravitreal implant is a drug delivery system, injected or surgically implanted in the vitreous of the eye, for sustained release of a pharmacologic agent to the posterior and intermediate segments of the eye. Three intravitreal corticosteroid implants, ie, fluocinolone acetonide 0.59 mg (Retisert), fluocinolone acetonide 0.19 mg (Iluvien), and dexamethasone 0.7 mg (Ozurdex) are reviewed herein. Fluocinolone acetonide implants are nonerodible and deliver drug up to 30 to 36 months while dexamethasone implants are bioerodible and last up to 6 months.

A punctum implant is a drug delivery device that is inserted through the lower lacrimal punctum into the canaliculus, for sustained release of a pharmacologic agent to the ocular surface. Dexamethasone ophthalmic insert 0.4 mg (Dextenza) is the first corticosteroid intracanalicular insert and is reviewed herein.

**Uveitis**

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

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

For individuals with chronic noninfectious posterior uveitis affecting the posterior segment of the eye and who receive intravitreal fluocinolone acetonide implant (0.18 mg, Yutiq), 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, Yutiq) at both 6 and 12 months. However, serious limitations of these findings include inconsistency in the magnitude of the benefit at 12 months (odds ratio 67.09; 95% confidence interval 8.81-511.06 in published RCT and odds ratio 3.04; 95% confidence interval 1.52, 6.08 in the unpublished RCT) and, with more imputed recurrences in the sham groups than the treatment groups, we also can’t 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). Due to these inconsistencies and serious methodological limitations, the evidence is insufficient to determine the effects of the technology on health outcomes.

**Macular Edema**

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

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

**Diabetic Macular Edema**

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

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

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 3 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with sham control, 2 identically designed RCTs showed clinically meaningful improvements in vision with dexamethasone implants that peaked at 3 months and maintained 39 months (with retreatment). The difference in the proportion of patients with a gain of 15 or more letters in best-corrected visual acuity from baseline was 9.3% and 13.0% in the 2 trials, respectively, favoring implant versus sham at 39 months postimplant. Subgroup analysis of these trials showed greater improvements in visual acuity in patients who were pseudophakic compared with those who were phakic. Additionally, evidence from various small and/or short-term trials and retrospective studies have found that, compared with primarily antivascular endothelial growth factor 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Findings from both RCTs were consistent in demonstrating that although adding dexamethasone to an antivascular endothelial growth factor 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. Based on the consistent lack of improvement in visual acuity, increased risk of intraocular pressure elevation, and imprecision, these RCTs provide insufficient evidence to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status,
functional outcomes, quality of life, and treatment-related morbidity. One RCT with 1-year follow-up demonstrated that combination implants plus laser photocoagulation compared with laser photocoagulation alone resulted in better visual acuity (as measured by a gain of ≥10 letters) at 9 months but not at 12 months. However, the generally accepted standard outcome measure for change is 15 or more letters, and this standard was not used in this trial. The use of dexamethasone implants resulted in higher incidences of cataracts and elevated intraocular pressure. Further, a differential loss to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis preclude interpretation of results. A larger RCT with adequate power is needed to confirm these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Age-Related Macular Degeneration**

For individuals with age-related macular degeneration who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor inhibitor, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of this trial did not demonstrate clinically meaningful reductions in the ranibizumab injection-free interval between combined treatments (34 days) and antivascular endothelial growth factor alone (29 days; p=0.016). Further, intraocular pressure was elevated in a greater proportion of patients receiving implants without any additional clinical benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Other Conditions**

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

For individuals with cystoid macular edema related to retinitis pigmentosa who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes a small observation-controlled RCT, a small prospective, oral acetazolamide-controlled cohort study, and multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Studies have noted mixed results for anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. Larger RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with cystoid macular edema related to retinitis pigmentosa. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with idiopathic macular telangiectasia type 1 who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Case reports have noted mixed results for visual acuity and inflammation-related outcomes. Long-term follow-up for efficacy and safety is limited. Better quality studies with long-term follow-up are needed to permit conclusions on the efficacy of corticosteroid implants in patients with idiopathic macular telangiectasia type 1. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

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

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

For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert (0.4 mg), the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. All 3 trials noted significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints of absence of pain at 8 days and absence of anterior chamber cells at day 14. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive prophylaxis with intravitreal dexamethasone 0.7 mg (Ozurdex), the best evidence includes 1 single-center, open-label RCT of 43 patients in India. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Compared with oral corticosteroids, intravitreal dexamethasone 0.7 mg had similar benefits and avoided need for early steroid taper due to adverse effects on blood glucose, but potentially increased risk of developing intraocular pressure. Due to important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding, evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Background
Eye Conditions

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

The classification scheme recommended by the Uveitis Study Group and the Standardization of Uveitis Nomenclature 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
Chronic inflammation associated with posterior segment uveitis can lead to cataracts, glaucoma, and structural damage to the eye, resulting in severe and permanent vision loss.

**Treatment**
The primary goal of therapy for uveitis is to preserve vision. Noninfectious uveitis typically responds well to corticosteroid treatment. Immunosuppressive therapy (eg, 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 and branch retinal vein occlusion differ in pathophysiology, clinical course, and therapy. Central retinal vein occlusions are categorized as ischemic or nonischemic. Ischemic central retinal vein occlusions are referred to as severe, complete, or total vein obstruction, and account for 20% to 25% of all central retinal vein occlusions. Macular edema and permanent macular dysfunction occur in virtually all patients with ischemic central retinal vein occlusion, and in many patients with nonischemic central retinal vein occlusion. Branch retinal vein occlusion is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more often than central retinal vein occlusion.

**Treatment**
Intravitreal injections of triamcinolone are used to treat macular edema associated with central retinal vein occlusion, 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.

Macular photocoagulation with grid laser improves vision in branch retinal vein occlusion but is not recommended for central retinal vein occlusion. Although intravitreal injections of triamcinolone have also been used for branch retinal vein occlusion, the serious adverse events have stimulated the evaluation of new treatments, including intravitreal steroid implants or the intravitreal injection of antivascular endothelial growth factor.

**Diabetic Macular Edema**
Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The 2 most serious complications for vision are diabetic macular edema and proliferative diabetic retinopathy. At its earliest stage (nonproliferative retinopathy), microaneurysms occur. As the disease progresses, blood vessels that nourish the retina are blocked, triggering the
growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from leakage of blood into the vitreous. Diabetic macular edema is characterized by swelling of the macula due to gradual leakage of fluids from blood vessels and breakdown of the blood-retinal barrier. Moderate vision loss can arise from the fluid accumulating in the center of the macula (macular edema) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main blinding complication of diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

**Treatment**

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 off-label adjunctive therapy for diabetic macular edema. 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 diabetic macular edema.

**Age-Related Macular Degeneration**

Age-related macular degeneration is a degenerative disease of the retina that results in loss of central vision with increasing age. Two 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, which greatly increases the risk of developing severe irreversible loss of vision. Choroidal neovascularization is categorized as classic or occult.

**Treatment**

Effective specific therapies for exudative or wet age-related macular degeneration are an intravitreous injection of a vascular endothelial growth factor inhibitor, possibly thermal laser photocoagulation (in selected patients), and photodynamic therapy.

**Intravitreal and Punctum Implants**

Intravitreal and punctum implants deliver a continuous concentration of a pharmacologic agent to the eye over a prolonged period. The goal of therapy is to reduce inflammation in the eye while minimizing the adverse events 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 (eg, 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 events 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 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 a 25-gauge applicator. 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.1,2

- **Dextenza®** (biodegradable dexamethasone intracanalicular insert; Ocular Therapeutix™) is a rod-shaped hydrogel device that is designed to deliver a sustained and tapered release of 0.4 mg of dexamethasone over 4 weeks. Following ophthalmic surgery, it is inserted through the inferior punctum into
the canaliculus of the operative eye. To allow for visualization and retention monitoring, the hydrogel device is conjugated with fluorescein. No removal is required as the device is designed to resorb and exit the nasolacrimal system independently.

- **Yutiq** (non-biodegradable fluocinolone acetonide intravitreal implant; EyePoint Pharmaceuticals U.S., Inc.) is a sterile 3.3 mm-long implant consisting of fluocinolone acetonide 0.18 mg that is preloaded into a single-dose applicator and injected directly into the vitreous. It is designed to provide a sustained release of fluocinolone acetonide at an initial rate of 0.25 mcg/day within over a 36-month period.

**Regulatory Status**

In 2009, Ozurdex® (dexamethasone 0.7 mg intravitreal implant; Allergan) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion. Subsequently, in September 2010, the indication was expanded to include treatment of noninfectious uveitis affecting the segment of the eye. In 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 the FDA for the treatment of diabetic macular edema in patients previously treated with a course of corticosteroids and without a clinically significant rise in intraocular pressure.

