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Intravitreal Corticosteroid Implants

Summary

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

The evidence for intravitreal corticosteroid implants in individuals who have inflammation or edema of the eye (e.g., noninfectious uveitis, edema following retinal vein occlusion, diabetic macular edema) includes a number of high-quality trials submitted to U.S. Food and Drug Administration (FDA) in support of new technologies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Overall, results have shown a modest improvement in visual outcomes in a relatively small number of patients, with a significantly higher rate of cataracts and increased intraocular pressure (IOP) compared with controls. As a result, one FDA-approved indication for a fluocinolone implant limits treatment to patients who have previously shown an improvement with corticosteroid treatment without an increase in IOP. Overall, intravitreal implants might be considered a reasonable alternative when patients are intolerant or refractory to topical or systemic therapy, in patients for whom systemic steroid-related adverse effects are expected to be more frequent and/or severe than ocular adverse effects, or in patients who have failed to respond to other intravitreal therapies. Given the modest improvement in vision and the potential for adverse events, patients should be informed about the potential for cataracts, increased IOP or hypotony, endophthalmitis, and risk of additional surgical procedures. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

FDA REGULATORY STATUS

In April 2005, Retisert® (fluocinolone acetonide intravitreal implant) received fast-track approval by the U.S. Food and Drug Administration (FDA) as an orphan drug for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. Drugs granted orphan drug status are used to treat rare conditions, defined by the FDA as affecting fewer than 200,000 persons in the U.S. Because of the lack of data on the long-term effects of Retisert®, the FDA required that a postmarketing analysis be conducted. Outcome analyses will be targeting complications associated with cataract extractions, monitoring for delamination of the implants, and assessing the effect of the implant on the corneal endothelium.

Iluvien™ (nonbiodegradable injectable intravitreal implant with fluocinolone acetonide; Alimera Sciences Inc.) received FDA approval in 2014 for the treatment of DME in patients previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.
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A dexamethasone intravitreal implant (Ozurdex™; Allergan, Inc), composed of a biodegradable copolymer of lactic acid and glycolic acid with 0.7 mg micronized dexamethasone, received premarket approval by the FDA in 2009 for the treatment of macular edema following branch or central retinal vein occlusion and in 2010 for the treatment of non-infectious ocular inflammation, or uveitis, affecting the posterior segment of the eye. In 2014, FDA approved Ozurdex® for the treatment of DME for patients who are pseudophakic (have an artificial lens implant) or are phakic and scheduled for cataract surgery.

The FDA analysis notes that the safety and efficacy effects seen with this product are class effects related to steroids. Among other effects, prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. The labeling contains the following warnings and precautions:

"Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex."

Other formulations are also being investigated but are not yet available for the treatment of vitreoretinal disorders in the U.S.

**POLICY STATEMENT**

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

A fluocinolone acetonide intravitreal implant approved by the U.S. Food and Drug Administration may be considered **medically necessary** for the treatment of
- Chronic noninfectious intermediate, posterior, or panuveitis, (i.e., Retisert®) or
- Diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (Iluvien®)

A dexamethasone intravitreal implant approved by the U.S. Food and Drug Administration (i.e., Ozurdex™) may be considered **medically necessary** for the treatment of:
- Non-infectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye, or
- Macular edema following branch or central retinal vein occlusion, or
- Diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery.

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

**POLICY GUIDELINES**

An intravitreal implant may be an acceptable alternative in patients who are intolerant or refractory to other therapies or in patients who are judged likely to experience severe adverse events from systemic corticosteroids. Patients should be informed about the potential adverse effects of a corticosteroid intravitreal implant, including cataracts, increased intraocular pressure or hypotony, endophthalmitis, and risk of need for additional surgical procedures. Because of the differing benefits and risks of treatment with intravitreal implants in comparison with systemic corticosteroid therapy or intraocular injections, patients should make an informed choice between treatments.
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**RATIONALE**

