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Intravitreal, Punctum, and Intracameral Implants

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Intravitreal and Punctum Corticosteroid Implants

An intravitreal and punctum corticosteroid implant used according to the United States Food and Drug Administration approved indications **may be considered medically necessary** when used:

- As an alternative in patients who are intolerant or refractory to other therapies; OR
- In patients who are likely to experience severe adverse events from systemic corticosteroids.

Fluocinolone Acetonide Intravitreal Implant (e.g., Retisert®, Iluvein®, Yutiq®)

A. Retisert®

A fluocinolone acetonide intravitreal implant 0.59 mg (e.g., Retisert®) **may be considered medically necessary** in patients 12 years of age or older for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

A fluocinolone acetonide intravitreal implant 0.59 mg (e.g., Retisert®) **is considered not medically necessary** for patients with active viral, bacterial, mycobacterial or fungal infections of ocular structures.

B. Iluvein®

A fluocinolone acetonide intravitreal implant 0.19 mg (e.g., Iluvien®) **may be considered medically necessary** for the treatment of diabetic macular edema (DME) in adult patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (IOP) (or had the rise in IOP adequately treated prior to placement of the implant).

A fluocinolone acetonide intravitreal implant 0.19 mg (e.g., Iluvein®) **is considered not medically necessary** for patients with the following contraindications:

- Active ocular or periocular infections; OR
- Glaucoma with a cup to disc ratio of greater than 0.8.

C. Yutiq®

A fluocinolone acetonide intravitreal implant 0.18 mg (e.g., Yutiq®) **may be considered medically necessary** in adult patients for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

A fluocinolone acetonide intravitreal implant 0.18 mg (e.g., Yutiq®) **is considered not medically necessary** for members with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

D. Other Uses of Fluocinolone Acetonide Intravitreal Implant (e.g., Retisert®, Iluvein®, Yutiq®)

All other uses of a fluocinolone acetonide intravitreal implant (e.g., Retisert®, Iluvein®, Yutiq®) **are considered experimental, investigational and/or unproven** including but not limited to the following conditions:

- Birdshot retinochoroidopathy;
- Cystoid macular edema related to retinitis pigmentosa;
- Idiopathic macular telangiectasia type 1;
- Postoperative macular edema;
- Circumscribed choroidal hemangiomas;
- Proliferative vitreoretinopathy;

- Radiation retinopathy;
- Prophylaxis of cystoid macular edema in patients with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery.

Dexamethasone Punctum and Intravitreal Implants (e.g., Ozurdex™, Dextenza®)

A. Ozurdex™

A dexamethasone intravitreal implant 0.7 mg (e.g., Ozurdex™) **may be considered medically necessary** in adult patients 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 (DME).

A dexamethasone intravitreal implant 0.7 mg (e.g., Ozurdex™) **is considered not medically necessary** for patients with the following contraindications:

- Ocular or periocular infections (viral, bacterial, or fungal); OR
- Advanced glaucoma with a cup to disc ratio of greater than 0.8; OR
- Torn or ruptured posterior lens capsule.

Dexamethasone intravitreal implant 0.7 mg (e.g., Ozurdex™) **is considered experimental, investigational and/or unproven** including but not limited to the following conditions:

- Birdshot retinochoroidopathy;
- Cystoid macular edema related to retinitis pigmentosa;
- Idiopathic macular telangiectasia type 1;
- Postoperative macular edema;
- Circumscribed choroidal hemangiomas;
- Proliferative vitreoretinopathy;
- Radiation retinopathy.
- Prophylaxis of cystoid macular edema in patients with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery.

A dexamethasone intravitreal implant 0.7 mg (e.g., Ozurdex™) combined with cataract surgery **is considered experimental, investigational, and/or unproven** for the treatment of cataract and macular edema.

B. Dextenza®

A punctum dexamethasone ophthalmic insert for intracanicular use 0.4 mg (e.g., Dextenza®) **may be considered medically necessary** in adult patients for the treatment of:

- Ocular inflammation and pain following ophthalmic surgery; OR
- Ocular itching associated with allergic conjunctivitis.

A punctum dexamethasone ophthalmic insert for intracanicular use 0.4 mg (e.g., Dextenza®) **is considered not medically necessary** for patients with the following contraindication:

- Active corneal, conjunctival or canalicular infections.

All other uses of a punctum dexamethasone ophthalmic insert 0.4 mg (e.g., Dextenza®) **are considered experimental, investigational and/or unproven**.

Intracameral Bimatoprost Implant
A bimatoprost implant for intracameral administration (e.g., Durysta®) **may be considered medically necessary** in adult patients with open angle glaucoma (OAG) or ocular hypertension (OHT) when:

- Patient has had a trial and failure or intolerance to at least two intraocular pressure-lowering eye-drop agents with different mechanisms of action, and one of which must include a prostaglandin analog (e.g., bimatoprost, latanoprost, travoprost, or tafluprost); AND
- The affected eye has not received prior treatment with an intracameral bimatoprost implant.

All other uses of a bimatoprost implant for intracameral administration (e.g., Durysta®) **are considered experimental, investigational and/or unproven**.

Intracameral Travoprost Implant
A travoprost implant for intracameral administration (e.g., iDose® TR) **may be considered medically necessary** in adult patients with open angle glaucoma (OAG) or ocular hypertension (OHT) when:

- Patient has had a trial and failure or intolerance to at least two intraocular pressure-lowering eye-drop agents with different mechanisms of action, and one of which must include a prostaglandin analog (e.g., bimatoprost, latanoprost, travoprost, or tafluprost); AND
- The affected eye has not received prior treatment with an intracameral travoprost implant.

All other uses of a travoprost implant for intracameral administration (e.g., iDose® TR) **are considered experimental, investigational and/or unproven**.

Policy Guidelines

None.

Description

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. Fluocinolone acetonide implants are non-erodible and deliver drug up to 30 to 36 months while dexamethasone implants are bio-erodible 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 (e.g., Dextenza®) is the first corticosteroid intracanalicular insert.

An intracameral implant is a drug delivery device that allows for sustained delivery of a substance directly into the anterior chamber of the eye. (1)

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 (U.S.), the primary site of inflammation is the choroid or retina (or both). Patients with intermediate or posterior uveitis typically experience minimal pain, decreased visual acuity, and the presence of floaters (bits of vitreous debris or cells that cast shadows on the retina). Chronic inflammation associated with posterior segment uveitis can lead to cataracts, 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 (e.g., antimetabolites, alkylating agents, T-cell inhibitors, tumor necrosis factor inhibitors) may also be used to control severe uveitis. Immunosuppressive therapy is typically reserved for patients who require chronic high dose systemic steroids to control their disease. While effective, immunosuppressants may have serious and potentially life threatening adverse effects, including renal and hepatic failure and bone marrow suppression.

Macular Edema After Retinal Vein Occlusion

Retinal vein occlusions are classified by whether the central retinal vein or one of its branches is obstructed. Central retinal vein occlusion 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, 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 (DME) 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. DME is characterized by swelling of the macula due to gradual leakage of fluids from blood vessels and breakdown of the blood-retinal barrier. Moderate vision loss can arise from the fluid accumulating in the center of the macula (macular edema) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main blinding complication of diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

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 DME. Angiostatic agents such as injectable vascular endothelial growth factor inhibitors, which block stages in the pathway leading to new blood vessel formation (angiogenesis), have demonstrated efficacy in DME.

Age-Related Macular Degeneration

Age related macular degeneration 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.

Glaucoma
Glaucoma is a disease that damages the eye's optic nerve due to a build-up of fluid in the anterior portion of the eye which increases the pressure in the eye. The most common type of glaucoma is primary open-angle glaucoma. This type of glaucoma is painless and causes no vision changes in the early stages. As the disease progresses, blind spots develop in the peripheral vision. (2)

Treatment
While damage from glaucoma is permanent and cannot be reversed, medicine and surgery can help to stop further damage. Glaucoma is most commonly treated with eye drops that work to lower eye pressure. As an alternative to daily eye drops which can be challenging for many patients and lead to poor compliance, recently there has been an increased interest in biodegradable, intracameral implants that allow for 24/7 medication delivery over several months. (2)

Intravitreal and Punctum Corticosteroid Implants
An intravitreal and/or punctum implant used according to U.S. Food and Drug Administration (FDA) 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 potential adverse events, patients should be informed about the potential adverse events of a corticosteroid intravitreal implant (including cataracts), increased intraocular pressure (IOP), or hypotony, endophthalmitis, and risk 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 among treatments.

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 (e.g., hourly) administration and may not adequately penetrate the posterior segment of the eye due to their poor ability to penetrate ocular tissues. Systemically administered drugs penetrate poorly into the eye because of the blood-retinal barrier, and high-dose or long-term treatments may be necessary. Long-term systemic therapies can be associated with substantial adverse events such as hypertension and osteoporosis, while repeated (every 46 weeks) intraocular corticosteroid injections may result in pain, intraocular infection, globe perforation, fibrosis of the extraocular muscles, reactions to the delivery vehicle, increased IOP, and cataract development.

Corticosteroid implants 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.
- Iluvein® (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. (3, 4)
- 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® (nonbiodegradable 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.

Intracameral Bimatoprost Implant

Durysta® is an ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant. The implant is a solid polymer matrix containing 10 mcg of bimatoprost and is approximately 1 mm in length. It is preloaded into a single-use applicator that is used to inject the implant directly into the anterior chamber of the eye. Following administration, the implant is intended to settle within the inferior angle to deliver a sustained release of bimatoprost for several months. Bimatoprost is believed to lower IOP by increasing the outflow of aqueous humor through both the trabecular meshwork and the uveoscleral routes. Placement of the implant within the anterior chamber angle allows for close proximity to the tissues involved in both of these outflow pathways. (5)

Intracameral Travoprost Implant

iDose® TR is a travoprost delivery system consisting of an intracameral implant containing 75 mcg of travoprost that is pre-loaded in a single-dose inserter that is administered through a small, clear corneal incision and is anchored into the sclera at the iridocorneal angle. (100) Although the exact mechanism of action is unknown, travoprost is believed to reduce IOP by increasing uveoscleral outflow.