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

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

In November 2018, Dextenza® (dexamethasone 0.4 mg intracanalicular implant; Ocular Therapeutix) was approved by the FDA for the treatment of ocular inflammation and pain following ophthalmic surgery.

**Rationale**

This evidence review was created in June 2010 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through January 20, 2020.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures
are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Noninfectious Uveitis

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)

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

Table 1. Summary of Results From the FDA Pivotal Trial in Noninfectious Posterior Uveitis

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Uveitis Recurrence Rates, n (%)</th>
<th>Study 1 (N=108)</th>
<th>Study 2 (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 wk preimplant</td>
<td>58 (53.7)</td>
<td>46 (39.7)</td>
<td></td>
</tr>
<tr>
<td>34 wk postimplant</td>
<td>2 (1.8)</td>
<td>15 (12.9)</td>
<td></td>
</tr>
<tr>
<td>1 y postimplant</td>
<td>4 (3.7)</td>
<td>15 (12.9)</td>
<td></td>
</tr>
<tr>
<td>2 y postimplant</td>
<td>11 (10.2)</td>
<td>16 (13.8)</td>
<td></td>
</tr>
<tr>
<td>3 y postimplant</td>
<td>22 (20.4)</td>
<td>20 (17.2)</td>
<td></td>
</tr>
<tr>
<td>3 y postimplantc</td>
<td>33 (30.6)</td>
<td>28 (24.1)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bausch & Lomb (2012). FDA: U.S. Food and Drug Administration.

Recurrence of uveitis for all postimplantation time points was compared with the 34-week preimplantation time point.
Jaffe et al (2006) reported results of one of the pivotal trials. These trials are not discussed in detail 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 and cataracts were observed in implanted eyes compared with nonimplanted eyes. The second trial was reported only in FDA documents and results were similar to the first trial.

**Additional Randomized Controlled Trials**

Pavesio et al (2010) reported on results of an industry-sponsored, open-label trial in which 140 patients with chronic noninfectious posterior uveitis were randomized to the fluocinolone acetonide 0.59-mg implant (n=66) or systemic corticosteroid therapy (and immunosuppression when indicated; n=74). To be included in the trial, subjects had to have at least a 1-year history of recurrent uveitis. The primary efficacy outcome was time to the 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 with 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 cataracts. Visual acuity in the systemic corticosteroid group remained consistent over the 2-year study.

The Multicenter Uveitis Steroid Treatment Trial (2010), sponsored by the National Eye Institute, is a partially blind RCT (N=255) designed to compare visual acuity at 2 years using fluocinolone acetonide implants with 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 using the Early Treatment Diabetic Retinopathy Study chart was blinded. After 24 and 54 months of follow-up, the vision improvements from baseline in the implant groups compared with systemic therapy group were 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).\textsuperscript{8,10} 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, 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, 0.40; p=0.13), respectively. The incidences of other systemic adverse events, 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 on results of a Cochrane review of RCTs comparing fluocinolone acetonide or dexamethasone intravitreal implants with standard therapy in patients who had at least 6 months of follow-up posttreatment.\textsuperscript{7} The primary outcome was a recurrence of uveitis. Selected trials enrolled patients of all ages who had chronic noninfectious posterior uveitis, intermediate uveitis, or panuveitis with vision that was “better than hand motion.” Two trials, Pavesio et al (2010)\textsuperscript{6,} and Kempen et al (2011),\textsuperscript{8} were included and judged to be of moderate quality (both are discussed above). Because the 2 trials were designed to answer different questions (one measured recurrence, one 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 intraocular pressure (RR=7.48; 95% CI, 3.94 to 14.19; 599 eyes) in the implant group compared with the standard therapy group through 2 years of follow-up. Reviewers were unable to conclude that the implants were superior to traditional systemic therapy for the treatment of noninfectious uveitis.

**Adverse Events**

As listed in the prescribing label, nearly all phakic patients who receive implants are expected to develop cataracts and require cataract surgery.\textsuperscript{3,} Further, 75% of patients may experience elevated intraocular pressure and/or glaucoma severe enough to require intraocular pressure lowering medications and 35% filtering surgeries. Separation of implant components is another potential complication, and 6-year cumulative risk of a spontaneous dissociation is 4.8% (95% CI, 2.4% to 9.1%).\textsuperscript{11} Late-onset endophthalmitis is also recognized as a surgical complication of intraocular implants.

**Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Noninfectious Uveitis**

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

**Intravitreal Dexamethasone Implant (0.7 mg)**

The evidence for dexamethasone intravitreal implants consists of a pivotal, double-blind RCT, Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis (HURON - A Study of the Safety and Efficacy of a New Treatment for Non-Infectious Intermediate or Posterior Uveitis). In this 8-week, manufacturer-sponsored, multicenter trial (46 study sites in 18 countries), 229 patients with noninfectious intermediate or posterior uveitis were randomized to 0.7-mg implants (n=77), 0.35-mg implants (n=76), or sham procedure (n=76). The primary outcome measure was the proportion of eyes with a vitreous haze score of 0 (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 a gain of 15 or more letters in best-corrected visual acuity from baseline, was achieved by 40% of patients who received implants compared with 10% who received sham control. The incidences of elevated intraocular pressure (≥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 are not available. Lightman et al (2013) reported on 26-week data for vision-related functioning using National Eye Institute-Visual Function Questionnaire from HURON trial. Using the distribution- and anchor-based methods, the authors reported that a clinically meaningful change for the National Eye Institute-Visual Function Questionnaire-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 the composite score at week 26 was 58% (42/73) in the 0.7-mg implant group and 32% (24/74) in the sham-controlled arm (p<0.05).

**Adverse Events**

As listed in the prescribing label, in controlled studies, the most common adverse reactions reported by 20% to 70% of patients were cataracts, increased intraocular pressure, and conjunctival hemorrhage.
Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Noninfectious Uveitis
One RCT comparing 2 doses of implants with sham control has supported the efficacy of dexamethasone implants (0.7 mg) for patients with noninfectious intermediate or posterior uveitis. Results of this trial have demonstrated the efficacy of the dexamethasone 0.7-mg implant in reducing inflammation and resulted in clinically meaningful improvements in the vision at week 8 compared with 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 intraocular pressure.

Intravitreal Fluocinolone Acetonide Implant (0.18 mg, Yutiq)

Clinical Context and Test Purpose
The purpose of Intravitreal Fluocinolone Acetonide Implant (0.18 mg, Yutiq) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard therapy, in patients with chronic noninfectious posterior uveitis affecting the posterior segment of the eye.

The question addressed in this evidence review is: Does intravitreal fluocinolone acetonide implant (0.18 mg, Yutiq) improve the net health outcome in patients with chronic noninfectious posterior uveitis affecting the posterior segment of the eye.

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with chronic noninfectious posterior uveitis affecting the posterior segment of the eye.

Interventions
The intervention of interest is the intravitreal fluocinolone acetonide implant (0.18 mg).

Comparators
The comparators of interest are standard of care.

Outcomes
The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

For individuals with chronic (≥1-year history) noninfectious uveitis affecting the posterior segment of one or both eyes who receive fluocinolone acetonide (0.18 mg), the pivotal evidence includes 2 double-blind, randomized trials of 282 patients (range, 129-153) 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 Insert in Subjects With Chronic Non-infectious Uveitis Affecting the Posterior Segment of the Eye (study #PSV-FAI-005) (Table 2). Results of one 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 proportion of recurrence of uveitis within 6 months. Secondary outcomes at 12-months have also been reported. The publication by Jaffe et al (2019) indicates that at least study PSV-FAI-001 is a 3-year trial; consequently, longer-term findings are expected in the future.

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 (Table 3). 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 (Tables 4 and 5) 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 occurrence of uveitis-related symptoms, it is unclear whether such symptoms
would meet the rigorous threshold for a clinical diagnosis of recurrence (eg, 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, we can’t rule 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 we also can’t rule 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, we can’t rule 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 effect on health outcomes.