**Noninfectious Posterior Uveitis**

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

In the first (Pivotal) Phase III trial, reported in 2006, 278 patients with noninfectious posterior uveitis were randomly assigned in a 2:3 ratio to receive the 0.59 mg (n=110) or 2.1 mg (n=168) fluocinolone acetonide implant. (6) Pooled results from both doses showed a reduction in recurrence rate in the implanted eye compared with an increase in recurrence in the nonimplanted eye over the pre- and postimplant periods. Improvement of 3 or more lines in visual acuity was seen in significantly more implanted eyes compared with the nonimplanted eyes. An increase in intraocular pressure was seen at week 4 with both doses, (approximately 6 mm Hg) compared with no significant change in intraocular pressure (IOP) in the nonimplanted eyes. Over the 34-week course of the study, increases of 10 mm Hg or more in IOP were seen in 59% of the implanted eyes compared with only 11% of the nonimplanted eyes. Cataracts severe enough to require surgery were more commonly seen in implanted eyes versus nonimplanted eyes (9.9% vs. 2.7%, respectively).

In the second Phase III trial, 239 patients with noninfectious posterior uveitis were randomly assigned to receive fluocinolone acetonide 0.59 mg or 2.1 mg in a 1:1 ratio. (3) A reduction in recurrence rate was seen in the implanted eye over the 34-week study, while an increase in recurrence rate was seen in the nonimplanted eye. There was a greater improvement in visual acuity from baseline in the implanted eye compared with the nonimplanted eye. A reduction in cystoid macular edema was also seen in the implanted eye compared with the nonimplanted eye (69% vs. 23%, respectively). The most commonly reported adverse events (50-90%) in the clinical trials included cataracts, increased intraocular pressure, postprocedural complications associated with implant insertion, and ocular pain. Other ocular adverse events included decreased visual acuity, glaucoma, blurred vision, and abnormal sensation in the eye, eye irritation, and a change in tearing (either increased or decreased). Based on data available at this time, 60% of patients will experience an increase in intraocular pressure sufficient to require drug treatment within 34 weeks of implant; 32% of patients will require filtering procedures within 2 years of implant to control intraocular pressure, and nearly all phakic eyes will develop cataracts and require surgery within 2 years of receiving the implant. (1) In addition, 31% of patients in these studies reported headache.

In 2010, Pavesio and colleagues published 2-year results from a manufacturer-sponsored multicenter (10 European countries and 37 centers) randomized open-label controlled trial of the sustained release fluocinolone acetonide implant (0.59 mg) compared to standard of care. (4) To be included in the study, subjects had to have a 1-year or longer history of recurrent or recrudescent unilateral or asymmetric noninfectious posterior uveitis not associated with significant systemic activity of any underlying disease, with the last episode occurring within 8 months of enrollment; systemic therapy for 1 month or longer; “quiet eyes” at the time of treatment, with either 0.2 mg/kg or more daily prednisolone, or the equivalent of 0.1 mg/kg or more daily prednisolone plus immunosuppressant at the time of randomization. At baseline, more subjects in the standard-of-care group were on tritherapy (8 vs. 4, respectively), indicating greater severity in the control group following randomization. Subjects in the implant group received the implant in 1 eye, followed by tapering of the steroids or other agents over a period of 12 weeks; this 12-week period was excluded from the analysis of implant efficacy to allow tapering of pre-study and postoperative anti-inflammatory therapy. The standard-of-care group received prednisolone or an equivalent corticosteroid (less than 15 mg/day for the average weight), or an immunosuppressive agent combined with a reduced dose of corticosteroid. After 6 months, if the disease was controlled, the treatment doses were tapered according to the standard guideline of each investigational site.
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A total of 146 subjects were enrolled and randomly assigned to implants or standard of care; 6 subjects discontinued before treatment and were excluded from the intention-to-treat population. A total of 131 patients (90%) completed the 2-year visit. Reasons for discontinuation before the 2-year visit included adverse events (n=4), withdrawal of consent (n=1), and loss to follow-up (n=3). Subjects returned to the study site on weeks 1, 4, 8, 12, 18, 24, 30, and 34, then every 3 months from 1–3 years for safety and efficacy assessments. Assessments made at 34 weeks and yearly thereafter included physical examination, medical history, clinical laboratory tests, complete ophthalmic examination, visual field tests, and fluorescein angiography and bilateral fundus photography (masked assessments). In the event of a clinical recurrence, subjects were treated as appropriate, with corticosteroid injections as the preferred first-line therapy.