Regulatory Status

In 2009, Ozurdex® (dexamethasone 0.7 mg intravitreal implant; Allergan) was approved by the U.S. 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 DME. Per the FDA label, Ozurdex™ is contraindicated in patients with ocular or periocular infections (viral, bacterial, or fungal), advanced glaucoma with a cup to disc ratio of greater than 0.8 and in patients with a torn or ruptured posterior lens capsule. (6)

In September 2014, Iluvien® (fluocinolone acetonide 0.19 mg intravitreal implant; Alimera Sciences) was approved by the FDA for the treatment of DME in patients previously treated with a course of corticosteroids and without a clinically significant rise in IOP. Per the FDA label, Iluvein is contraindicated in patients with active ocular and periocular infections or in patients diagnosed with glaucoma with a cup to disc ratio of greater than 0.8. (7)

In November 2004, 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. Per the FDA label, Retisert® is contraindicated in patients with active viral, bacterial, mycobacterial and fungal infections of ocular structures. Additionally, the safety and effectiveness of Retisert has not been established for use in pediatric patients below 12 years of age. (8)

In October 2018, Yutiq® (fluocinolone acetonide 0.18 mg intravitreal implant; EyePoint Pharmaceuticals, Inc.) was approved by the FDA for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. Per the FDA label, Yutiq is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. In addition, the safety and effectiveness of Yutiq has not been established in pediatric patients. (9)

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. In October 2021, the indication was expanded to include treatment of ocular itching associated with allergic conjunctivitis. Per the FDA label, Dextenza is contraindicated in patients with active corneal, conjunctival or canalicular infections. (10)

In March 2020, Durysta® (bimatoprost implant, for intracameral administration; Allergan) was approved by the FDA for the reduction of IOP in patients with open angle glaucoma or ocular hypertension. Per the FDA label, Durysta is contraindicated in patients with ocular or periocular infections, corneal endothelial cell dystrophy, prior corneal transplantation, absent or ruptured posterior lens capsule, and hypersensitivity. Additionally, Durysta should not be re-administered to an eye that received a prior Durysta implant. (1)

In December 2023, IDose® TR (travoprost intracameral implant; Glaukos) was approved by the FDA for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Per the FDA label, IDose® TR is contraindicated in patients with ocular or periocular infections, corneal endothelial cell dystrophy, prior corneal transplantation, and hypersensitivity. iDose® TR should not be readministered to an eye that received a prior iDose® TR. (100)

Rationale

This medical policy was created in June 2011 and has been updated regularly with searches of the PubMed. The most recent literature update was performed through August 2022.

Medical policies 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.

INTRAVITREAL AND PUNCTUM CORTICOSTEROID IMPLANTS

Noninfectious Uveitis

Intravitreal Fluocinolone Acetonide Implant (0.59 mg) (e.g., Retisert™)

Clinical Context and Therapy Purpose

The purpose of intravitreal fluocinolone acetonide implant (0.59 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 chronic noninfectious intermediate or posterior uveitis.

The question addressed in this medical policy is: Does intravitreal fluocinolone acetonide implant (0.59 mg) improve the net health outcome in patients with chronic noninfectious intermediate or posterior uveitis?

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

Populations:
The relevant population of interest is individuals with chronic noninfectious intermediate or posterior uveitis.

Interventions:
The intervention of interest is the intravitreal fluocinolone acetonide implant (0.59 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.

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 post implantation compared with the rates of recurrence in the 34-week period preimplantation. Data from 224 patients were included. (8) Subsequently, the FDA reported recurrence rates 1, 2, and 3 years post implantation. Results are summarized in Table 1.

Table 1. Summary of Results From the FDA Pivotal Trial in Noninfectious Posterior Uveitis (8)

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

Table Key*:* FDA: U.S. Food and Drug Administration.

[a] Recurrence of uveitis for all post implantation time points was compared with the 34-week preimplantation time point.

[b] $p<0.01$

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

Jaffe et al. (2006) reported on the results of one of the pivotal trials. (11) 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 (IOP) and cataracts were observed in the implanted eyes compared with nonimplanted eyes. The second trial was reported only in the FDA documents (12), 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). (13) 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). (14) 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 (BCVA) using the Early Treatment Diabetic Retinopathy Study chart was blinded. After 24 (15), and 54 months (16), of follow-up, the vision improvements from baseline in the implant groups compared with systematic 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). (15, 17) 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. (14) 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) (13) and Kempen et al. (2011) (15) 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 metanalysis of common side effects, which showed increased risks of needing cataract surgery (RR=2.98; 95% CI, 2.33 to 3.79; 371 eyes) and surgery to lower IOP (RR=7.48; 95% CI, 3.94 to 14.19; 599 eyes) in the implant group compared with the standard therapy group through 2 years of follow-up. Reviewers were unable to conclude that the implants were superior to traditional systemic therapy for the treatment of noninfectious uveitis.

Adverse Events

As listed in the prescribing label, nearly all phakic patients who receive implants are expected to develop cataracts and require cataract surgery. (8) Further, 75% of patients may experience elevated IOP and/or glaucoma severe enough to require IOP lowering medications and 35% filtering surgeries. Separation of implant components is another potential complication, and 6-year cumulative risk of a spontaneous dissociation is 4.8% (95% CI, 2.4% to 9.1%). (18) 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 IOP lowering medications and 35% requiring filtering surgeries.

Intravitreal Dexamethasone Implants 0.7 mg (e.g., Ozurdex™)

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies or observation alone in patients with noninfectious intermediate or posterior uveitis.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in patients with noninfectious intermediate or posterior uveitis?

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

Populations:
The relevant population of interest is individuals with noninfectious intermediate or posterior uveitis.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 mg).

Comparators:
The comparators of interest are observation alone.

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.

Randomized Controlled Trials
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 Noninfectious Intermediate or Posterior Uveitis). (19) 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 BCVA from baseline, was achieved by 40% of patients who received implants compared with 10% who received sham control. The incidences of elevated IOP (≥25 mm Hg) and cataracts in phakic eyes were higher in 0.7 mg implant treated eyes versus sham control eyes (7.1% vs. 4.2% and 15% vs. 7%, respectively). Unlike the fluocinolone acetonide 0.59 mg implant, the long-term efficacy and safety data for the dexamethasone 0.7 mg implant 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. (20) 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. (21) 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 IOP, and conjunctival hemorrhage. (6)

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 IOP.

Intravitreal Fluocinolone Acetonide Implant 0.18 mg (e.g., Yutiq)

Clinical Context and Therapy 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 medical policy 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 policy.

Populations:
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.

Randomized Controlled Trials
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, multinational, multicenter, randomized, masked, controlled, safety and efficacy study of a fluocinolone acetonide intravitreal insert in subjects with chronic noninfectious uveitis affecting the posterior segment of the eye (study #PSV-FAI-001) and a multicenter, controlled, safety and efficacy study of a fluocinolone acetonide intravitreal (FAI) insert in subjects with chronic noninfectious uveitis affecting the posterior segment of the eye (study #PSV-FAI-005) (Table 2). (9, 22) Results of one of the pivotal trials (study #PSV-FAI-001) were reported by Jaffe et al. (2019). (22) The second trial was reported only in the FDA documents. (9) 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.

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 smaller in the unpublished trial. Similarly, at 12 months, both trials found significantly lower recurrence rates in the fluocinolone groups, but the odds ratio had more than doubled in the published trial and decreased in the

unpublished trial. Results were inconsistent between trials for the remainder of the key outcomes, appearing more favorable in the published trial. Most notable were the differences between trials in mean change in BCVA at 12 months (higher in the published trial, lower in the unpublished trials) and risk of increased IOP 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 the occurrence of uveitis-related symptoms, it is unclear whether such symptoms would meet the rigorous threshold for a clinical diagnosis of recurrence (e.g., a 2-step or more increase in the number of cells in the anterior chamber per high-powered field [1.6 using a 1-mm]; a 2-step or more increase in vitreous haze; or a deterioration in visual acuity of 15 letters or more of best-corrected visual acuity). Therefore, 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." (22) Therefore, because of the inconsistency in key findings between the pivotal studies and the questions raised by the use of the imputed recurrence rates, the evidence is not sufficient to draw strong conclusions on the effect on health outcomes.

In 2020, the 3-year results from the pivotal study PSV-FAI-001 study were published (Table 3). (23) Over 36 months of treatment, cumulative uveitis recurrences were significantly reduced with fluocinolone acetonide (0.18 mg) compared with sham (65.5% vs 97.6%, respectively). The time to the first recurrence in the fluocinolone acetonide (0.18 mg) group was significantly longer compared to sham-treatment (median 657 days; 95% CI, 395 to 105 vs median 70.5

days; 95% CI, 57 to 91). The number of recurrences per eye occurring over 36 months was significantly lower in the treatment group compared to sham and a higher proportion of eyes in the fluocinolone acetonide (0.18 mg) group had no uveitis recurrence compared to sham (34.5% vs 2.4%). Additionally, a greater proportion of eyes in the treatment group compared to sham had uveitis recur only once in 3 years (33.3% vs 11.9%, respectively). Of note, the 36-month results included imputed recurrences, as in the initial results. However, observed protocol-defined uveitis recurrences occurred in a greater percentage of the sham-treated eyes, whereas the percentage of eyes with an imputed recurrence was more similar in the 2 groups (59.8% and 69.0%, respectively). At 36 months, more eyes in the treatment group had a 15-letter or greater increase in best-corrected visual acuity from baseline compared to the sham-treated group (33.3% vs 14.7%). There was also a significantly greater mean change in best-corrected visual acuity over 36 months in the treatment group compared to sham.

IOP was well-controlled in both groups and similar for both groups at month 36. The proportion of eyes in the fluocinolone acetonide (0.18 mg) group that underwent IOP lowering surgery was approximately half that in the sham-treated group. Cataract surgery was required more frequently over 36 months in the treatment group compared with the sham-treated group.

Table 2. Summary of Key RCT Characteristics

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	*Comparator*
Jaffe et al. (2019); Study PSV-FAI-001; NCT01694186 (22)	U.S., Europe, Israel, and India	33	2013-2015	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	Fluocinolone acetonide (0.18 mg), N=87	Sham, N=42
PSV-FAI-005 (9)	India	33	Unknown	Same as Jaffe et al. 2019	Fluocinolone acetonide (0.18 mg), N=101	Sham, N=52

Table Key*:* NCT: National Clinical Trial; U.S.: United States; y: year; mg: milligram; ≥: greater than 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.