Table 2. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaffe et al (2019); Study PSV-FAI-001; NCT01694186</td>
<td>U.S., Europe, Israel, and India</td>
<td>33</td>
<td>2013-2015</td>
<td>Diagnosis of noninfectious uveitis affecting the posterior segment of at least 1 eye (with or without anterior uveitis) for ≥ 1 y, with ≥ 2 recurrences requiring intervention</td>
<td>Fluocinolone acetonide (0.18 mg), N=87</td>
</tr>
<tr>
<td>PSV-FAI-005</td>
<td>India</td>
<td>33</td>
<td>Unknown</td>
<td>Same as Jaffe et al 2019</td>
<td>Fluocinolone acetonide (0.18 mg), N=101</td>
</tr>
</tbody>
</table>

RCT: Randomized Controlled Trials; NCT: National Clinical Trial; US: United States; y: year; mg: milligram; ≥: greater than
PSV-FAI-001: A Phase III, Multi-National, Multi-Center, Randomized, Masked, Controlled, Safety
Table 3. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>6-mo Recurrence</th>
<th>12-mo Recurrence</th>
<th>Mean change in BCVA at 12 mos</th>
<th>Increased intraocular pressure within 12 mo</th>
<th>Cataract within 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluocinolone acetonide (0.18 mg)</td>
<td>24 (27.6%)</td>
<td>33 (37.9%)</td>
<td>+5.8</td>
<td>23 (26.4%)</td>
<td>24 (27.6%)</td>
</tr>
<tr>
<td>Sham</td>
<td>38 (90.5%)</td>
<td>41 (97.6%)</td>
<td>+3.3</td>
<td>11 (26.2%)</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>24.94 (8.04-77.39)</td>
<td>67.09 (8.81-511.06)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PSV-FAI-005</td>
<td>153</td>
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</tr>
<tr>
<td>Fluocinolone acetonide (0.18 mg)</td>
<td>22 (22%)</td>
<td>33 (33%)</td>
<td>+3.0</td>
<td>29 (28.7%)</td>
<td>12 (11.9%)</td>
</tr>
<tr>
<td>Sham</td>
<td>28 (54%)</td>
<td>31 (60%)</td>
<td>+7.4</td>
<td>1 (1.9%)</td>
<td>7 (13.5%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>4.2 (2.0-8.6)</td>
<td>3.04 (1.52, 6.08)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

BCVA: best-corrected visual acuity; CI: confidence interval; OR: odds ratio; NR: Not Reported; 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; RCT: randomized controlled trial.

1 Primarily imputed, not observed recurrence.
2 from FDA statistical review.

Table 4. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaffe et al (2019); Study PSV-FAI-001; NCT01694186</td>
<td>1. Imputed recurrence: 16% for active, 57% for sham</td>
<td>1. Imputed recurrence: 16% for active, 57% for sham</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV-FAI-005</td>
<td>5. Inadequately described in FDA review materials</td>
<td>1. Imputed recurrence: 12% for active, 39% for sham</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

FDA: U.S. Food and Drug Administration; PSV-FAI-001: 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; 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; RCT: randomized controlled trial.

1 Primarily imputed, not observed recurrence.
2 from FDA statistical review.
Segment of the Eye.


d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Table 5. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaffe et al (2019); Study PSV-FAI-001; NCT01694186</td>
<td>4. Study participants did not have severe active inflammation at the time of the initial study treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV-FAI-005</td>
<td>4. Study participants did not have severe active inflammation at the time of the initial study treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

PSV-FAI-001: 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;

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.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.18 mg, Yutiq) for Noninfectious Uveitis

For individuals with chronic noninfectious posterior uveitis affecting the posterior segment of the eye and who receive intravitreal fluocinolone acetonide implant (0.18 mg, Yutiq), 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, Yutiq) at both 6 and 12 months. However, serious limitations of these findings include inconsistency in the magnitude of the benefit at 12 months (OR 67.09; 95% CI 8.81-511.06 in published RCT and OR 3.04; 95% CI 1.52, 6.08 in the unpublished RCT) and, with more imputed recurrences in the sham groups than the treatment groups, we also can’t 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). Due to these inconsistencies and serious methodological limitations, the evidence is insufficient to determine the effects of the technology on health outcomes.

Macular Edema After Retinal Vein Occlusion
In 2015, the American Academy of Ophthalmology published a technology assessment on therapies for macular edema associated with central retinal vein occlusion.18 The Academy identified 4 clinical trials that provided level I evidence supporting the use of antivascular endothelial growth factor 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 the long-term efficacy of corticosteroid treatments is limited and that intravitreal corticosteroids led to a higher frequency of adverse events, including cataracts and intraocular pressure elevation compared with antivascular endothelial growth factor treatments. There are limited data on combination therapy with antivascular endothelial growth factor and corticosteroid injections compared with monotherapy.

A Bayesian network meta-analysis of the efficacy and safety of treatments for macular edema secondary to branch retinal vein occlusion was published in 2015.19 Eight RCTs (total N=1743 patients) were included; patients were treated with ranibizumab 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 of 15 letters or more, was highest for monotherapy of antivascular endothelial growth factor 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 antivascular endothelial growth factor monotherapy (, 13.1).
Intravitreal Dexamethasone Implant (0.7 mg)
Data presented to FDA for the dexamethasone intravitreal implant (Ozurdex) were from two 6-month, double-masked RCTs called Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA(GENEVA) (167 clinical sites in 24 countries).1,20. A 6-month open-label extension of these 2 pivotal trials was reported in 2011.1,2. A total of 1267 patients who had clinically detectable macular edema associated with either central retinal vein occlusion or branch retinal vein occlusion 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 best-corrected visual acuity. A secondary outcome was the proportion of eyes achieving a 15-or-more letter improvement from baseline at 180 days. In individual studies and pooled analysis, time to achieve a 15-or-more letter (3-line) improvement in best-corrected visual acuity was significantly faster with implants than with sham (p<0.01) (data not shown). As evident from Table 6, the proportion of patients with a 15-or-more letter improvement from baseline in best-corrected visual acuity was higher in the implant with the FDA-approved dose (0.7 mg) than with 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 6. Summary of Results From the FDA Pivotal Trial in Retinal Vein Occlusion

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Implant (0.7 mg)</td>
<td>Sham</td>
</tr>
<tr>
<td>Day 30</td>
<td>40 (20)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Day 60</td>
<td>58 (29)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Day 90</td>
<td>45 (22)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Day 180</td>
<td>39 (19)</td>
<td>37 (18)</td>
</tr>
</tbody>
</table>

Adapted from Allergan (2014).15.
BCVA: best-corrected visual acuity; FDA: U.S. Food and Drug Administration.

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)
No RCTs were identified assessing the fluocinolone acetonide implants for the treatment of macular edema following retinal vein occlusion.

Additional Studies
Several additional RCTs have evaluated the comparative effects of dexamethasone intravitreal implants to other therapies and found mixed results.21,22,19,20,23,24,25. In the largest trial, Kupperman et al (2007) reported on results for an RCT in which 315 patients with persistent macular edema of different etiology (diabetic retinopathy [n=172], branch retinal vein occlusion [n=60], central retinal vein occlusion [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.22. 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 on results for 30 patients randomized to dexamethasone implants plus bevacizumab or bevacizumab monotherapy and found no additional benefit for visual acuity with the combination treatment at 6 months. Compared to anti-vascular endothelial growth factor for 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. 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, evidence includes the open-label multicenter PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT; NCT02374060) 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 pericentral 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. Proportion of eyes with macular edema resolution varied between treatments at 8 weeks (61% for dexamethasone, 47% for intravitreal triamcinolone, 20% for pericentral 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 pericentral 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.

**Adverse Events**
As listed in the prescribing label, in controlled studies, the most common adverse reactions reported by 20% to 70% of patients were cataracts, increased intraocular pressure, and conjunctival hemorrhage.
Section 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 sham control. Compared with sham, both doses of the dexamethasone implant resulted in clinically meaningful improvements in visual acuity within 1 to 3 months postimplantation. Further, implant-treated patients achieved improvement in vision faster than the sham controls. However, the vision gain was similar at 6 months. Several additional RCTs and a meta-analysis 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 intraocular pressure.

No trials assessing the use of fluocinolone acetonide implants were identified.

Diabetic Macular Edema

A Cochrane review (2008) evaluated the efficacy of intravitreal steroids for macular edema in diabetes.26 Seven studies, involving 632 eyes with diabetic macular edema, were included. Four trials examined the effectiveness of intravitreal triamcinolone acetate injection, and 3 examined intravitreal steroid implantation with fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system (including the Kuppermann et al [2007] trial previously described). Cochrane reviewers concluded that steroids placed inside the eye by intravitreal injection or surgical implantation might improve visual outcomes in eyes with persistent or refractory diabetic macular edema. However, questions remained whether intravitreal steroids could be of value in other (earlier) stages of diabetic macular edema or combination with other therapies, such as laser photocoagulation.

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)

Pearson et al (2011) 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 diabetic macular edema (referred to as refractory diabetic macular edema) were randomized to implants (n=127) or standard of care, defined as additional laser as needed after 6 months or observation (n=69).27 All patients had received focal/grid laser photocoagulation before randomization. At 6 months, the proportions of patients who received laser retreatment in the 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 best-corrected visual acuity at 6 months before any additional laser treatment) was achieved in 16.8% of implanted eyes versus 1.4% of the 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 difference between the groups (eg, 31.1% of implanted eyes vs. 20.0% of the standard of care eyes improved ≥15 letters). As expected, there were higher incidences of elevated intraocular pressure (≥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 with 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.

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Diabetic Macular Edema
One RCT comparing fluocinolone acetonide implants (0.59 mg) with the standard of care (as needed laser or observation) has supported the efficacy of implants for patients with diabetic macular edema. The primary efficacy outcome, at least a 15-letter improvement in best-corrected visual acuity 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 intraocular pressure. Due to the substantial increase in adverse events and availability of agents with safer tolerability profiles (eg, Vascular Endothelial Growth Factor inhibitors), this implant is not indicated for diabetic macular edema.