The primary efficacy outcome was time to first recurrence of uveitis (recurrent inflammation or inferred by use of adjunctive therapy at a level sufficient to reduce the potential for ocular inflammation). In a number of implant subjects, the tapering of anti-inflammatory therapy was insufficient. This led to early imputed or inferred failures, and in some subjects, uveitis medications were increased before the study eye experienced protocol-defined uveitis recurrence. Results were therefore presented as both true recurrences and as the combination of true plus inferred recurrences. When recurrences inferred for reasons not related to protocol-defined ocular inflammation were censored (11 subjects were removed from the at-risk population), Kaplan Meier analysis showed a significant decrease in the time to uveitis recurrence (6.3 months for 12 failures vs. 7.0 months for 44 failures). When all subjects were included in the analysis, the time to uveitis recurrence was not statistically different (p=0.07).

Secondary efficacy outcomes included the percentage of subjects who had at least 1 recurrence, the number of recurrences per subject, the proportion of subjects with a visual acuity improvement greater than 15 letters from baseline, and in a subset of the subjects, whether cystoid macula edema (CME) was present at baseline, the change in the size of the area of CME on fluorescein angiography. The proportion of subjects with a reduction in the area of cystoid macular edema greater than 1 mm² was 12% (29/39) in the standard-of-care group. The proportion of subjects experiencing at least 1 recurrence was lower in the implant group when measured either by true plus inferred recurrence (35% vs. 65%, respectively) or by true recurrences of inflammation (18% vs. 64%, respectively). This indicates that patients in the implant group were more likely to be treated with an increase in medication in the absence of protocol-defined uveitis recurrence. Visual acuity in the standard-of-care group remained consistent over the course of the 2-year study. Visual acuity in the implant group decreased after the surgery and again in the 15- to 18-month interval as a result of cataracts, then returned to baseline levels at 24-months, following extraction of the cataracts (safety outcomes below).

Ocular adverse events considered to be related to treatment were reported in 96% of subjects in the implant group compared with 40% of subjects in the standard-of-care group. Implanted eyes also had a greater number of serious ocular adverse events compared with standard-of-care eyes (91% vs. 24%, respectively). The most commonly reported adverse events in the implant group were cataract and elevated intraocular pressure or glaucoma. Of 66 implanted eyes, 49 (74%) were phakic at 2 years, compared to 57 (77%) of 74 eyes that received standard of care. Of the eyes that were phakic, 90% of implanted eyes and 23% of phakic standard-of-care eyes had a change in lens opacity of 2 grades or more; cataracts were extracted in 88% (43/49) of phakic implanted study eyes in comparison with 19% (11/57) of phakic standard-of-care eyes. Thus, development of cataracts of a severity requiring extraction occurred in 65% of the implanted eyes and 15% of eyes receiving standard of care. During the 2-year follow-up, 55% of implanted eyes had an increase in intraocular pressure of 10 mm Hg or more from baseline compared with 11% of standard-of-care study eyes. Medication was required to control elevated intraocular pressure in 62% of implanted eyes compared with 20% of standard-of-care eyes, while intraocular-pressure-lowering surgery was performed in 21% of implanted eyes compared with 3% of standard-of-care eyes. The incidence of hypotony was significantly higher in implanted eyes (20% vs. 1%, respectively). By the 2-year follow-up visit, 8 eyes (12%) had been explanted: 3 because of hypotony, 2 because of elevated intraocular pressure, and 1 eye each because of scleral thinning; implant extrusion; and postoperative complications. A greater proportion of patients in the implant group had a decrease in visual acuity of 3 lines or more during the 2-year follow-up, 79% in the implanted eyes versus 42% in the standard-of-care eyes. The decrease in visual acuity in implanted eyes was attributed...
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to the implantation procedure at the 1-day post-implantation visit (31% of implanted eyes) and cataract progression (47% of implanted eyes at 18 months). Visual acuity was similar in the two groups following cataract removal. Other serious ocular adverse events in implanted eyes included 3 cases of endophthalmitis (4.5%) compared with none (0%) for standard-of-care eyes. Rates of nonocular adverse events considered to be treatment-related were higher in the standard-of-care group (26% vs. 0%); 3 of the 19 adverse events in the standard-of-care group were considered to be serious (4% of the total standard-of-care group).