Table 3. Summary of Key RCT Results

Study	6-mo Recurrence	12-mo Recurrence	Mean change in BCVA at 12 mo	Increased IOP within 12 mo[2]	Cataract within 12 mo
Jaffe et al. (2019) (22, 9)	129	129	124	129	129
Fluocinolone acetonide (0.18 mg)	24 (27.6%)[1]	33 (37.9%)	+5.8	23 (26.4%)	24 (27.6%)
Sham	38 (90.5%)[1]	41 (97.6%)	+3.3	11 (26.2%)	2 (4.8%)
OR (95% CI)	24.94 (8.04-77.39)	67.09 (8.81-511.06)	NR	NR	NR
PSV-FAI-005 (9)	153	153	142	153	153
Fluocinolone acetonide (0.18 mg)	22 (22%)[1]	33 (33%)[2]	+3.0	29 (28.7%)	12 (11.9%)
Sham	28 (54%)[1]	31 (60%)[2]	+7.4	1 (1.9%)	7 (13.5%)
OR	4.2 (2.0-8.6)	3.04 (1.52, 6.08)	NR	NR	NR
	36-mo Recurrence	**Mean number of recurrences per eye at 36-mo (SD)**	**Mean change in BCVA at 36 mo (SD**	**Increased IOP within 36 mo**	**Cataract surgery over 36 mo**
Jaffe et al. (2020) 3-year results (23)	129	129	129	129	129
Fluocinolone acetonide (0.18 mg)	57 (65.5%)[1]	1.7 (2.4)	+9.1 (13)	14.5 (16.6%)	73.8%
Sham	41 (97.6%)[1]	5.3 (3.8)	+2.5 (14.2)	14.8 (35.2%)	23.8%
OR (95% CI)	21.58 (2.83 to 164.7)	NR	NR	NR	NR
p-value	<.001	<.001	<.020	NR	NR

Table Key*:* BCVA: best-corrected visual acuity; CI: confidence interval; IOP: intraocular pressure; OR: odds ratio; mo: months; 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; SD: standard deviation; RCT: randomized controlled trial.

[1] Primarily imputed, not observed recurrence.

[2] From the FDA statistical review.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Jaffe et al. (2019); Study PSV-FAI-001; NCT01694186 (22)				1. Imputed recurrence: 16% for active, 57% for sham		
PSV-FAI-005 (9)	5. Inadequately described in FDA review materials			1. Imputed recurrence: 12% for active, 39% for sham		
Jaffe et al. (2020) 3-year results (23)				1. Imputed recurrence: 59.8% for active, 69% for sham		

Table Key: The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
FDA: U.S. Food and Drug Administration. NCT: National Clinical Trial; 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] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias. 5. Inadequate description of methods
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Jaffe et al. (2019); Study PSV-FAI-001; NCT01694186 (22)	4. Study participants did not have severe active inflammation at the time of the initial study treatment				
PSV-FAI-005 (9)	4. Study participants did not have severe active inflammation at the time of the initial study treatment				
Jaffe et al. (2020) 3-year results (23)					

Table Key: The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
NCT: National Clinical Trial; 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 significance
[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.

The 3-year follow-up for Jaffe et al. also found statistically significant lower uveitis recurrence rates at 36 months. However, serious limitations of these findings include inconsistency in the magnitude of the benefit at 12 months (odds ratio [OR]=67.09; 95% CI, 8.81 to 511.06 in published RCT and OR 3.04; 95% CI, 1.52 to 6.08 in the unpublished RCT) and with more imputed recurrences in the sham groups than the treatment groups, we also cannot rule out an overestimation of the treatment effect. For the remainder of key outcomes, results were inconsistent between RCTs, appearing more favorable in the published trial. Most notable were the differences between RCTs in mean change in BCVA at 12 months (higher for fluocinolone acetonide in the published trial, lower in the unpublished trials) and risk of increased IOP within 12 months (increased risk in the unpublished trial, but not in the published trial).

Macular Edema After Retinal Vein Occlusion

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) or intravitreal fluocinolone acetonide implant (0.59 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies or observation alone in patients with macular edema after retinal vein occlusion.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) or intravitreal fluocinolone acetonide implant (0.59 mg) improve the net health outcome in patients with macular edema after retinal vein occlusion?

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

Populations

The relevant population of interest is individuals with macular edema after retinal vein occlusion.

Interventions

The intervention of interest is the intravitreal dexamethasone implant (0.7 mg) or intravitreal fluocinolone acetonide implant (0.59 mg).

Comparators

The comparators of interest are observation alone.

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.

Intravitreal Dexamethasone Implant (e.g., Ozurdex™ 0.7 mg)
Systematic Reviews
In 2015, the American Academy of Ophthalmology (AAO) published a technology assessment on therapies for macular edema associated with central retinal vein occlusion. (24) 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 IOP 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 2014. (25) Eight RCTs (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 (OHT) than patients given antivascular endothelial growth factor monotherapy (odds ratio, 13.1).

Randomized Controlled Trials

Data presented to the 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). (3, 26) A 6-month open label extension of these 2 pivotal trials was reported in 2011. (4, 6) 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 BCVA. 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 BCVA 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 BCVA 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

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

Table Key*:* BCVA: best corrected visual acuity; FDA: U.S. Food and Drug Administration.

Additional Studies

Several additional RCTs have evaluated the comparative effects of dexamethasone intravitreal implants to other therapies and found mixed results. (20-26) 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. (28) 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 0.35mg 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. (25) Gado and Macky (2014; n=60) reported no significant differences in visual acuity outcomes between dexamethasone implants and bevacizumab. (27) 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. (26) Compared to antivascular endothelial growth factor for treatment of macular edema after branch retinal vein occlusion, a metanalysis by Ji et al. (2019) of 6 studies (1 RCT, 4 retrospective studies, 1 prospective study; N=452 eyes) found similar BCVA change at 3 or 6 months with dexamethasone intravitreal implants (0.7 mg), but a higher risk of IOP elevation for dexamethasone treatment. (30) 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 BCVA 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) (29).

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 periocular triamcinolone acetonide 40 mg, intravitreal triamcinolone acetonide 4 mg, or the 0.7 mg intravitreal dexamethasone implant. (31) 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 periocular triamcinolone) but not at 24 weeks (41%, 36%, and 35%, respectively). Change in BCVA was similar for intravitreal dexamethasone, intravitreal triamcinolone and periocular triamcinolone at 8 weeks (+9.53 vs. +9.70 vs. +4.37 letters) and 24 weeks (+9.21 vs. +9.60 vs. +4.07). The main limitation was that, at 24 weeks, follow-up was relatively short-term. Longer-term data will be needed to confirm these findings.

In 2021, Fraser-Bell et al. performed an open-label, prospective, real-world study evaluated the effectiveness of dexamethasone intravitreal implant (0.7 mg) in a subgroup of patients with treatment-naive diabetic macular edema (DME). (32) Of the 200 eyes enrolled in the original AUSSIEDEX study, 57 were treatment-naive. Changes in mean BCVA and central subfield retinal thickness from baseline to 52 weeks in this subgroup were +3.4 letters (p=.042) and -89.6 micrometers (p<.001), respectively, with a mean of 2.5 injections of dexamethasone intravitreal implant 0.7 mg. The most common adverse event was increased IOP, with 20% of eyes requiring IOP lowering medications.

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 IOP, and conjunctival hemorrhage. (6)

<u>Intravitreal Fluocinolone Acetonide Implant 0.59 mg (e.g., Retisert®)</u>

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

Section Summary: Intravitreal Dexamethasone Implant 0.7 mg (e.g., Ozurdex) or Intravitreal Fluocinolone Acetonide Implant 0.59 mg (e.g., Retisert) 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 post implantation. Further, implant treated patients achieved improvement in vision faster than the sham controls. However, the vision gain was similar at 6 months. Several additional RCTs 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 IOP.

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

Diabetic Macular Edema

Intravitreal Fluocinolone Acetonide Implant (e.g., Retisert 0.59 mg)

Clinical Context and Therapy Purpose

The purpose of intravitreal fluocinolone acetonide implant (0.59 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with refractory DME.

The question addressed in this medical policy is: Does intravitreal fluocinolone acetonide implant (0.59 mg) improve the net health outcome in patients with refractory DME?

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

Populations:
The relevant population of interest is individuals with refractory DME.

Interventions:
The intervention of interest is the intravitreal fluocinolone acetonide implant (0.59 mg).

Comparators:
The comparators of interest are standard of care (as needed laser or observation).

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.

Systematic Reviews

Rittiphairoj et al. (2020) published a Cochrane review that evaluated the efficacy of intravitreal steroids for macular edema in diabetes. (33) It is an update of the previously published Cochrane review by Grover et al. (2008). (34) Ten trials were included, involving 4505 eyes with DME. Among those, 4 trials examined the effectiveness of intravitreal steroid implantation with fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system compared with sham or an anti-vascular endothelial growth factor agent (all discussed below) and 6 examined triamcinolone. Cochrane reviewers concluded that, compared to sham or control, intravitreal steroids may improve visual outcomes in people with DME, but that these benefits should be weighed against the risk of IOP elevation.

Randomized Controlled Trials

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 DME (referred to as refractory DME) were randomized to implants (n=127) or standard of care, defined as additional laser as needed after 6 months or observation (n=69). (35) 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 BCVA 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 (e.g., 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 IOP (≥30 mm Hg; 61.4% vs. 5.8%), need for surgery to treat glaucoma (33.8% vs. 2.4%), and cataracts extraction in phakic eyes (91% vs. 20%), respectively, for eyes treated with implants compared 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 (e.g., Retisert) 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 DME. The primary efficacy outcome, at least a 15-letter improvement in BCVA was significantly improved in a greater proportion of patients given implants versus laser at all time points assessed, except at or beyond 30 months. Note that this implant is active for 30 months. As a class effect, in patients with phakic eyes, use of implants resulted in 90% requiring cataract surgery and 60% developing elevated IOP. Due to the substantial increase in adverse events and availability of agents with safer tolerability profiles (e.g., Vascular Endothelial Growth Factor inhibitors), this implant is not indicated for DME.

Intravitreal Fluocinolone Acetonide Implant 0.19 mg (e.g., Iluvein)

Clinical Context and Therapy Purpose

The purpose of intravitreal fluocinolone acetonide implant (0.19 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with DME.

The question addressed in this medical policy is: Does intravitreal fluocinolone acetonide implant (0.19 mg) improve the net health outcome in patients with DME?

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

Populations:
The relevant population of interest is individuals with DME.

Interventions:
The intervention of interest is the intravitreal fluocinolone acetonide implant (0.19 mg).

Comparators:
The comparators of interest are standard of care (observation alone).

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.