Intravitreal Fluocinolone Acetonide Implant (0.19 mg)
Two double-blind, randomized trials Fluocinolone Acetonide in Diabetic Macular Edema (FAME) has assessed patients with diabetic macular edema previously treated with laser photocoagulation. The primary efficacy endpoint 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, the FDA approved the 0.19-mg dose based only 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 7. Campochiaro et al (2012) subsequently reported on 3-year results. 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 with those who were phakic (difference in mean change in a 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 from 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) diabetic macular edema. The difference in the proportion of patients who gained 15 or more letters in the implant group versus the sham control group with chronic diabetic macular edema patients was 21% and -5.5% among nonchronic diabetic macular edema patients.

Table 7. Summary of 2-Year Results From the FDA Pivotal Trials in Diabetic Macular Edema

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study 1 (N=285)</th>
<th>Study 2 (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Implant (n=190)</td>
<td>Sham (n=95)</td>
</tr>
<tr>
<td>15 letters</td>
<td>51 (27)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>≥15 letters</td>
<td>26 (14)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

Adapted from Alimera Sciences (2014) 29.
Values are n (%) or as otherwise indicated.
CI: confidence interval; FDA: U.S. Food and Drug Administration.

Massin et al (2016) reported on the results of a small prospective noncomparative study in 16 patients with diabetic macular edema insufficiently responsive to laser and antivascular endothelial growth factor who received fluocinolone acetonide 0.19-mg implants. Two groups of patients were evaluated: group 1 (n=6) included patients ineligible antivascular endothelial growth factor 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 antivascular endothelial growth factor 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 best-corrected visual acuity 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. A small number of patients and lack of a control arm limit the interpretation of these findings.

Adverse Events
As listed in the prescribing label, at the end of the 3-year follow-up, 82% (192/235) of phakic eyes with implants underwent cataract surgery compared with 50% (61/121) receiving the sham control.29 Among these patients, 80% of implant patients versus 27% of sham-controlled had cataract surgery, generally within the first 18 months of the trials. The proportion of patients with intraocular pressure elevation of 10 mm Hg or more from baseline was 3 times higher in the implant group (34%) versus the sham group (10%). Respective proportions of patients with intraocular pressure of 30 mm Hg or more were 20% and 4%, respectively. As a consequence, a higher proportion of patients in the implant group required surgery for glaucoma (5% vs. 1%).

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.19 mg) for Diabetic Macular Edema
Two RCTs have established the efficacy of fluocinolone acetonide implants (0.19 mg) for patients with diabetic macular edema. Both trials demonstrated the
superiority of implants over sham controls. Implant-treated eyes showed clinically meaningful improvements in the vision at 2 and 3 years postimplant. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic than those who were phakic. The major limitation of these implants is that nearly 80% of all phakic patients will develop cataracts and will require cataract surgery. Further, intraocular pressure 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 intraocular pressure.

**Intravitreal Dexamethasone Implant (0.7 mg)**

Two double-blind, randomized trials have assessed patients with diabetic macular edema. These trials randomized patients to a 0.7-mg or a 0.35-mg implant or a sham procedure. Retreatment was allowed if it was at least 6 months since the prior treatment and there was evidence of residual edema. The primary efficacy endpoint 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, the FDA approved the 0.7-mg dose. Relevant results with the FDA-approved dosing are summarized in Table 8. Only 14% of study patients completed the month 39 visit (16.8% from the implant, 12.2% from sham). The visual acuity improvements from baseline increased during a treatment cycle, peaked at 3 months posttreatment and diminished after that (data not shown). This result was due to loss of vision related to the 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 8. Summary of 39-Month Results From the FDA Pivotal Trials in Diabetic Macular Edema

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study 1 (N=328)</th>
<th>Study 2 (N=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Implant (n=163)</td>
<td>Sham (n=165)</td>
</tr>
<tr>
<td>15 letters</td>
<td>34 (21)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>15 letters</td>
<td>15 (9)</td>
<td>17 (10)</td>
</tr>
</tbody>
</table>

Adapted from Allergan (2014). Values are n (%). CI: confidence interval; FDA: U.S. Food and Drug Administration.

Subsequent to the 2014 pivotal trials and FDA approval, several small and/or short-term trials and retrospective studies have been published that evaluate the comparative effects of intravitreal dexamethasone implant (0.7 mg) versus other treatments – primarily antivascular endothelial growth factor in various subgroups of patients with diabetic macular edema (Table 9). In general,
compared with primarily antivascular endothelial growth factor 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 9. Summary of Additional Studies of Intravitreal Dexamethasone Implant (0.7 mg) in Diabetic Macular Edema

<table>
<thead>
<tr>
<th>Author, Year, study design, sample size</th>
<th>Population</th>
<th>Comparator</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyer et al (2014), BEVOREX RCT, N=86</td>
<td>Patients with DME</td>
<td>Bevacizumab</td>
<td>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 &gt; 10 letters and more adverse events.</td>
</tr>
<tr>
<td>Sharma et al 2019, RCT, N=40</td>
<td>Centre involved DME (CiDME)</td>
<td>Bevacizumab 1.25 mg or ranibizumab 0.5 mg</td>
<td>Dexamethasone had greater improvements in 3-mo retinal thickness, but similar visual acuity</td>
</tr>
<tr>
<td>Unpublished RCT, NCT02471651, N=40</td>
<td>Persistent DME following anti-VEGF therapy</td>
<td>Continue on various anti-VEGF therapy</td>
<td>Treatments similar in 9-mo retinal thickness and visual acuity improvements</td>
</tr>
<tr>
<td>Bolukbasi et al 2019, retrospective study; N=57</td>
<td>Early treatment period of naive DME with serous retinal detachment</td>
<td>Intravitreal aflibercept 2 mg, 3 monthly injections</td>
<td>Dexamethasone had greater improvements in 3-mo retinal thickness, but similar visual acuity</td>
</tr>
<tr>
<td>Cakir et al 2019; retrospective study, N=39 eyes</td>
<td>Treatment-naive DME with concurrent epiretinal membrane</td>
<td>Ranibizumab 0.5 mg</td>
<td>Dexamethasone had greater CMT reduction at 1 mo, but lower at 2-3 mos. Similar visual acuity.</td>
</tr>
<tr>
<td>Coelho et al 2019, retrospective study; N=46 eyes</td>
<td>Persistent or recurrent DME</td>
<td>Fluocinolone acetonide implant 0.19 mg</td>
<td>Similar in 24-mo retinal thickness and visual acuity improvements</td>
</tr>
</tbody>
</table>

BCVA: best-corrected visual acuity; BEVOREX: Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema; RCT: randomized controlled trial; DME: Diabetic Macular Edema; VEGF: vascular endothelial growth factor; mg: milligrams; CMT: central macular thickness; NCT02471651: Dexamethasone Intravitreal Implant (0.7mg) for the Treatment of Persistent Diabetic Macular Edema Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy.

Section 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 diabetic macular edema. The 2 RCTs compared
2 doses of the implant with sham control. Compared with sham, both doses of the dexamethasone implant resulted in clinically meaningful improvements in visual acuity at 39 months postimplantation. The visual acuity improvement peaked at 3 months posttreatment but diminished after that, 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 and retrospective studies have found that, compared with primarily antivascular endothelial growth factor 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

Clinical Context and Test Purpose
The purpose of intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard therapy, in patients with diabetic macular edema.

The question addressed in this evidence review is: Does intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy improve the net health outcome in patients with diabetic macular edema.

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with diabetic macular edema.

Interventions
The intervention of interest is intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy.

Comparators
The comparators of interest are standard of care.

Outcomes
The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity. Follow-up over the first few weeks following surgery is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy, the evidence includes 2 small randomized controlled trials of 169 patients (N range, 40-129) (Table 10).\textsuperscript{34,39} The first RCT, published by Maturi et al (2015), was single-blinded and used bevacizumab as the antivascular endothelial growth factor treatment.\textsuperscript{39} The second RCT, published by Maturi et al (2018) was double-blinded, used ranibizumab as the antivascular endothelial growth factor treatment, and focused on a ranibizumab-resistant population with persistent diabetic macular edema despite previous treatment.\textsuperscript{34} Findings from both trials (Table 11) were consistent in demonstrating that although adding dexamethasone to an antivascular endothelial growth factor 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 (Tables 12 and 13) were their small sample size and the relatively short-term follow-up in the 2018 RCT. Based on the consistent lack of improvement in visual acuity, increased risk of intraocular pressure elevation, and imprecision, these RCTs provide insufficient evidence to determine that the technology results in a meaningful improvement in the net health outcome.