The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group reported a National Eye Institute funded randomized comparison of the fluocinolone acetonide intravitreal implant versus systemic anti-inflammatory therapy for intermediate, posterior, and panuveitis in 2011. (5,7,8) Included were 255 patients (479 eyes) randomized to implant or systemic therapy (corticosteroids and corticosteroid-sparing immunosuppressive drugs). Groups were comparable at baseline except for more osteopenia/osteoporosis and poorer visual field sensitivity in the implant group. Over 95% of patients received their assigned therapies. Visual acuity measured by masked examiners was found to improve over 24 months for both groups. Intent-to-treat analysis showed no significant difference between the implant and systemic groups for improvement in visual acuity (+6.0 and +3.2 letters), improvement in vision-related quality of life (+11.4 and +6.8), change in EuroQol-EQ5D health utility (+0.02 and -0.02) or residual active uveitis (12% and 29%), respectively. Control of uveitis was more frequent in the implant group (88% vs. 71%) and fewer had macular edema (20% vs. 34%). Over the 24-month period, implant-assigned eyes had a higher risk of cataract surgery (80% vs. 31%, hazard ratio [HR]: 3.3), treatment for elevated intraocular pressure (61% vs. 20%, HR: 4.2), and glaucoma (17% vs. 4%, HR: 4.2). Patients assigned to systemic therapy had more prescription-requiring infections than patients assigned to implant therapy (0.60 vs. 0.36/person-year) without notable long-term consequences.

Fifty-four month results from the MUST trial were reported in 2015.(7,8) Both groups had an approximate mean improvement of 0.5 lines of vision, which was not statistically significant. By 54 months, approximately 21% of patients in the systemic group had received an implant, typically as rescue therapy. Throughout follow-up, control of inflammation was superior in the implant group (p<0.05), although most eyes in the systemic therapy arm achieved complete control or low levels of inflammation. The proportion of patients who had active uveitis in the implant group ranged from 9% to 16%. For the systemic group, active uveitis was observed in 31% of patients at 24 months and 21% of patients at 54 months. Macular edema was present in about half of the patients in both groups. Cataract and cataract surgery occurred significantly more often in the implant group. IOP elevation also occurred more frequently in the implant group, and that group had more cases of glaucoma (26.3% vs 10.2%) and IOP-lowering surgery (HR=14.4, p<0.001). Potential complications of systemic therapy did not differ between groups. Quality of life and 36-Item Short-Form Health Survey Physical Component Summary scores were modestly superior in the implant group, with a 3.17-point difference on a scale of 100 (p=0.01).

A retrospective review of medical records of all patients receiving fluocinolone acetonide intravitreal implants over an 8-year period at one institution revealed a significant risk of increased IOP requiring glaucoma surgery. (9) Nineteen of 42 eyes (45%) that received implants during the 8-year study period required surgical intervention for glaucoma, with a mean time to IOP-lowering surgery of 14 months after implantation. At 24 months postoperatively, success of IOP-lowering surgery was achieved in 92% of eyes and patients who underwent IOP-lowering surgery had an average 2-line gain in visual acuity measured 3 years after receiving a fluocinolone acetonide intravitreal implant.