Randomized Controlled Trials

Two double-blind, randomized trials Fluocinolone Acetonide in Diabetic Macular Edema (FAME) has assessed patients with DME 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). (36) 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). (7, 39) Relevant results with FDA approved dosing are summarized in Table 5. Campochiaro et al. (2012) subsequently reported on 3-year results. (37) 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). (7, 39) 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) DME. (38) The difference in the proportion of patients who gained 15 or more letters in the implant group versus the sham control group with chronic DME patients was 21% and -5.5 % among nonchronic DME patients.

Table 7. Summary of 2-Year Results From the FDA Pivotal Trials in DME

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

Table Key*:* CI: confidence interval; FDA: U.S. Food and Drug Administration. Values are n (%) or as otherwise indicated.

Massin et al. (2016) reported on the results of a small prospective noncomparative study in 16 patients with DME insufficiently responsive to laser and antivascular endothelial growth factor who received fluocinolone acetonide 0.19-mg implants. (40) Two groups of patients were

evaluated: group 1 (n=6) included patients ineligible for 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 BCVA letter score was more limited and heterogeneous (the effect was more pronounced in pseudophakic eyes) with some patients achieving high improvements of visual acuity, whereas others did not improve. 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. (39) Among these patients, 80% of implant patients versus 27% of sham-controlled had cataract surgery, generally within the first 18 months of the trials. The proportion of patients with IOP elevation of 10 mm Hg or more from baseline was 3 times higher in the implant group (34%) versus the sham group (10%). Respective proportions of patients with IOP of 30 mm Hg or more were 20% and 4%, respectively. As a consequence, a higher proportion of patients in the implant group required surgery for glaucoma (5% vs. 1%).

Section Summary: Intravitreal Fluocinolone Acetonide Implant 0.19 mg (e.g., Iluvein) for Diabetic Macular Edema
Two RCTs have established the efficacy of fluocinolone acetonide implants (0.19 mg) for patients with DME. Both trials demonstrated the superiority of implants over sham controls. Implant treated eyes showed clinically meaningful 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, IOP 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 IOP.

Intravitreal Dexamethasone Implant 0.7 mg (e.g., Ozurdex)
Clinical Context and Therapy Purpose
The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with DME.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in patients with DME?

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

Populations:

The relevant population of interest is individuals with DME.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 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.

Randomized Controlled Trials
Two double-blind, randomized trials have assessed patients with DME. 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). (41) In 2014, the FDA approved the 0.7 mg dose. (6) 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). (39)

Table 8. Summary of 39-Month Results from the FDA Pivotal Trials in DME

Outcome	Study 1 (N=328)	Study 2 (N=328)

	Implant (n=163)	Sham (n=165)	Difference (95% CI)	Implant (n=165)	Sham (n=163)	Difference (95% CI)
Gain of ≥15 letters, n (%)	34 (21)	19 (12)	9.3 (1.4 to 17.3)	30 (18)	16 (10)	13.0 (2.7 to 23.4)
Loss of ≥15 letters, n (%)	15 (9)	17 (10)	-1.1 (-7.5 to 5.3)	30 (18)	18 (11)	7.1 (-0.5 to 14.7)

Values are n (%) or as otherwise indicated.
CI: confidence interval; DME: Diabetic macular edema; FDA: U.S. Food and Drug Administration.

Subsequent to the 2014 pivotal trials and the 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 DME (Table 9). (41-47) 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 DME

Author, Year, Study Design, Sample Size	Population	Comparator	Summary of Findings
Boyer et al. (2014), (41) BEVORDEX RCT, N=86	Patients with DME.	Bevacizumab.	Dexamethasone had greater reduction in 12-month retinal thickness and similar for BCVA improvement of ≥ 10 letters. But, dexamethasone resulted in greater risk of vision loss > 10 letters and more adverse events.
Callanan et al. (2017), (47) RCT, N=363	Patients with DME	Ranibizumab 0.5 mg	Dexamethasone was noninferior to ranibizumab in mean average BCVA change based on the prespecified noninferiority margin of 5 letters, similar in retinal thickness reduction, but

			ocular adverse events were more frequent for dexamethasone.
Sharma et al. 2019, (29) RCT, N=40	Centre involved DME (CiDME).	Bevacizumab 1.25 mg or ranibizumab 0.5 mg.	Dexamethasone had greater improvements in 3-mo retinal thickness, but similar visual acuity.
Unpublished RCT, NCT02471651, (46) N=40	Persistent DME following anti-VEGF therapy.	Continue on various anti-VEGF therapy.	Treatments similar in 9-mo retinal thickness and visual acuity improvements.
Bolukbasi et al. 2019, (43) retrospective study; N=57	Early treatment period of naïve DME with serous retinal detachment.	Intravitreal aflibercept 2 mg, 3 monthly injections.	Dexamethasone had greater improvements in 3-mo retinal thickness, but similar visual acuity.
Cakir et al. 2019, (44) retrospective study, N=39 eyes	Treatment-naïve DME with concurrent epiretinal membrane.	Ranibizumab 0.5 mg.	Dexamethasone had greater CMT reduction at 1 mo, but lower at 2-3 mos. Similar visual acuity.
Coelho et al. 2019, (45) retrospective study; N=46 eyes	Persistent or recurrent DME.	Fluocinolone acetonide implant 0.19 mg.	Similar in 24-mo retinal thickness and visual acuity improvements.

Table Key*:* 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; CMT: central macular thickness; DME; diabetic macular edema; NCT02471651: Dexamethasone Intravitreal Implant (0.7mg) for the Treatment of Persistent DME Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy.

Section Summary: Intravitreal Dexamethasone Implant 0.7 mg (e.g., Ozurdex) for Diabetic Macular Edema

Two identical RCTs have established the efficacy of dexamethasone intravitreal implants (0.7 mg) for patients with DME. The 2 RCTs compared 2 doses of 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 (e.g., Ozurdex) 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 DME.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy improve the net health outcome in patients with DME.

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

Populations:
The relevant population of interest is individuals with DME.

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.

Randomized Controlled Trials

For individuals with DME who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy, the evidence includes 2 small RCTs of 169 patients (N range, 40-129) (Table 10). (42, 48) The first RCT, published by Maturi et al. (2015),

was single blinded and used bevacizumab as the antivascular endothelial growth factor treatment. (48) 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 DME despite previous treatment. (42) 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 IOP 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 IOP 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

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	*Comparator*
Maturi et al. (2018) (42)	U.S.	40	2014-2016	Persistent DME, with visual acuity of 20/32 to 20/320 after at least 3 anti-VEGF injections; 57% White, 11.6% Black, 22.4% Hispanic/Latinx, 6.2% Asian, 0.8% Native Hawaiian/Pacific Islander	Dexamethasone 0.7 mg + continued 0.3-mg ranibizumab, n=65 eyes	Sham + continued 0.3 mg ranibizumab, n=64
Marturi et al. (2015) (48)	U.S.	1	NR	DME with a CST of .250 mm measured by time-domain optical coherence tomography; 93% White, 7% Black	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

Table Key*:* CST: central subfield thickness; DME: Diabetic Macular Edema; Mo: month; VEGF: Vascular Endothelial Growth Factor; mg: milligrams; NR: not reported; RCT: randomized controlled trial; U.S.: United States.

Table 11. Summary of Key RCT Results

Study	Mean improvement in visual acuity (SD), letters	Mean change in central subfield thickness (SD), µm	Increased IOP
Maturi et al. (2018)[a] (42)	127	127	127
Dexamethasone + continued ranibizumab	+2.7 (9.8)	-110 (86)	19 (29%)
Sham + continued ranibizumab	+3.0 (7.1)	-62 (97)	0
MD (95%CI)	-0.5 (-3.6 to 2.5)	-52 (-82 to -22)	P<0.001
Maturi et al. (2015)[b] (48)	35	35	35
Dexamethasone + bevacizumab	+5.4 (10.7)	-45 (107)	6 (33%)
Bevacizumab monotherapy	+4.9 (12.3)	-30 (100)	1 (5.9%)
P-value	0.9	0.03	NR

Table Key*:* SD: Standard deviation; MD: mean difference; CI: confidence interval; IOP: intraocular pressure; OR: odds ratio; RCT: randomized controlled trial; NR: Not Reported.
[a] 24 weeks.
[b] 12 months.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Maturi et al. (2018) (42)					4. Sample size lower than needed for 90% power	
Maturi et al. (2015) (48)	3. Unclear	1. Patients not blinded			1. Not reported	

Table Key*:* The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias. 5. Inadequate description of methods.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Maturi et al. (2018) (42)	4. Enrolled populations do not reflect relevant diversity				1. 24 weeks is a relatively short follow-up
Maturi et al. (2015) (48)	4. Enrolled populations do not reflect relevant diversity				

Table Key*:* 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. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[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 pre-specified.
Follow-up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Section Summary: Intravitreal Dexamethasone Implant 0.7 mg (e.g., Ozurdex) 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 IOP 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 (e.g., Ozurdex) Plus Laser Photocoagulation

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with DME.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation improve the net health outcome in patients with DME?

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

Populations:
The relevant population of interest is individuals with DME.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation.

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.

Randomized Controlled Trials

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 DME. (49) 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 IOP 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 (e.g., Ozurdex) *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 IOP.

Age-Related Macular Degeneration

Intravitreal Dexamethasone Implant 0.7 mg (e.g., Ozurdex) Plus Antivascular Endothelial Growth Factor Therapy

Clinical Context and Therapy 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 in patients with age-related macular degeneration.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy improve the net health outcome in patients with age-related macular degeneration?

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

Populations:
The relevant population of interest is individuals with age-related macular degeneration.

Interventions:
The intervention of interest is the 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.

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

Section Summary: Intravitreal Dexamethasone Implant 0.7 mg (e.g., Ozurdex) Plus Antivascular Endothelial Growth Factor Therapy for Age-Related Macular Degeneration
One RCT 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 IOP elevation in a greater proportion of patients receiving implants without any additional clinical benefit.

Other Conditions
Birdshot Retinochoroidopathy
Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) or intravitreal fluocinolone acetonide implant (0.59 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with birdshot retinochoroidopathy refractory or intolerant to standard therapy.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) or intravitreal fluocinolone acetonide implant (0.59 mg) improve the net health outcome in patients with birdshot retinochoroidopathy refractory or intolerant to standard therapy?

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

Populations:
The relevant population of interest is individuals with birdshot retinochoroidopathy refractory or intolerant to standard therapy.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 mg) or intravitreal fluocinolone acetonide implant (0.59 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.