Table 10. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maturi et al (2018)</td>
<td>U.S.</td>
<td>40</td>
<td>2014-2016</td>
<td>Persistent DME, with visual acuity of 20/32 to 20/320 after at least 3 anti-VEGF injections</td>
<td>Dexamethasone 0.7 mg + continued 0.3-mg ranibizumab, N=65 eyes + Sham + continued 0.3-mg ranibizumab, N=64</td>
</tr>
<tr>
<td>Marturi et al (2015)</td>
<td>U.S.</td>
<td>1</td>
<td>NR</td>
<td>DME with a CST of 250 mm measured by time-domain optical coherence tomography</td>
<td>Bevacizumab 1.25 mg intravitreally at baseline + dexamethasone 0.7 mg implant at the 1-mo visit, N=21 + Bevacizumab 1.25 mg intravitreally at baseline and Mo 1, N=19</td>
</tr>
</tbody>
</table>

CST: central subfield thickness; DME: Diabetic Macular Edema; VEGF: Vascular Endothelial Growth Factor; mg: milligrams; NR: Not Reported; RCT: randomized controlled trial.

Table 11. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean improvement in visual acuity (SD), letters</th>
<th>Mean change in central subfield thickness (SD), μm</th>
<th>Increased intraocular pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maturi et al (2018)a</td>
<td>127</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone + continued ranibizumab</td>
<td>Sham + continued ranibizumab</td>
<td>MD (95%CI)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------------------------------</td>
<td>-----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>+2.7 (9.8)</td>
<td>+3.0 (7.1)</td>
<td>-0.5 (-3.6 to 2.5)</td>
</tr>
<tr>
<td></td>
<td>-110 (86)</td>
<td>-62 (97)</td>
<td>-52 (-82 to -22)</td>
</tr>
<tr>
<td></td>
<td>19 (29%)</td>
<td>0</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: Standard deviation; MD: mean difference; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial; NR: Not Reported.

a 24-weeks.
b 12 months.

Table 12. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maturi et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Sample size lower than needed for 90% power</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.


d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. 4. Insufficient power

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Table 13. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maturi et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. 24 wks is a relatively short follow-up</td>
</tr>
<tr>
<td>Maturi et al (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study
population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

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 antivascular endothelial growth factor treatment can lead to a greater mean reduction in central subfield thickness compared to the antivascular endothelial growth factor 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.40. 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%, p<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 lost to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis limit interpretation of results. Use of dexamethasone implants resulted in higher incidences of cataracts and elevated intraocular pressure.

Age-Related Macular Degeneration
Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy

Kuppermann et al (2015) reported on the results of industry-sponsored, single-masked, sham-controlled, randomized trial in which 243 patients with choroidal neovascularization secondary to age-related macular degeneration were allocated to dexamethasone implants (n=123) or a sham procedure (n=120). All patients received 2 protocol-mandated intravitreal ranibizumab injections with the next injection given as needed based on established study criteria. The primary efficacy endpoint 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 best-corrected visual acuity. More patients in the dexamethasone implant group had increased intraocular pressure (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 Antivascular Endothelial Growth Factor Therapy for Age-Related Macular Degeneration

One RCT has evaluated the impact of adding implants to a standard vascular endothelial growth factor inhibitor for patients with age-related macular degeneration. Results of this trial failed to demonstrate clinically meaningful reductions in the ranibizumab injection-free interval. Further, there was an intraocular pressure elevation in a 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% of patients at baseline and 0% at 3-year follow-up. More than 20% reduction in central retinal thickness was noted in all patients with cystoid macular edema at 6 months, 1 year, 2 years, and 3 years postimplant. Another retrospective cohort study (2013), which included 11 eyes with birdshot chorioretinitis, reported improved control of inflammation and decreased reliance on adjunctive therapy with fluocinolone acetonide implants.
Authors observed a more robust increase in intraocular pressure compared with the observed elevation in patients with other types of posterior uveitis and panuveitis. In another retrospective study, which included 32 eyes with birdshot chorioretinopathy who received fluocinolone acetonide implant (0.59 mg) with 12-month follow-up, Rush et al (2011) also reported a 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 best-corrected visual acuity of at least 20/25 during treatment. In the second, there was a mean improvement of 70 letters on best-corrected visual acuity using the Early Treatment Diabetic Retinopathy Study 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 the current standard of treatment. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in refractory or intolerant patients with birdshot retinopathy.

**Cystoid Macular Edema Related to Retinitis Pigmentosa**

Retinitis pigmentosa is a degenerative process of the retina primarily affecting the rod photoreceptors and retinal pigment epithelium. Many studies have shown a prevalence of cystoid macular edema in 10% to 15% of patients with retinitis pigmentosa. No large, multi-center, sham-controlled RCTs were identified on the treatment of this indication for any corticosteroids intravitreal implants. For individuals who have cystoid macular edema related to retinitis pigmentosa, the evidence includes a small (N=14), single-center, observation-controlled RCT from South Korea, a small (N=30), single-center oral acetazolamide-controlled, propensity score-matched observational study, and multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Improvements have been mixed across studies. In the 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 one 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. In the observational study, after 12 months, compared to 30 eyes in patients who were treated with oral acetazolamide 500 mg/day,
there were greater decreases in mean central retinal thickness (-327 µm vs. -180 µm; P< 0.001) and greater improvements in mean best-corrected visual acuity (+4.2 letters vs. +1.6 letters; P< 0.05) among the 30 eyes treated with intravitreal dexamethasone implant 0.7 mg. However, due to the lack of a sham-intravitreal control group in either study, it is impossible to rule out that any effects in the intravitreal dexamethasone group were due to incidental effects of the implantation procedure.

Additionally, multiple case reports describing the use of dexamethasone implants in 8 patients with macular edema as a consequence of retinitis pigmentosa have been published. All case reports have a short follow-up (<1 year), and a few lacked a complete description of benefit. Overall, these reports found mix improvements on various anatomic and functional outcomes with transient benefits to complete recovery of cystoid macular edema. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Section Summary: Cystoid Macular Edema Related to Retinitis Pigmentosa**
No sham-controlled RCTs were identified on the treatment of cystoid macular edema with any corticosteroids intravitreal implants. Available evidence includes a small RCT, a small prospective cohort study, and multiple case reports that have noted mixed results for anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. Larger multi-center, sham-controlled RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with cystoid macular edema related to retinitis pigmentosa. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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 a permanent visual loss. No RCTs were identified on the treatment of this indication with any corticosteroids intravitreal implants. Multiple case series have assessed improvements in visual acuity and anatomic changes.\textsuperscript{56,57,58,59,60,61,62} 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. Effectiveness and safety of dexamethasone implants for postsurgical macular oedema including Irvine-Glass syndrome (EPISODIC), a 2017 observational retrospective study conducted in France, included 100 patients with postsurgical macular edema who received dexamethasone implants between 2011 and 2014 and who had a minimum of 1-year follow-up.\textsuperscript{63} Mean improvement in best-corrected visual acuity was 9.6 Early Treatment Diabetic Retinopathy Study letters at month 6 and 10.3 at month 12. The proportions of eyes with gains in best-corrected visual acuity of 15 or more letters were 32.5% and 37.5% at months 6 and 12, respectively. The average reduction in central subfield macular thickness was 135.2 and 160.9 μm at months 6 and 12.

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

Circumscribed Choroidal Hemangioma
Circumscribed choroidal hemangiomas are benign vascular hamartomas without systemic associations. No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroids intravitreal implants. A single case report (2012) 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.\textsuperscript{64}

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 a 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 a case series and a 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 a retrospective chart review of 5 patients with choroidal melanoma treated with dexamethasone implants for radiation macular edema, Baillif et al (2013) reported mix improvements in visual acuity were reported. The mean improvement in Early Treatment Diabetic Retinopathy Study 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.

Ocular Inflammation and Pain Following Ophthalmic Surgery
Clinical Context and Test Purpose
The purpose of punctum dexamethasone insert (0.4 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as
standard therapy, in patients with ocular inflammation and pain following ophthalmic surgery.

The question addressed in this evidence review is: Does punctum dexamethasone insert (0.4 mg) improve the net health outcome in patients in patients with ocular inflammation and pain following ophthalmic surgery.

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with ocular inflammation and pain following ophthalmic surgery.

**Interventions**
The intervention of interest is the corticosteroid intracanalicular insert, dexamethasone implant (0.4 mg), which is placed in the punctum by a physician during ophthalmic surgery.