**Dexamethasone Intravitreal Implant**

In 2011, investigators from the manufacturer-sponsored multicenter Ozurdex HURON study group (46 study sites in 18 countries) reported safety and efficacy outcomes of a randomized double-masked controlled trial of the dexamethasone intravitreal implant in 229 patients with uveitis. (10) Eyes with noninfectious intermediate or posterior uveitis were stratified by baseline vitreous haze and randomized to a single treatment with a 0.7 mg implant (n=77), 0.35 mg implant (n=76), or sham procedure (n=76). Key exclusion criteria were active ocular disease or infection; uveitis unresponsive to prior corticosteroid treatment; the use of IOP-lowering medications within the last month and a history of glaucoma, ocular
hypertension, or clinically significant IOP elevation in response to corticosteroid treatment; IOP more than 21 mm Hg at baseline; best-corrected visual acuity (BCVA) less than 34 letters in the nonstudy eye; or any uncontrolled systemic disease. Outcomes were measured by an investigator masked to treatment condition at 2, 6, 8, 12, 16, 20, and 26 weeks. At baseline, the mean vitreous haze score was approximately +2 (moderate blurring of the optic nerve head). At 8 weeks after treatment, the proportion of eyes with a vitreous haze score of 0 (no inflammation; primary outcome measure) was 47% with the 0.7 mg implant, 36% with the 0.35 mg implant, and 12% with the sham procedure. The benefit of treatment lasted through the 6-month trial, with 217 patients (95%) included in follow-up. Two patients had discontinued due to adverse events, and 1 patient discontinued because of lack of efficacy. A gain of 15 or more letters from baseline BCVA was seen in more eyes in the implant groups than the sham group at all study visits (about 40% vs. 10%), although the efficacy of the lower 0.35 mg dexamethasone dose began to decline at 4 months after implantation. Use of rescue therapy with systemic immunosuppressive therapy or corticosteroids was based on set criteria and occurred more frequently in the sham than implant groups. For example, at week 26, rescue medication was used in 38% of the sham group and 25% and 22% of the 0.35 and 0.7 mg groups, respectively. The percentage of eyes with intraocular pressure of 25 mm Hg or more peaked at 7.1% for the 0.7 mg implant, 8.7% for the 0.35 mg implant, and 4.2% for the sham group. The incidence of cataract in the phakic eyes was 9 of 62 (15%) with the 0.7 mg implant, 6 of 51 (12%) with the 0.35 mg implant, and 4 of 55 (7%) with the sham procedure. Vision-related functioning, assessed with the National Eye Institute Visual Function Questionnaire–25 (NEI VFQ-25) showed significant improvement with the 0.7-mg implant compared with sham at both 8 weeks (p=0.007) and 26 weeks (p=0.001) (11). The 0.35-mg implant group showed significant improvement compared with sham at 8 weeks (p=0.012) but not at 26 weeks. Interpretation of these results is limited by the higher baseline scores for the sham group.

Section Summary: Noninfectious Uveitis

Retisert has been approved by the Food and Drug Administration (FDA) as an orphan drug for the treatment of chronic noninfectious posterior uveitis. There is strong evidence of efficacy for treatment of noninfectious uveitis with the fluocinolone acetonide implant (Retisert). There are at least 4 multicenter RCTs that have examined the fluocinolone acetonide intravitreal implant. Sham-controlled RCTs support greater efficacy over placebo for posterior uveitis. Open-label RCTs support similar outcomes between systemic therapy and fluocinolone acetonide intravitreal implants for intermediate, posterior, and panuveitis. In all studies, there is a higher risk of cataracts and glaucoma with the implants compared with alternatives. Due to the higher incidence of ocular adverse events, this procedure might be considered a reasonable alternative when patients are intolerant or refractory to systemic therapy, or in patients for whom systemic steroid-related adverse effects are expected to be more frequent and/or severe than the ocular adverse effects.

Ozurdex is approved for the treatment of noninfectious uveitis affecting the posterior segment of the eye. This dexamethasone implant has been studied in a single multicenter, double-masked RCT in patients with intermediate or posterior uveitis, which showed a significant increase in the percentage of patients who gained 15 or more letters compared with sham treatment.

Macular Edema Following Retinal Vein Occlusion

In 2015, the American Academy of Ophthalmology published a technology assessment of therapies for macular edema associated with central retinal vein occlusion (CRVO). (12) They identified 4 clinical trials that provided level I evidence supporting the use of antivascular endothelial growth factor (anti-VEGF) pharmacotherapies and 2 clinical trials providing level I evidence for intravitreal corticosteroid injection with the dexamethasone intravitreal implant or triamcinolone. Evidence on the safety and efficacy of other reported interventions was of lesser strength. The assessment noted that evidence on long-term efficacy of corticosteroid treatments is limited and that intravitreal corticosteroids led to a higher frequency of adverse events, including cataract and IOP elevation compared with anti-VEGF treatments.
There was limited information on combination therapy with anti-VEGF and corticosteroids compared with monotherapy.