Retrospective Cohort Studies
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 corticosteroid 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). (51) 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 (0.59 mg). (52) Authors observed a more robust increase in IOP 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. (53) In 2 small retrospective studies with 6 eyes in 3 patients (54) and 6 eyes in 4 patients, (55) respectively, reported the favorable effects of dexamethasone implants on ocular inflammation and macular edema during treatment. All eyes exhibited control of ocular inflammation and macular edema. In the first study, all 3 patients achieved BCVA of at least 20/25 during treatment. In the second, there was a mean improvement of 70 letters on BCVA using the Early Treatment Diabetic Retinopathy Study chart.

Section Summary: Birdshot Retinochoroidopathy

No RCTs were identified on the treatment of birdshot retinochoroidopathy with any corticosteroid intravitreal implants. Available evidence includes multiple observational studies that noted improvements in anatomic and visual acuity outcomes in patient's 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.

Individuals with Cystoid Macular Edema Who Receive Intravitreal Dexamethasone Implant (0.7 mg)

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard therapy, in individuals with cystoid macular edema.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in individuals with cystoid macular edema?

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

Populations:

The relevant population of interest is individuals with cystoid macular edema. Cystoid macular edema results from cystic accumulation of fluid in multiple layers of the retina following the breakdown of the blood-retinal barriers. It is a sub-type of macular edema which can be caused

by many underlying conditions, including uveitis, retinal vein occlusion, DME, retinitis pigmentosa, as well as following procedures such as cataract extraction.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 mg).

Comparators:
Various drugs and therapeutic strategies are used to treat cystoid macular edema, with no consensus on the optimal approach or combination of drugs. (56) Intravitreally administered vascular endothelial growth factor antagonists (anti-VEGF) are an established treatment option. (57) Other treatment options may include carbonic anhydrase inhibitors and/or nonsteroidal anti-inflammatory drugs. (58) In those that do not respond to anti-VEGF agents, intravitreal corticosteroids are typically used. (59)

Outcomes:
The beneficial outcomes of general 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. For visual acuity, the FDA considers a 3-line or 15-or-more letter improvement from baseline in best-corrected visual acuity as a clinically significant change. (60)

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.

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

The only RCT identified for this indication is for individuals who have cystoid macular edema related to retinitis pigmentosa. Park et al. (2019) published a small (N=14), single-center, observation-controlled RCT from South Korea. (61) In this RCT, 14 patients with bilateral cystoid macular edema related to retinitis pigmentosa with macular cystic changes as shown by spectral domain optical coherence tomography with central macular thickness of .250 mm in both eyes had 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<.001) and median change of BCVA (+6 vs. +1; p<.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.

Comparative Observational Studies

Three observational studies have compared intravitreal dexamethasone to other treatments in patients with cystoid macular edema. (57, 59, 62) Tables 14 and 15 summarize their key characteristics and results. These studies are heterogenous in the type of cystoid macular edema treated, the comparator treatment, and outcome assessment approaches. The strength and relevancy of their findings are limited as they have included only small numbers of patients and lack responder analysis of the proportion of patients with a 15-or-more letter improvement from baseline in best-corrected visual acuity.

Table 14. Summary of Key Comparative Observational Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-Up
Ozkok et al. (2016) (59)	Pro-spective	US	2009-2013	Refractory cystoid macular edema due to retinal vein occlusion, initially treated with bevacizumab	Intravitreal dexamethasone, n=35	Intravitreal triamcinolone, n=39	12 w
Laine et al. (2017) (57)	Retro-spective	Finland	2011-2015	Treatment-naive cystoid macular edema due to retinal vein occlusion	Intravitreal dexamethasone, n=14	Intravitreal bevacizumab, n=121	12 w
Veritti et al. (2019) (62)	Pro-spective	Italy	2015-2016	Cystoid macular edema secondary to retinitis pigmentosa	Intravitreal dexamethasone, n=30	Oral acetazolamide 500 mg/day, n=30	12 Mo.

Table Key: Mo: month; w: weeks; U.S.: United States.

Table 15. Summary of Key Comparative Observational Study Results: Dexamethasone versus Comparator

Study	BCVA	Central Retinal Thickness	IOP (mmHg)

Ozkok et al. (2016) (59)	Final: 0.36 vs. 0.36; p=.920	Final: 310.3 vs. 311.6; p=.962	IOP increase >6 mmHg or needed IOP decreasing drops: 20% vs. 25.6%; p=.462
Laine et al. (2017) (57)	3-month mean gain estimated from graph: 0.33 vs. 0.37; p- value NR, but described as not significantly different	3-month reduction estimated from graph: -150 vs. -200; p-value NR, but described as not significantly different	IOP ≥ 25 mmHg and elevation ≥ 5 mmHg from baseline: 2 (14%) vs. 0; p=.010
Veritti et al. (2019) (62)	+4.2 letters vs. +1.6 letters; p<.05	-327 µm vs. -180 µm; p< .001	Elevated IOP requiring topical treatment: 4 (13%) vs. 0; p=.11

Table key: BCVA: best-corrected visual acuity; IOP: intraocular pressure; NR: not reported; vs.: versus

Noncomparative Observational Studies

Multiple case series have assessed improvements in visual acuity and anatomic changes following intravitreal dexamethasone implant (0.7 mg) in patients with cystoid macular edema of various etiologies. (56, 63, 64, 65, 66) However, these studies have generally included only small numbers of patients (N range of 26 to 112) and lacked responder analysis of clinically meaningful changes in outcomes. One exception is the case series by Fortoul et al. (2015), which evaluated the efficacy of the first intravitreal injection of dexamethasone implant in 26 eyes with cystoid macular edema secondary to retinal vein occlusion over 6 months in a single center in France. (65) Fortoul et al. (2015) reported that although 88% of patients achieved at least a 3-line improvement in BCVA 2 months, this was not sustained and only 27.8% of eyes still achieved clinically significant response at 6 months.

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Cystoid Macular Edema

Evidence for this indication includes 1 observation-controlled RCT (N=14), 3 comparative observational studies, and numerous case series. The RCT found improved mean visual acuity and eye anatomy outcomes with intravitreal dexamethasone compared to the control eyes, but these differences were not sustained at 6 months. The comparative observational studies included 269 patients (range, 60 to 135) and lacked responder analysis of the proportion of patients with a 15-or-more letter improvement. One case series evaluated the proportion of patients with a 3-line improvement in best-corrected visual acuity. Although 88% of patients achieved this outcome at 2 months, the proportion with improvement was not sustained at 6 months (27.8%). Additional blinded, multicenter RCTs are needed that compare intravitreal dexamethasone to another established treatment. The trials should be adequately powered for measuring the proportion of patients in whom vision had improved by 15 letters or more.

Idiopathic Macular Telangiectasia Type 1

Clinical Context and Therapy Purpose
The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with idiopathic macular telangiectasia type 1.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in individuals with idiopathic macular telangiectasia type 1?

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

Populations:
The relevant population of interest is individuals with 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.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 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.

Case Reports
No RCTs were identified on the treatment of macular telangiectasia with any corticosteroids intravitreal implants. Three case reports with a total of 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. (55, 67, 68)

Section Summary: Idiopathic Macular Telangiectasia Type 1

No RCTs were identified on the treatment of idiopathic macular telangiectasia type 1 with any corticosteroid intravitreal implants. Available evidence includes multiple case reports, which have noted mixed 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.

Individuals with Postoperative Chronic Macular Edema Who Receive Intravitreal Dexamethasone Implant (0.7 mg)

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard therapy, in individuals with postoperative chronic macular edema.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in individuals with postoperative chronic macular edema.

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

Populations:

The relevant population of interest is individuals with 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.

Interventions:

The intervention of interest is the intravitreal dexamethasone implant (0.7 mg).

Comparators:

There are no FDA approved treatments specifically for postoperative chronic macular edema. Also, there are no guidelines or position statements that provide definitive guidance on standard of care for postoperative chronic macular edema. However, first-line treatment typically involves topical corticosteroids and nonsteroidal anti-inflammatory drugs, either as monotherapy or combined therapy. (74, 75) When postoperative chronic macular edema persists following topical treatments, then intravitreal corticosteroids and anti-vascular endothelial growth factor agents may be an option.

Outcomes:

The beneficial outcomes of general 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. For visual acuity, the FDA considers a 3-line or 15-or-more letter improvement from baseline in BCVA as a clinically significant change. (65)

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.

Randomized Controlled Trials

Mylonas et al. (2017) published an RCT that compared dexamethasone intravitreal implant to triamcinolone intravitreal injection in 29 patients with refractory postoperative cystoid macular edema. (71) Key characteristics and results of Mylonas et al. (2017) are reported in Tables 16 and 17 below. Participants were mostly female (72%) and the mean age was 73 years in the dexamethasone group and 71 years in the triamcinolone group. No primary outcome was specified. There were no significant differences between the groups in improvement in mean BCVA, but central millimeter retinal thickness reduction was significantly greater for triamcinolone at 1 week and 6 months. Minimal information on adverse events was reported.

Table 16. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Mylonas et al. (2017) (71)	Austria, Greece	2	Not reported	Refractory (minimum 3 months) macular edema, developing after cataract extraction or vitreoretinal surgery	Dexamethasone intravitreal implant, 0.7 mg	Triamcinolone intravitreal injection, 4 mg; retreatment after 3 months was dependent on functional and anatomic outcome

Table key: RCT: randomized controlled trial.

Table 17. Summary of Key RCT Results

Study	BCVA	Central Millimeter Thickness	IOP
Mylonas et al. (2017) (71)	Mean (SD) at baseline, 1mo, 3mo, and 6mo	Mean (SD) at baseline, 1w, 1mo, 3mo, and 6mo	Data not provided; "All cases of IOP elevation were managed readily by observation or topical pressure lowering medications and no glaucoma surgery was necessary"
Dexamethasone	60 (10), 72 (10), 72 (11) and 66 (13)	548 (110), 406 (72), 357 (69), 391 (102), and 504 (159)	
Triamcinolone	63 (13), 73 (11), 73 (11), and 71 (13)	516 (121), 350 (54) 355 (59), 389 (89), and 365 (74)	
p-value	>.05	≤.05 at 1w and 6mo	

Table key: BCVA: best-corrected visual acuity; IOP: intraocular pressure; mo: month(s); RCT: randomized controlled trial; SD: standard deviation; w: week(s)

Tables 18 and 19 summarize the relevance and design and conduct limitations of Mylonas et al. (2017). (71)

Table 18. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Mylonas et al. (2017) (71)	1. Refractory was undefined; thus, the adequacy of the intensity and duration of the first- line therapy regimen is unclear			6. The proportion of patients in whom vision had improved by 15 letters or more was not reported	

Table key: The evidence limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps 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 19. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Complete-ness[d]	Power[e]	Statistical[f]
Mylonas et al. (2017) (71)	3. Allocation concealment unclear	1. All the examiners were unmasked to the injected medication used			2. Power not calculated for primary outcome	

Table key: The evidence limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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.