**Comparators**
The comparators of interest are standard of care.

**Outcomes**
The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity. Follow-up over the first few weeks following surgery is of interest for relevant outcomes.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert (0.4 mg), the best evidence includes 3 double-blind, sham-controlled trials of 926 patients (n range, 241 to 438) (Table 14). The 2 initial phase 3 pivotal trials upon which the FDA approval was based were reported together in one publication by Walters et al (2016). The subsequent larger phase 3C trial was reported by Tyson et al (2019). Coprimary endpoints were identical across all 3 trials and included evaluating the absence of anterior chamber cells at day 14 and absence of pain at day 8.
Compared with the sham insert, all 3 trials generally consistently found significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints, as well as for absence of ocular pain at 14 days, with 2 exceptions (Table 15). In the second pivotal trial, the difference between the punctum dexamethasone insert (0.4 mg) and sham did not reach statistical significance for the proportion of patients with an absence of anterior chamber cells at day 14 (absolute difference was 8.1% compared with 18.5% to 21.5%). The other exception was that, absence of pain at day 14 was not reported as a secondary outcome in the large phase 3C trial by Tyson et al (2019). Although that secondary outcome was not prespecified in the protocol, as anterior chamber cells were assessed at day 14, it seems reasonable that pain could have been assessed at that time as well. This raises a question about potential reporting bias. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. The most common types of adverse events were anterior chamber inflammation, iritis, and increased intraocular pressure. Although allocation concealment methods are unclear across the studies, they had no major methodological limitations (Tables 16 and 17). Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Table 14. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walters et al (2016); Study 1 (OTX-13-002; NCT02034019)</td>
<td>U.S.</td>
<td>16</td>
<td>Not reported</td>
<td>≥ 18 yrs of age, with a visually significant cataract and scheduled to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens</td>
<td>Punctum dexamethasone insert (0.4 mg), N=164</td>
<td>Sham, N=83</td>
<td></td>
</tr>
<tr>
<td>Walters et al (2016); Study 2 (OTX-13-003; NCT02089113)</td>
<td>U.S.</td>
<td>16</td>
<td>Not reported</td>
<td>Same as Walters et al 2016 study 1</td>
<td>Punctum dexamethasone insert (0.4 mg), N=161</td>
<td>Sham, N=80</td>
<td></td>
</tr>
<tr>
<td>Tyson et al (2019) (NCT02736175)</td>
<td>U.S.</td>
<td>21</td>
<td>Not reported</td>
<td>≥ 18 yrs of age, presence of acataract and plans to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens</td>
<td>Punctum dexamethasone insert (0.4 mg, N=216)</td>
<td>Sham, N=222</td>
<td></td>
</tr>
</tbody>
</table>

of Ocular Inflammation and Pain After Cataract Surgery; NCT02736175: A Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3C Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain After Cataract Surgery; RCT: randomized controlled trial.

### Table 15. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Absence of Ocular Pain at Day 8</th>
<th>Absence of Ocular Pain at Day 14</th>
<th>Absence of Anterior Chamber Cells at Day 14</th>
<th>Serious adverse events</th>
<th>Increased intraocular pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walters et al (2016) Study 1</td>
<td>247</td>
<td>247</td>
<td>247</td>
<td>246</td>
<td>246</td>
</tr>
<tr>
<td>Punctum dexamethasone insert (0.4 mg)</td>
<td>n NR (80.4%)</td>
<td>n NR (79.6%)</td>
<td>54 (33.1%)</td>
<td>3 (1.9%)</td>
<td>11 (6.8%)</td>
</tr>
<tr>
<td>Sham</td>
<td>n NR (43.4%)</td>
<td>n NR (39.8%)</td>
<td>12 (14.5%)</td>
<td>5 (6.0)</td>
<td>3 (3.6%)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0018</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Walters et al (2016); Study 2</td>
<td>241</td>
<td>241</td>
<td>241</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Punctum dexamethasone insert (0.4 mg)</td>
<td>n NR (77.5%)</td>
<td>n NR (76.9%)</td>
<td>63 (39.4%)</td>
<td>2 (1.2%)</td>
<td>7 (4.4%)</td>
</tr>
<tr>
<td>Sham</td>
<td>n NR (58.8%)</td>
<td>n NR (57.5%)</td>
<td>25 (31.3%)</td>
<td>3 (3.8%)</td>
<td>4 (5.0%)</td>
</tr>
<tr>
<td>P-value</td>
<td>=0.0025</td>
<td>=0.0019</td>
<td>=0.2182</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tyson et al (2019)</td>
<td>438</td>
<td>NA</td>
<td>438</td>
<td>437</td>
<td>437</td>
</tr>
<tr>
<td>Punctum dexamethasone insert (0.4 mg)</td>
<td>n NR (79.6%)</td>
<td>NR</td>
<td>n NR (52.3%)</td>
<td>3 (1.4%)</td>
<td>16 (7.4%)</td>
</tr>
<tr>
<td>Sham</td>
<td>n NR (61.3%)</td>
<td>NR</td>
<td>n NR (31.1%)</td>
<td>2 (0.9%)</td>
<td>6 (2.7%)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>NR</td>
<td>&lt;0.0001</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>


### Table 16. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intervention&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comparator&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Outcomes&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Follow-Up&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walters et al (2016) Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walters et al (2016) Study 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyson et al (2019)</td>
<td>1. 14-day absence of pain not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

Study 1 (OTX-13-002): Phase 3 Study Evaluating Safety and Efficacy of OTX-DP for Treatment of Ocular Inflammation and Pain After Cataract Surgery; Study 2 (OTX-13-003): A Prospective,

a. Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b. Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c. Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


Table 17. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyson et al (2019)</td>
<td>3. Allocation concealment unclear</td>
<td>4. Described as double-blind, but outcome assessor unspecified</td>
<td>2. Although 14-day pain was not listed as a planned outcome in the CT.gov protocol, it could have reasonably been assessed at day 14 along with chamber cells</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.


d. Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e. Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f. Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.
Section Summary: Ocular Inflammation and Pain Following Ophthalmic Surgery
For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert (0.4 mg), the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Compared with the sham insert, all 3 trials generally consistently found significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints of absence of pain at 8 days and absence of anterior chamber cells at day 14. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Intravitreal Dexamethasone 0.7 mg (Ozurdex) as Prophylaxis of Cystoid Macular Edema in Patients with Noninfectious Intermediate Uveitis or Posterior Uveitis and Cataract Undergoing Cataract Surgery

Clinical Context and Test Purpose
The purpose of intravitreal dexamethasone 0.7 mg (Ozurdex) as prophylaxis of cystoid macular edema in patients with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as systematic corticosteroids.

The question addressed in this evidence review is: Does intravitreal dexamethasone 0.7 mg (Ozurdex) as prophylaxis of cystoid macular edema improve the net health outcome in patients with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery.

Interventions
The intervention of interest is the intravitreal dexamethasone 0.7 mg (Ozurdex)

Comparators
The comparators of interest are standard of care.

Outcomes
The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity.
Study Selection Criteria
Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive of intravitreal dexamethasone 0.7 mg (Ozurdex), the best evidence includes 1 single-center, open-label RCT of 43 patients in India (Table 18). Compared with prophylaxis with systemic corticosteroids, intravitreal dexamethasone 0.7 mg led to similar rates of cystoid macular edema and change in best-corrected visual acuity and avoided need for early steroid taper due to adverse effects on blood glucose, but potentially increased risk of developing intraocular pressure (Table 19). These findings should be interpreted with caution, however, to due important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding (Tables 20 and 21). Due to these important limitations, evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Table 18. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudhalkar et al (2019)</td>
<td>India</td>
<td>1</td>
<td>2015-2016</td>
<td>≥ 18 yrs of age, previous unilateral recurrent noninfectious intermediate uveitis or posterior uveitis with CMO and cataract of sufficient degree to warrant surgery; well-controlled uveitis for at least 3 mos prior to scheduled date of cataract surgery</td>
<td>Intravitreal dexamethasone 0.7 mg, N=20 (Active Comparator) Oral corticosteroids, N=23</td>
</tr>
</tbody>
</table>

CMO: cystoid macular edema; RCT: randomized controlled trial.

Table 19. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Development of CMO at 6 mos</th>
<th>BCVA at 6 mos</th>
<th>Developed ocular hypertension</th>
<th>Required rapid taper of systemic steroids due to adverse blood glucose effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudhalkar et al (2019)</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>
Intravitreal dexamethasone 0.7 mg | 1 (5%) | 0.04 logMAR | 4 (20%) | 0
Oral corticosteroids | 2 (8%) | 0.06 logMAR | 0 | 3 (13%)
P-value | NR, but described as NSD | 0.42 | NR | NR

NR=not reported; NSD: not significantly different; CMO: cystoid macular edema; BCVA: best-corrected visual acuity; RCT: randomized controlled trial.