Comparative Observational Studies

Two observational studies have compared intravitreal dexamethasone to other treatments in patients with postoperative macular edema. (72, 73) Tables 20 and 21 summarize their key characteristics and results. However, these studies have included only small numbers of patients and lack responder analysis of the proportion of patients with a 15-or-more letter improvement from baseline in BCVA.

Table 20. Summary of Key Comparative Observational Study Characteristics

Study	Study Type	Country	Dates	Participants	Treat-ment 1	Treat-ment 2	Follow-Up
Dang et al. (2014) (72)	Prospective	China	2011 - 2013	Patients with diabetes and persistent PCME after 1-month of topical diclofenac	Intravitreal	Intravitreal	6 mo.

				and fixed-dose combination product of tobramycin/dexamethasone			
Guclu et al. (2019) (73)	Retrospective	Turkey	2013 - 2015	Previously untreated Irvine-Gass syndrome after phacoemulsification with posterior chamber intraocular lens implantation	Intravitreal dexamethasone, n=32	Topical nepafenac, n=30	6 mo.

Table key: Mo: month(s); PCME: pseudophakic cystoid macular edema.

Table 21. Summary of Key Observational Comparative Study Results ,

Study	Improvement in BCVA	IOP (mmHg)	Other adverse events
Dang et al. (2014) (72)	Percentage of patients who gained improvements ≥ 10 ten letters: n=43	Mean change, n=43	% with conjunctival hemorrhage, n=43
Intravitreal dexamethasone	33%	+1.6	4/18 (22.2%)
Intravitreal triamcinolone	36%	+3.4	2/25 (8%)
p-value	.856	.006	.184
Guclu et al. (2019) (73)	Mean BCVA at baseline and 6 months (change), n=62	Mean at baseline and 6 months (change), n=62	Surgery-related complications (posterior capsule rupture, iridodialysis, vitreous incarceration, zonular dialysis)
Intravitreal dexamethasone	25 vs 49.3 (+24.3)	13.1 vs 14.9 (+1.8)	10/32 (31%)
Topical nepafenac	20.9 vs 32.9 (+12)	13.6 vs 13.6 (+0)	9/30 (30%)
p-value	.000	.184	NR

Table key: BCVA: best-corrected visual acuity; IOP: intraocular pressure; NR: not reported.

-

Case Series

Multiple case series have assessed improvements in visual acuity and anatomic changes. (74-81) 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 edema 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. (82) Mean improvement in BCVA was 9.6. The proportions of eyes with gains in BCVA 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

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

Circumscribed Choroidal Hemangioma

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) plus photodynamic therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with circumscribed choroidal hemangioma.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) plus photodynamic therapy improve the net health outcome in individuals with circumscribed choroidal hemangioma?

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

Populations:

The relevant population of interest is individuals with circumscribed choroidal hemangioma. Circumscribed choroidal hemangiomas are benign vascular hamartomas without systemic associations.

Interventions:

The intervention of interest is the intravitreal dexamethasone implant (0.7 mg) plus photodynamic 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.

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.

Case Reports
No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroid 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. (83)

Section Summary: Circumscribed Choroidal Hemangiomas
No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroid 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
Clinical Context and Therapy Purpose
The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with proliferative vitreoretinopathy.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in individuals with proliferative vitreoretinopathy?

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

Populations:
The relevant population of interest is individuals with 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.

Interventions:
The intervention of interest is the intravitreal dexamethasone implant (0.7 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.

Case Series/Reports
No RCTs were identified on the treatment of proliferative vitreoretinopathy with any corticosteroid intravitreal implants. A case series (2017) of 5 patients with proliferative vitreoretinopathy has described the combined use of surgery, endolaser, and dexamethasone implants. (84) 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. (85)

Section Summary: Proliferative Vitreoretinopathy
No RCTs were identified on the treatment of proliferative vitreoretinopathy with any corticosteroid 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

Clinical Context and Therapy Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with radiation retinopathy.

The question addressed in this medical policy is: Does intravitreal dexamethasone implant (0.7 mg) improve the net health outcome in individuals with radiation retinopathy?

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

Populations:

The relevant population of interest is individuals with radiation retinopathy. Radiation retinopathy is delayed-onset damage to the retina due to exposure to ionizing radiation, typically after months and is slowly progressive.

Interventions:

The intervention of interest is the intravitreal dexamethasone implant (0.7 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.

Retrospective Cohort Studies

No RCTs were identified on the treatment of radiation retinopathy with any corticosteroid intravitreal implants. In a retrospective study (2015), 12 eyes diagnosed with radiation maculopathy secondary to plaque brachytherapy were treated with dexamethasone implants.

(86) 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. (87) 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 mixed improvements in visual acuity. (88) 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 corticosteroid 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/Itching and Pain Following Ophthalmic Surgery

Clinical Context and Test Purpose

The purpose of punctum dexamethasone insert 0.4 mg (e.g., Dextenza®) 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/itching and pain following ophthalmic surgery.

The question addressed in this medical policy is: Does punctum dexamethasone insert 0.4 mg improve the net health outcome in patients in patients with ocular inflammation/itching and pain following ophthalmic surgery.

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

Populations:

The relevant population of interest is individuals with ocular inflammation/itching 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.

Randomized Controlled Trials
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 22). (89, 90) 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). (90) The subsequent larger phase 3C trial was reported by Tyson et al. (2019). (89) 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 the absence of ocular pain at 14 days, with 2 exceptions (Table 23). 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). (89) 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 IOP. Although allocation concealment methods are unclear across the studies, they had no major methodological limitations (Tables 24 and 25).

Table 22. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Walters et al. (2016); Study 1 (OTX-13-002;	U.S.	16	Not reported	≥ 18 years of age, with a visually significant cataract	Punctum dexamethasone	Sham, n=83

NCT02034019) (90)				and scheduled to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber IOLs	insert (0.4 mg), n=164	
Walters et al. (2016); Study 2 (OTX-13-003; NCT02089113) (90)	U.S.	16	Not reported	Same as Walters et al. 2016 study 1	Punctum dexamethasone insert (0.4 mg), n=161	Sham, n=80
Tyson et al. (2019) (NCT02736175) (89)	U.S.	21	Not reported	≥ 18 years of age, presence of a cataract and plans to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber a posterior chamber IOLs	Punctum dexamethasone insert (0.4 mg, n=216	Sham, n=222

Table Key*:* mg: milligrams; IOLs: intraocular lens; U.S.: United States; 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, Multicenter, Randomized, Parallel Arm, Double Masked, Vehicle Controlled Phase 3B Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment 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 23. Summary of Key RCT Results

Study	Absence of Ocular Pain at Day 8	Absence of Ocular Pain at Day 14	Absence of Anterior Chamber Cells at Day 14	Serious Adverse Events	Increased IOP

Walters et al. (2016) Study1 (90)	247	247	247	246	246
Punctum dexamethasone insert (0.4 mg)	NR (80.4%)	NR (79.6%)	54 (33.1%)	3 (1.9%)	11 (6.8%)
Sham	NR (43.4%)	NR (39.8%)	12 (14.5%)	5 (6.0)	3 (3.6%)
p-value	<0.0001	<0.0001	0.0018		NR
Walters et al. (2016); Study 2 (90)	241	241	241	240	240
Punctum dexamethasone insert (0.4 mg)	NR (77.5%)	NR (76.9%)	63 (39.4%)	2 (1.2%)	7 (4.4%)
Sham	NR (58.8%)	NR (57.5%)	25 (31.3%)	3 (3.8%)	4 (5.0%)
p-value	.0025	.0019	.2182		NR
Tyson et al. (2019) (89)	438	NA	438	437	437
Punctum dexamethasone insert (0.4 mg)	NR (79.6%)	NR	NR (52.3%)	3 (1.4%)	16 (7.4%)
Sham	NR (61.3%)	NR	NR (31.1%)	2 (0.9%)	6 (2.7%)
p-value	<0.0001	NR	<0.0001	NR	NR

Table Key*:* IOP: intraocular pressure; mg: milligrams; mg: milligrams; NR: not reported; NA: not applicable; 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, Mu Double-Masked, Vehicle Controlled Phase 3B 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 24. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Walters et al. (2016) Study 1(90)					
Walters et al. (2016) Study 2 (90)					
Tyson et al. (2019) (89)	1. 14 day				

	absence of pain not reported				

Table Key*:* The study limitations stated in this table are those notable in the current literature 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, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3B Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain After Cataract Surgery.
[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 25. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Walters et al. (2016) Study 1 (90)	3. Allocation concealment unclear					
Walters et al. (2016) Study 2 (90)	3. Allocation concealment unclear					
Tyson et al. (2019) (89)	3. Allocation concealment unclear	4. Described as double-blind, but outcome assessor unspecified	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			

Table Key*:* The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps limitations assessment. CT: clinical trials; 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, Multicenter, Randomized, Parallel Arm, Double Masked, Vehicle Controlled Phase 3B Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain After Cataract Surgery.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[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.

In 3 randomized, multicenter, double-masked, parallel group, vehicle-controlled efficacy trials, patients received Dextenza or its vehicle utilizing a repeat conjunctival allergen challenge model (NCT02445326, NCT02988882, NCT04050865). (10) In all 3 trials, Dextenza resulted in lower mean ocular itching scores compared with the vehicle group at all time points throughout the one-month duration of the study. In 2 of the 3 studies, a higher proportion of patients had statistically significant reductions in ocular itching on Day 8, at 3 minutes, 5 minutes and 7 minutes post-challenge in the Dextenza group than in the vehicle group. Results are shown in Table 26.

Table 26. Reduction in Ocular Itching (10)

	Study 1				**Study 2**			**Study 3**		
Visit	**Time Point**	**Dextenza (N=35)**	**Vehicle (N=38)**	**Diff (95% CI)**	**Dextenza (N=44)**	**Vehicle (N=42)**	**Diff (95% CI)**	**Dextenza (N=44)**	**Vehicle (N=42)**	**Diff (95% CI)**

		Least Square Means			Least Square Means			Least Square Means		
Day 8	3 min	1.9	2.7	-0.7 (-1.2, -0.3)	2.1	2.3	-0.2 (-0.7, 0.3)	1.8	2.7	-0.9 (-1.2, -0.4)
	5 min	2.1	2.8	-0.7 (-1.2, -0.3)	2.1	2.3	-0.2 (-0.8, 0.3)	1.8	2.7	-1.0 (-1.4, -0.6)
	7 min	1.9	2.7	-0.8 (-1.2, -0.4)	2.1	2.4	-0.3 (-0.8, 0.3)	1.7	2.7	-1.0 (-1.4, -0.6)

Table key: Diff: difference.

Section Summary: Ocular Inflammation/Itching 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 an 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. In study 1, dextenza resulted in lower mean ocular itching scores at all time points up to 1 month duration. In 2 of the 3 studies, a higher proportion of patients had statistically significant reductions in ocular itching on Day 8, at 3 minutes, 5 minutes and 7 minutes post-challenge in the Dextenza group compared to the vehicle group. 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 (e.g., 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 medical policy is: Does intravitreal dexamethasone 0.7 mg (e.g., 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 policy.

Populations
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.

Randomized Controlled Trials
For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive prophylactic intravitreal dexamethasone 0.7 mg (Ozurdex), the best evidence includes 1 single- center, open-label RCT of 43 patients in India (Table 27). (91) 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 (BCVA) and avoided the need for early steroid taper due to adverse effects on blood glucose, but potentially increased risk of developing IOP (Table 27). 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 29 and 30).

Table 27. Summary of Key RCT Characteristics

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	*Comparator*

Sudhalkar et al. (2019) (91)	India	1	2015-2016	≥ 18 years 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 months prior to scheduled date of cataract surgery	Intravitreal dexamethasone 0.7 mg, n=20	Oral corticosteroids, n=23

Table Key*:* CMO: cystoid macular edema; mg: milligram; n: number; RCT: randomized controlled trial.

Table 28. Summary of Key RCT Results

Study	Development of CMO at 6 months	BCVA at 6 months	Developed ocular hypertension, n (%)	Required rapid taper of systemic steroids due to adverse blood glucose effects, n (%)
Sudhalkar et al. (2019) (91)	43	43	43	43
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

Table Key*:* logMAR: Logarithm of the Minimum Angle of Resolution; mg:milligram; NR=not reported; NSD: not significantly different; CMO: cystoid macular edema; BCVA: best corrected visual acuity; RCT: randomized controlled trial.

Table 29. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Sudhalkar et al. (2018) (91)	4. Study population potentially had better prognosis than intended use				

Table Key*:* The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps limitation 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 present.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 30. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Sudhalkar et al. (2018) (91)	3. Allocation concealment unclear	1. Not blinded				

Table Key: The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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 anal.
[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 (e.g., 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 IOP. Due to important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding, conclusions cannot be drawn based on these findings.

Summary of Evidence

Uveitis

For individuals with chronic noninfectious intermediate or posterior uveitis who receive an intravitreal fluocinolone acetonide implant (0.59 mg; Retisert), 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 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. 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=.16) and +2.4 and 3.1 letters (p=.073), respectively. However, nearly all phakic patients receiving implants developed cataracts and required cataract surgery. Further, most also developed glaucoma, with 75% of patients requiring intraocular pressure (IOP) lowering medications and 35% requiring filtering surgeries. Systemic adverse events such as hyperlipidemia, diabetes, osteoporosis, fractures, and blood count/chemistry abnormalities were infrequent and not statistically distinguishable between groups. The incidence of hypertension was greater in the systemic therapy group (27%) 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 an 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 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 (BCVA) from baseline was »40% with implants and 10% with sham). Further, at week 26, patients treated with implants reported meaningful increases in vision related functioning. The major limitation of this trial was its lack of long-term follow-up. Use of implants resulted in higher incidences of cataracts and elevated IOP. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 to 511.06 in published RCT and odds ratio 3.04; 95% confidence interval 1.52 to 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 BCVA at 12 months (higher for fluocinolone acetonide in the published trial, lower in the unpublished trials) and risk of increased IOP within 12 months (increased risk in the unpublished trial, but not in the published trial). Based on the Food and Drug Administration (FDA) approval, intravitreal fluocinolone acetonide implant (0.18 mg, Yutiq), may be indicated in adult patients for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. The FDA denotes Yutiq is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. In addition, the safety and effectiveness of Yutiq has not been established in pediatric patients.

<u>Macular Edema</u>

For individuals with macular edema after retinal vein occlusion who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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 BCVA from baseline was more than 10% in favor implants versus sham in both studies at 30, 60 and 90 days, but not at 180 days postimplant. Use of implants resulted in higher incidences of cataracts and elevated IOP. Several additional RCTs and a metanalysis have evaluated the comparative effects of dexamethasone intravitreal implants versus other therapies and found mixed results. Based on the FDA approval, an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), may be indicated in adult patients for the treatment of macular edema following branch or central retinal vein occlusion. The FDA denotes Ozurdex is contraindicated in patients with ocular or periocular infections (viral, bacterial, or fungal), in patients with advanced glaucoma with a cup to disc ratio of greater than 0.8 and in patients with a torn or ruptured posterior lens capsule. In addition, the safety and effectiveness of Yutiq has not been established in pediatric patients.

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

Diabetic Macular Edema

For individuals with refractory (persistent or recurrent) diabetic macular edema (DME) who receive an intravitreal fluocinolone acetonide implant 0.59 mg (e.g., Retisert®), 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 IOP. Due to the substantial increase in adverse events and availability of agents with better tolerability profiles (e.g., antivascular endothelial growth factor inhibitors), implant use in DME is questionable. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with DME who receive an intravitreal fluocinolone acetonide implant 0.19 mg (e.g., Iluvein), 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, IOP was elevated in 34% of patients who received this implant compared with 10% of controls. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with DME who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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 BCVA from baseline was 9.3% and 13.0% in the 2 trials, respectively, favoring implant versus sham at 39 months postimplant. Subgroup analysis of these trials showed greater improvements in visual acuity in patients who were pseudophakic compared 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 DME who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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 IOP elevation. Based on the consistent lack of improvement in visual acuity, increased risk of IOP 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 DME who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), plus laser photocoagulation, the evidence includes 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 IOP. Further, a differential loss to follow-up, lack of power

calculations for sample size estimation, and lack of intention-to-treat analysis preclude interpretation of results. A larger RCT with adequate power is needed to confirm these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

Age-Related Macular Degeneration

For individuals with age-related macular degeneration who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex) plus antivascular endothelial growth factor inhibitor, the evidence includes 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, IOP 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

Birdshot Retinochoroidopathy

For individuals with birdshot retinochoroidopathy refractory or intolerant to standard therapy who receive an intravitreal fluocinolone acetonide implant 0.59 mg (e.g., Retisert) or intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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.

Cystoid Macular Edema

For individuals with cystoid macular edema who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex) the evidence includes 1 observation-controlled RCT (N=14), 3 comparative observational studies, and numerous case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The RCT found improved mean visual acuity and eye anatomy outcomes with intravitreal dexamethasone compared to the control eyes, but these differences were not sustained at 6 months. The comparative observational studies included 269 patients (range, 60 to 135) and also lacked responder analysis of the proportion of patients with a 15-or-more letter improvement. One case series evaluated the proportion of patients with a 3-line improvement in best-corrected visual acuity; although 88% of patients achieved this outcome at 2 months, the proportion with improvement was not sustained at 6 months (27.8%). Additional blinded, multicenter RCTs are needed that compare intravitreal dexamethasone to another established treatment. The trials should be adequately powered for measuring the proportion of patients in whom vision had improved by 15 letters or more. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Idiopathic Macular Telangiectasia Type 1

For individuals with idiopathic macular telangiectasia type 1 who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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 that technology results in an improvement in the net health outcomes.

Postoperative Chronic Macular Edema (Pseudophakic Cystoid Macular Edema, Irvine-Gass Syndrome)

For individuals with postoperative chronic macular edema (pseudophakic cystoid macular edema, Irvine-Gass syndrome) who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), the evidence includes 1 RCT (N=29) that compared dexamethasone intravitreal implant, 0.7 mg to triamcinolone intravitreal injection 4 mg, 2 comparative observational studies and numerous case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The RCT found no statistically significant difference between treatments in mean visual acuity improvement at 3 or 6 months. The proportion of patients in whom vision had improved by 15 letters or more was not reported. The comparative observational studies included only small numbers of patients and lack responder analysis of the proportion of patients with a 15-or-more letter improvement. In the largest case series (N=100), 2 of every 5 patients experienced clinically meaningful improvements in visual acuity after 1 year of follow-up. Additional RCTs are needed that have clearly defined and representative populations (i.e., for chronic and refractory patients, documentation of intensity and duration of the first-line therapy regimens) and are adequately powered for measuring the proportion of patients in whom vision had improved by 15 letters or more. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Choroidal Hemangiomas

For individuals with circumscribed choroidal hemangiomas who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex) 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 that the technology results in an improvement in net health outcomes.

Proliferative Vitreoretinopathy

For individuals with proliferative vitreoretinopathy who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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 that the technology results in an improvement in net health outcome

Radiation Retinopathy
For individuals with radiation retinopathy who receive an intravitreal dexamethasone implant 0.7 mg (e.g., Ozurdex), 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 that the technology results in an improvement in net health outcomes.

Clear Corneal Cataract Surgery
For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert 0.4 mg (e.g., Dextenza), 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 an improvement in the net health outcome.

Noninfectious Intermediate Uveitis or Posterior Uveitis and Cataract
For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive prophylaxis with intravitreal dexamethasone 0.7 mg (e.g., 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 IOP. 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 net health outcome.

Practice Guidelines and Position Statements
American Academy of Ophthalmology (AAO)

In 2019, the AAO published its preferred Practice Pattern® for retinal vein occlusions. (92) 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.”

In 2019, the AAO also published its preferred Practice Pattern® for diabetic retinopathy. (93) Related to therapy with intravitreal corticosteroids, the Academy stated: "Because of their side-effect profile, including cataract progression and elevated IOP [intraocular pressure], they [intravitreal corticosteroids] are generally used as second-line agents for DME [diabetic macular edema], especially for phakic patients."