**Table 20. Relevance Limitations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomed</th>
<th>Follow-Upd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudhalkar et al (2018)</td>
<td>4. Study population potentially had better prognosis than intended use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 21. Study Design and Conduct Limitations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.
Section Summary: Intravitreal Dexamethasone 0.7 mg (Ozurdex) as Prophylaxis of Cystoid Macular Edema in Patients With Noninfectious Intermediate Uveitis or Posterior Uveitis and Cataract Undergoing Cataract Surgery

For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive of intravitreal dexamethasone 0.7 mg (Ozurdex), the best evidence includes 1 single-center, open-label RCT of 43 patients in India. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Compared with oral corticosteroids, intravitreal dexamethasone 0.7 mg had similar benefits and avoided need for early steroid taper due to adverse effects on blood glucose, but potentially increased risk of developing intraocular pressure. Due to important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding, evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Summary of Evidence

Uveitis

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

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

For individuals with chronic noninfectious posterior uveitis affecting the posterior segment of the eye and who receive intravitreal fluocinolone acetonide implant (0.18 mg, Yutiq), 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, Yutiq) at both 6 and 12 months. However, serious limitations of these findings include inconsistency in the magnitude of the benefit at 12 months (odds ratio 67.09; 95% confidence interval 8.81-511.06 in published RCT and odds ratio 3.04; 95% confidence interval 1.52, 6.08 in the unpublished RCT) and, with more imputed recurrences in the sham groups than the treatment groups, we also can’t 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). Due to these inconsistencies and serious methodological limitations, the evidence is insufficient to determine the effects of the technology on health outcomes.

**Macular Edema**

For individuals with macular edema after retinal vein occlusion who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with sham controls, implants resulted in clinically meaningful improvements in visual acuity within 1 to 3 months postimplant and improvement in vision occurred faster. The difference in the proportion of patients with gain of 15 or more letters in best-corrected visual acuity from baseline was more than 10% in favor implants versus sham in both studies at 30, 60 and 90 days, but not at 180 days postimplant. Use of implants resulted in higher incidences of cataracts and elevated intraocular pressure. Several additional RCTs and a meta-analysis have evaluated the comparative effects of dexamethasone intravitreal implants versus other therapies and found mixed results. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals with macular edema after retinal vein occlusion who receive an intravitreal fluocinolone acetonide implant (0.59 mg), no studies were identified. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Diabetic Macular Edema**

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

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

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 3 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with sham control, 2 identically designed RCTs showed clinically meaningful improvements in vision with dexamethasone implants that peaked at 3 months and maintained 39 months (with retreatment). The difference in the proportion of patients with a gain of 15 or more letters in best-corrected visual acuity from baseline was 9.3% and 13.0% in the 2 trials, respectively, favoring implant versus sham at 39 months.
postimplant. Subgroup analysis of these trials showed greater improvements in visual acuity in patients who were pseudophakic compared with those who were phakic. Additionally, evidence from various small and/or short-term trials and retrospective studies have found that, compared with primarily antivascular endothelial growth factor 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Findings from both RCTs were consistent in demonstrating that although adding dexamethasone to an antivascular endothelial growth factor 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. Based on the consistent lack of improvement in visual acuity, increased risk of intraocular pressure elevation, and imprecision, these RCTs provide insufficient evidence to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 1-year follow-up demonstrated that combination implants plus laser photocoagulation compared with laser photocoagulation alone resulted in better visual acuity (as measured by a gain of ≥10 letters) at 9 months but not at 12 months. However, the generally accepted standard outcome measure for change is 15 or more letters, and this standard was not used in this trial. The use of dexamethasone implants resulted in higher incidences of cataracts and elevated intraocular pressure. Further, a differential loss to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis preclude interpretation of results. A larger RCT with adequate power is needed to confirm these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Age-Related Macular Degeneration**

For individuals with age-related macular degeneration who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor inhibitor, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of this trial did not demonstrate clinically meaningful reductions in the ranibizumab injection-free interval between combined treatments (34 days) and antivascular endothelial growth factor alone (29 days; p=0.016). Further, intraocular pressure was elevated in a greater proportion of patients receiving
implants without any additional clinical benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Other Conditions**

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

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

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

For individuals with postoperative chronic macular edema who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Among the multiple observational studies, a large retrospective analysis of 100 patients showed that 2 of every 5 patients experienced clinically meaningful improvements in the vision at 1-year follow-up. An RCT is needed to confirm the efficacy of corticosteroid implants in patients with postoperative chronic macular edema. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with circumscribed choroidal hemangiomas who receive an intravitreal dexamethasone implant (0.7 mg) plus photodynamic therapy, the evidence includes a case report. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of the case report do not permit conclusions about the efficacy or safety of adding dexamethasone implants for circumscribed choroidal hemangiomas to photodynamic therapy. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert (0.4 mg), the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. All 3 trials noted significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints of absence of pain at 8 days and absence of anterior chamber cells at day 14. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive prophylaxis with intravitreal dexamethasone 0.7 mg (Ozurdex), the best evidence includes 1 single-center, open-label RCT of 43 patients in India. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Compared with oral corticosteroids, intravitreal dexamethasone 0.7 mg had similar benefits and avoided need for early steroid taper due to adverse effects on blood glucose,
but potentially increased risk of developing intraocular pressure. Due to important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding, evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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

In response to requests, input was received from 1 physician specialty society and 1 academic medical center while this policy was under review in 2011. Input supported the use of intravitreal corticosteroid implants, confined to indications labeled by the U.S. Food and Drug Administration (FDA). It was noted that Ozurdex (intravitreal dexamethasone implant 0.7 mg) is used for short-term uveitis control while the Retisert (intravitreal fluocinolone acetonide implant 0.59 mg) implant is used for more long-term control of uveitis.

Practice Guidelines and Position Statements

American Academy of Ophthalmology
In 2019, the American Academy of Ophthalmology published its preferred Practice Pattern® for retinal vein occlusions. These stated: “Macular edema may complicate both central retinal vein occlusions and branch retinal vein occlusions. The first line of treatment for associated macular edema is anti-vascular endothelial growth factors. Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation surgery in branch retinal vein occlusion has a potential role in treatment.” The pivotal Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) trials were not rated for quality.

National Institute for Health and Care Excellence
In 2019, the National Institute for Health and Care Excellence (NICE) released guidance on the use of fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien) for treating chronic diabetic macular edema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye). The NICE guidance states, “Fluocinolone acetonide intravitreal implant is not recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye).” The NICE committee reached this conclusion based on their interpretation that “results from [Fluocinolone Acetonide in Diabetic Macular Edema] FAME may not be general is able to people with chronic diabetic macular oedema in phakic
eyes with symptomatic cataract seen in the NHS” because “in FAME, very few people had symptomatic cataract at baseline” and that the type of rescue therapy used in FAME is not used in NHS clinical practice.

In 2019, the NICE released guidance on the use of fluocinolone acetonide intravitreal implant for treating recurrent non-infectious uveitis. NICE’s guidance stated, "Fluocinolone acetonide intravitreal implant is recommended, within its marketing authorisation, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye."

In 2017, the NICE released guidance on the use of dexamethasone intravitreal implant (with adalimumab) for the treatment of noninfectious uveitis. NICE recommended the implant only in cases of “active disease” with “worsening vision” and the “risk of blindness.”

In 2011, the NICE provided guidance on the use of the dexamethasone intravitreal implant for macular edema secondary to retinal vein occlusion. The dexamethasone implant was recommended as an option for the treatment of macular edema following retinal vein occlusion. NICE also recommended it as an option for treating macular edema following branch retinal vein occlusion when treatment with laser photocoagulation has not been beneficial or suitable.

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

In 2013, the NICE updated its guidance on the intravitreal fluocinolone acetonide implant (Iluvien), recommending Iluvien as an option for treating chronic diabetic macular edema that is insufficiently responsive to available therapies only if:

- “the implant is to be used in an eye with an intraocular [pseudophakic] lens and
- their diabetic macular oedema has not got better with other treatments.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 22.
<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02556424a</td>
<td>Efficacy and Tolerance Comparison Between Subconjunctival Injection of Triamcinolone and Intravitreal Implant of Dexamethasone for the Treatment of Inflammatory Macular Edema</td>
<td>142</td>
<td>Oct 2020</td>
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<tr>
<td>NCT02623426</td>
<td>Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial</td>
<td>240</td>
<td>Jan 2020</td>
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<tr>
<td>NCT01998412a</td>
<td>Iluvien Registry Safety Study (IRISS)</td>
<td>559</td>
<td>Jan 2020</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02399657a</td>
<td>Effect of Dexamethasone Implant in Hard Exudate Complicated With Diabetic Macular Edema</td>
<td>48</td>
<td>Dec 2016 (unknown)</td>
</tr>
<tr>
<td>NCT01827722a</td>
<td>Ozurdex® Versus Ranibizumab Versus Combination for Central Retinal Vein Oclusion</td>
<td>45</td>
<td>Dec 2016 (unknown)</td>
</tr>
<tr>
<td>NCT02684084a</td>
<td>Combination OZURDEX® &amp; LUCENTIS® vs. OZURDEX® Monotherapy in Incomplete-Responders With Diabetic Macular Edema</td>
<td>60</td>
<td>Dec 2016 (unknown)</td>
</tr>
<tr>
<td>NCT02902744</td>
<td>Fluocinolone Acetonide Insert (ILUVIEN®) for Diabetic Macular Edema (FAD) Study</td>
<td>0</td>
<td>Aug 2017 (withdrawn)</td>
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<tr>
<td>NCT02471651a</td>
<td>Dexamethasone Intravitreal Implant for the Treatment of Persistent Diabetic Macular Edema</td>
<td>40</td>
<td>Oct 2018 (has results, but no peer-reviewed publication)</td>
</tr>
<tr>
<td>NCT02731911a</td>
<td>Study of OZURDEX® in the Treatment of Diabetic Macular Edema (DME) in Australia - The AUSSIEDEX Study</td>
<td>202</td>
<td>Oct 2018 (completed)</td>
</tr>
<tr>
<td>NCT02951975</td>
<td>Ozurdex® in Patients With Non-infectious Uveitis Affecting the Posterior Segment of the Eye</td>
<td>400</td>
<td>Oct 2018 (terminated, business decision)</td>
</tr>
<tr>
<td>NCT03003416</td>
<td>Efficacy of Ozurdex® in the Treatment of Diabetic Macular Edema</td>
<td>260</td>
<td>Dec 2018 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