National Institute for Health and Care Excellence (NICE)

In 2019, the NICE released guidance on the use of fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien) for treating chronic DME that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye). (94) The NICE committee reached this conclusion based on their interpretation that “results from [Fluocinolone Acetonide in Diabetic Macular Edema] FAME may not be generalisable 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. (95) 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. (96) 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. (97) 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. (98) Ozurdex was recommended as a possible treatment for DME 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 DME 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 edema has not got better with other treatments." (99)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 31.

Table 31. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02556424[a]	Efficacy and Tolerance Comparison Between Subconjunctival Injection of Triamcinolone and Intravitreal Implant of Dexamethasone for the Treatment of Inflammatory Macular Edema.	142	Feb 2021
NCT02623426	Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial.	240	Jul 2022
NCT01998412[a]	Iluvien Registry Safety Study (IRISS).	559	Jan 2020 (active, not recruiting)
NCT05101928	Ozurdex as Monotherapy for Treatment of Non-infectious Intermediate, Posterior, or Panuveitis.	84	Feb 2025
NCT05003258	Functional and Anatomical Outcomes of Dexamethasone Intra-vitreal Implant in Patients With Macular Edema Due to Retinal Vein Occlusion.	25	Oct 2024
Unpublished			
NCT01827722[a]	Ozurdex® Versus Ranibizumab Versus Combination for Central Retinal Vein Occlusion.	45	Dec 2016 (unknown)
NCT02471651[a]	Dexamethasone Intravitreal Implant for the Treatment of Persistent Diabetic Macular Edema.	40	Oct 2018 (has results, but no peer reviewed publication)
NCT03003416	Efficacy of Ozurdex® in the Treatment of Diabetic Macular Edema.	115	Dec 2018 (completed)

Table Key: NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

INTRACAMERAL BIMATOPROPROST IMPLANT

Durysta®

The efficacy of Durysta was evaluated in two multicenter, randomized, parallel-group, controlled 20-month (including 8-month extended follow-up) studies compared to twice daily topical timolol 0.5% drops, in patients with open angle glaucoma (OAG) or OHT. Durysta demonstrated an IOP reduction of approximately 5-8 mmHg in patients with a mean baseline IOP of 24.5 mmHg. The most common ocular adverse reaction observed in the two trials was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, IOP increased, corneal endothelial cell loss, vision blurred, and iritis. Due to possible corneal endothelial cell loss, administration of durysta should be limited to a single implant per eye without retreatment. (1)

Summary of Evidence

The U.S. Food and Drug Administration (FDA) approved bimatoprost implant (Durysta®) for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) based on two randomized, controlled clinical studies. The safety, efficacy, and the improvement on health outcomes were adequately demonstrated, therefore Durysta may be considered medically necessary when established criteria are met. Durysta is considered experimental, investigational, and/or unproven for all other indications.

INTRACAMERAL TRAVOPROST IMPLANT

iDose® TR

iDose TR was evaluated in two multicenter, 12-month, randomized, parallel-group, double-masked, controlled clinical trials in patients with OAG or OHT. In both trials (GC-010, NCT03519386, and GC012, NCT03868124), iDose TR was compared to twice-daily topical administration of timolol maleate ophthalmic solution, 0.5%. In the first 3 months following administration, iDose TR demonstrated an IOP change from baseline of -6.6 to -8.4 mmHg in the study eye of patients with a mean baseline IOP of 24 mmHg. iDose TR demonstrated non-inferiority to timolol ophthalmic solution in IOP reduction during the first 3 months. Subsequently, iDose TR did not demonstrate non-inferiority over the next 9 months. (100)

Summary of Evidence

The U.S. Food and Drug Administration (FDA) approved travoprost implant (iDose® TR) for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) based on two randomized, controlled clinical studies. The safety, efficacy, and the improvement on health outcomes were adequately demonstrated, therefore iDose® TR may be considered medically necessary when established criteria are met. iDose® TR is considered experimental, investigational, and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0660T, 0661T, 67027, 67028, 68841 [deleted 1/2022: 0356T]
HCPCS Codes	J1096, J7311, J7312, J7313, J7314, J7351, J7355

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

07/01/2024	Document updated with literature review. The following change was made to Coverage: Added "A travoprost implant for intracameral administration (e.g., iDose® TR) may be considered medically necessary in adult patients with open angle glaucoma (OAG) or ocular hypertension (OHT) when: Patient has had a trial and failure or intolerance to at least two intraocular pressure-lowering eye-drop agents with different mechanisms of action, and one of which must include a prostaglandin analog (e.g., bimatoprost, latanoprost, travoprost, or tafluprost); AND the affected eye has not received prior treatment with an intracameral travoprost implant. All other uses of a travoprost implant for intracameral administration (e.g., iDose® TR) are considered experimental, investigational and/or unproven.
09/15/2023	Reviewed. No changes.
12/01/2022	Document updated with literature review. The following changes were made in Coverage: 1) Retisert: expanded the existing medically necessary statement to include" uveitis affecting the posterior segment of the eye"; 2) Dextenza: Expanded the medically necessary coverage statement to include use "in the treatment of ocular itching associated with allergic conjunctivitis." Added references 5, 7, 10, 23, 32, 33, 39, 47, 56-60, 62-66, 69-73, 81, 93; others updated, some removed.
09/15/2021	Reviewed. No changes.
10/01/2020	Document updated with literature review. The following Changes were made in Coverage: 1) Retisert: a) Added "in patients 12 years of age or older" to the medically necessary coverage statement and "viral, bacterial, mycobacterial and fungal infections of ocular structures" to the not medically necessary statement; 2) Iluvein: Expanded medically necessary coverage to state "adult patients" and " (or had the rise in IOP adequately treated prior to placement of the implant)"; 3) Yutiq: a) Added medically necessary statement "in adult patients for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye"; b) Added "suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases to the not medically necessary statement. 4) Expanded the experimental, investigational and/or unproven statement to a) include **"**Yutiq" as a type of fluocinolone acetonide intravitreal implant; and b) Added "Prophylaxis of cystoid macular edema in patients with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery"; 5) Ozurdex: a) Added "in adult patients" to the medically necessary criteria; b) Added "Prophylaxis of cystoid macular edema in patients with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery" to the experimental, investigational and/or unproven statement. 6) Dextenza: a) Added may be considered medically necessary in adult patients for the treatment of ocular inflammation and pain following ophthalmic surgery; b) Added not medically necessary

	statement for patients with active corneal, conjunctival or canalicular infections. c) Added "All other uses of a dexamethasone ophthalmic insert 0.4 mg (e.g., Dextenza®) are considered experimental, investigational and/or unproven". 7) Added conditional coverage for bimatoprost implant for intracameral administration (e.g., Durysta®). Added references 16, 17, 23-25, 35-39, 47-49, 69-76, and 81-82. Title changed from "Intravitreal Corticosteroid Implants".
06/15/2018	Reviewed. No changes.
01/01/2018	Document updated with literature review. The following was added to Coverage: 1) Added individual doses to the Retisert®, Iluvien® and Ozurdex™ coverage statements 2) Added medically necessary coverage for intravitreal implant when used according to the FDA approved indications as an alternative in patients who are intolerant or refractory to other therapies or in patients who are likely to experience severe adverse events from systemic corticosteroids. 3) Not medically necessary coverage was added for fluocinolone acetonide intravitreal implant 0.59 mg (e.g., Retisert®) for patients with active ocular or periocular infections. 4) Not medically necessary coverage was added for fluocinolone acetonide intravitreal implant 0.19 mg (e.g., Iluvein®) for patients with active ocular or periocular infections or in patients with glaucoma with a cup to disc ratio of greater than 0.8. 5) Not medically necessary coverage was added for dexamethasone intravitreal implant (e.g., Ozurdex™) for patients with ocular or periocular infections (viral, bacterial, or fungal), advanced glaucoma with a cup to disc ratio of greater than 0.8. or torn or ruptured posterior lens capsule. 6) Added experimental, investigational and/or unproven coverage statement for the following conditions: Birdshot retinochoroidopathy; Cystoid macular edema related to retinitis pigmentosa; Idiopathic macular telangiectasia type 1; Postoperative macular edema; Circumscribed choroidal hemangiomas; Proliferative vitreoretinopathy; Radiation retinopathy and for the use of dexamethasone intravitreal implant (e.g., Ozurdex™) combined with cataract surgery for the treatment of cataract and macular edema.
07/15/2016	Reviewed. No changes.
04/01/2015	Document updated with literature review. The following was added to Coverage: 1) clarification that implants must be approved by the FDA, 2) ILUVIEN®, a fluocinolone acetonide intravitreal implant approved by the FDA, may be considered medically necessary for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids without a clinically significant rise in intraocular pressure.
11/15/2014	Document updated with literature review. The following was added to Coverage: Dexamethasone intravitreal implant approved by FDA (i.e., Ozurdex™) may be considered medically necessary for the treatment of diabetic macular edema.

10/15/2014	Document updated with literature review. The following was added to Coverage: Dexamethasone intravitreal implant approved by FDA (i.e., Ozurdex™) may be considered medically necessary for the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery.
07/15/2013	Document updated with literature review. Coverage unchanged; however, statement for fluocinolone acetonide implant was clarified that "posterior uveitis" is of the "posterior segment, including intermediate and posterior uveitis, and panuveitis."
12/01/2011	Document updated with literature review. Coverage now states: 1)A fluocinolone acetonide intravitreal implant approved by the U.S. Food and Drug Administration (i.e., Retisert®) may be considered medically necessary for the treatment of chronic noninfectious posterior uveitis; 2) A dexamethasone intravitreal implant approved by the U.S. Food and Drug Administration (i.e., Ozurdex™) may be considered medically necessary for the treatment of: a) non-infectious ocular inflammation, or uveitis, affecting the posterior segment of the eye, OR b) macular edema following branch or central retinal vein occlusion; c) All other uses of a corticosteroid intravitreal implant are considered experimental, investigational and unproven including but not limited to the treatment of diabetic macular edema. In addition, the policy title was changed from Intravitreal Implants.
06/15/2011	New Medical Document. 1) A fluocinolone acetonide intravitreal implant (e.g., Retisert™) may be considered medically necessary for the treatment of chronic noninfectious posterior uveitis, in one or both eyes, in patients who are intolerant of, refractory to, or not a candidate for systemic corticosteroids. All other indications are considered experimental, investigational and unproven. 2) A dexamethasone intravitreal implant (e.g., Ozurdex®) may be considered medically necessary for the treatment of macular edema with any one of the following: a) Post branch retinal vein occlusion (BRVO), or b) Post central retinal branch occlusion (CRVO). All other indications are considered experimental, investigational and unproven