REFERENCES


42. Bajwa A, Aziz K, Foster CS. Safety and efficacy of fluocinolone acetonide intravitreal implant (0.59 mg) in birdshot retinochoroidopathy. Retina. Nov 2014;34(11):2259-2268. PMID 24999722


64. Bazin L, Gambrelle J. [Combined treatment with photodynamic therapy and intravitreal dexamethasone implant (Ozurdex(R)) for circumscribed choroidal hemangioma] [French]. J Fr Ophtalmol. Dec 2012;35(10):798-802. PMID 23040445


Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>67027</td>
<td>Implantation of intravitreal drug delivery system (eg, ganciclovir implant), includes concomitant removal of vitreous</td>
</tr>
<tr>
<td>67028</td>
<td>Intravitreal injection of a pharmacologic agent (separate procedure)</td>
</tr>
<tr>
<td>J7311</td>
<td>Fluocinolone acetonide, intravitreal implant</td>
</tr>
<tr>
<td>J7312</td>
<td>Injection, dexamethasone, intravitreal implant, 0.1 mg</td>
</tr>
<tr>
<td>J7313</td>
<td>Injection, fluocinolone acetonide, intravitreal implant, 0.01 mg</td>
</tr>
<tr>
<td>J7314</td>
<td>Injection, fluocinolone acetonide, intravitreal implant (Yutiq), 0.01 mg</td>
</tr>
</tbody>
</table>

ICD-10 Codes:

- E10.311  Type 1 diabetes mellitus with unspecified diabetic retinopathy with Macular edema
- E10.321  Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
- E10.3211 Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
- E10.3212 Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
- E10.3213 Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
- E10.331  Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
- E10.3311 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
- E10.3312 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
- E10.3313 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
- E10.341  Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
- E10.3411 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
- E10.3412 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E10.3413 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E10.351 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.3511 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E10.3512 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E10.3513 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E11.311 Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.321 Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3211 Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E11.3212 Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E11.3213 Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E11.331 Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3311 Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E11.3312 Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E11.3313 Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E11.341 Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3411 Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E11.3412 Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E11.3413 Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E11.351 Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E11.3511 Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E11.3512 Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E11.3513 Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
H34.9 Unspecified retinal vascular occlusion
H34.811 Central retinal vein occlusion, right eye
H34.8110 Central retinal vein occlusion, right eye, with macular edema
H34.812 Central retinal vein occlusion, left eye
H34.8120  Central retinal vein occlusion, left eye, with macular edema
H34.813  Central retinal vein occlusion, bilateral
H34.8130  Central retinal vein occlusion, bilateral, with macular edema
H34.819  Central retinal vein occlusion, unspecified eye
H34.831  Tributary (branch) retinal vein occlusion, right eye
H34.8310  Tributary (branch) retinal vein occlusion, right eye, with macular edema
H34.832  Tributary (branch) retinal vein occlusion, left eye
H34.8320  Tributary (branch) retinal vein occlusion, left eye, with macular edema
H34.833  Tributary (branch) retinal vein occlusion, bilateral
H34.839  Tributary (branch) retinal vein occlusion, unspecified eye
H34.821  Venous engorgement, right eye
H34.822  Venous engorgement, left eye
H34.823  Venous engorgement, bilateral
H34.829  Venous engorgement, unspecified eye
H34.8330  Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H35.81  Retinal edema
H30.001  Unspecified focal chorioretinal inflammation, right eye
H30.002  Unspecified focal chorioretinal inflammation, left eye
H30.003  Unspecified focal chorioretinal inflammation, bilateral
H30.009  Unspecified focal chorioretinal inflammation, unspecified eye
H30.011  Focal chorioretinal inflammation, juxtapapillary, right eye
H30.012  Focal chorioretinal inflammation, juxtapapillary, left eye
H30.013  Focal chorioretinal inflammation, juxtapapillary, bilateral
H30.019  Focal chorioretinal inflammation, juxtapapillary, unspecified eye
H30.021  Focal chorioretinal inflammation of posterior pole, right eye
H30.022  Focal chorioretinal inflammation of posterior pole, left eye
H30.023  Focal chorioretinal inflammation of posterior pole, bilateral
H30.029  Focal chorioretinal inflammation of posterior pole, unspecified eye
H30.031  Focal chorioretinal inflammation, peripheral, right eye
H30.032  Focal chorioretinal inflammation, peripheral, left eye
H30.033  Focal chorioretinal inflammation, peripheral, bilateral
H30.039  Focal chorioretinal inflammation, peripheral, unspecified eye
H30.041  Focal chorioretinal inflammation, macular or paramacular, right eye
H30.042  Focal chorioretinal inflammation, macular or paramacular, left eye
H30.043  Focal chorioretinal inflammation, macular or paramacular, bilateral
H30.049  Focal chorioretinal inflammation, macular or paramacular, unspecified eye
H30.101  Unspecified disseminated chorioretinal inflammation, right eye
H30.102  Unspecified disseminated chorioretinal inflammation, left eye
H30.103  Unspecified disseminated chorioretinal inflammation, bilateral
H30.109  Unspecified disseminated chorioretinal inflammation, unspecified eye
H30.111  Disseminated chorioretinal inflammation of posterior pole, right eye
H30.112  Disseminated chorioretinal inflammation of posterior pole, left eye
H30.113  Disseminated chorioretinal inflammation of posterior pole, bilateral
H30.119  Disseminated chorioretinal inflammation of posterior pole, unspecified eye
H30.121  Disseminated chorioretinal inflammation, peripheral right eye

Intravitreal and Punctum Corticosteroid Implants 9.03.23
H30.122 Disseminated chorioretinal inflammation, peripheral, left eye
H30.123 Disseminated chorioretinal inflammation, peripheral, bilateral
H30.129 Disseminated chorioretinal inflammation, peripheral, unspecified eye
H30.131 Disseminated chorioretinal inflammation, generalized, right eye
H30.132 Disseminated chorioretinal inflammation, generalized, left eye
H30.133 Disseminated chorioretinal inflammation, generalized, bilateral
H30.139 Disseminated chorioretinal inflammation, generalized, unspecified eye
H30.141 Acute posterior multifocal placoid pigment epitheliopathy, right eye
H30.142 Acute posterior multifocal placoid pigment epitheliopathy, left eye
H30.143 Acute posterior multifocal placoid pigment epitheliopathy, bilateral
H30.149 Acute posterior multifocal placoid pigment epitheliopathy, unspecified eye
H30.891 Other chorioretinal inflammations, right eye
H30.892 Other chorioretinal inflammations, left eye
H30.893 Other chorioretinal inflammations, bilateral
H30.899 Other chorioretinal inflammations, unspecified eye
H30.90 Unspecified chorioretinal inflammation, unspecified eye
H30.91 Unspecified chorioretinal inflammation, right eye
H30.92 Unspecified chorioretinal inflammation, left eye
H30.93 Unspecified chorioretinal inflammation, bilateral
H30.20 Posterior cyclitis, unspecified eye
H30.21 Posterior cyclitis, right eye
H30.22 Posterior cyclitis, left eye
H30.23 Posterior cyclitis, bilateral
H30.811 Harada’s disease, right eye
H30.812 Harada’s disease, left eye
H30.813 Harada’s disease, bilateral
H30.819 Harada’s disease, unspecified eye

**Additional Policy Key Words**
N/A

**Policy Implementation/Update Information**
7/1/2015 New Policy; considered medically necessary when criteria is met.
4/1/2016 No policy statement changes.
4/1/2017 No policy statement changes.
5/1/2017 The Policy section was revised to include dosage information. Additional indications were added to the investigational policy statements as investigational. The intent of the policy was not changed.
4/1/18 No policy statement changes.
4/1/19 No policy statement changes.
4/1/20 No policy statement changes.
6/1/20 Added three new PICOs Added new policy statements for all 3 new indications – medically necessary for Dextenza for individuals with ocular inflammation and pain following ophthalmic surgery; investigational for Yutiq for treatment of chronic noninfectious posterior
uveitis affecting the posterior segment of the eye, and investigational for prophylactic Ozurdex for individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery. Policy title changed.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.