A Bayesian network meta-analysis of the efficacy and safety of treatments for macular edema secondary to branch retinal vein occlusion (BRVO) was published in 2015.(13) A total of 8 RCTs (1743 patients) were included, treated with ranibizumab given as needed, aflibercept monthly, dexamethasone implant, laser photocoagulation, ranibizumab plus laser, or sham intervention. The probability of being the most efficacious treatment, based on letters gained, or for a gain 15 letters or more, was highest for monotherapy of anti-VEGF treatments (30%-54% probability), followed by ranibizumab plus laser, and lowest (0%-2% probability) for the dexamethasone implant, laser, or sham. Treatment with ranibizumab resulted in an increase of an average 8 letters compared with the dexamethasone implant. Patients treated with the dexamethasone implant had statistically significant higher rates of ocular hypertension than patients given anti-VEGF monotherapy (odds ratio, 13.1).

**Fluocinolone Acetonide Implant:** No randomized controlled trials were identified with the fluocinolone acetonide implant for the treatment of macular edema following retinal vein occlusion.

**Dexamethasone Intravitreal Implant:** Evidence on the dexamethasone intravitreal implant for the treatment of macular edema following retinal vein occlusion includes 3 randomized controlled trials, 2 of which were sham-controlled.

Data presented to the FDA for the dexamethasone intravitreal implant (Ozurdex™) were from two 6-month double-masked multicenter studies that took place at 167 clinical sites in 24 countries. (14,15) A 6-month open-label extension of these 2 trials was reported in 2011.(16) A total of 1,267 patients who had clinically detectable macular edema associated with either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) were enrolled. The mean visual acuity at baseline was about 54 letters (20/80) and the mean central retinal thickness was approximately 550 microns. About 75% of the patients had macular edema for a duration of more than 3 months. Patients were randomized to a single treatment with a 0.7 mg dexamethasone implant (n=427), 0.35 mg dexamethasone implant (n=414), or sham control (n=426). The sham procedure included anesthetic and surgical preparation, with a needleless applicator placed against the conjunctiva to simulate the placement of study medication. The primary outcome measure for the first trial was the proportion of eyes achieving a 10- to 15-letter improvement from baseline. The primary outcome measure for the second trial, as requested by the FDA, was the time to reach a 15-letter improvement (3 lines) from baseline BCVA. Secondary outcome measures included the proportion of eyes exhibiting loss of equal to or greater than 15 letters from baseline and central subfield retinal thickness measured by optical coherence tomography (OCT).

For the combined trial data, the time to achieve a treatment response of equal to or greater than 15 letters' improvement was faster with the intravitreal implant, meeting the prespecified outcome. There was no significant difference in the proportion of patients who had improved by equal to or greater than 15 letters at 6-month follow-up. The proportion of sham-treated patients who achieved equal to or greater than 15 letters improvement was 7.5% at day 30, 11.3% at day 60, and 17.6% at day 180. The proportion of patients who achieved equal to or greater than 15 letters improvement with the 0.7 mg dexamethasone implant was 21.3% at day 30, 29.3% at day 60, and 21.5% at day 180. Thus, the maximal improvement in visual acuity gain compared to sham (e.g., 29.3% vs. 11.3% at day 60) was observed in the first months of treatment. By day 180, the proportion of sham-treated patients who achieved equal to or greater than 15 letters improvement approached that of the dexamethasone-treated group (17.6% for sham vs. 21.5% for dexamethasone 0.7 mg). The dexamethasone implant also resulted in a decrease in central subfield retinal thickness at day 90 (208 microns vs. 85 microns, respectively) but not at day 180 (119 microns vs. 119 microns, respectively) compared to sham-treated eyes. There was a small, but statistically significant decrease in the percentage of eyes with loss of equal to or greater than 15 letters throughout the study. For example, at 180 days, the percentage of eyes with a loss of equal to or greater than 15 letters was 6% for the dexamethasone 0.7 mg group and 11% for the sham-treated group. Although retinal neovascularization was decreased (0.7% vs. 2.6%, respectively), the overall incidence of ocular adverse events was higher with the dexamethasone implant (62%) than the sham group (43%). There were significant increases in eye pain (7.4% vs. 3.8%), ocular hypertension (4% vs. 0.7%), and anterior chamber cells (1.2% vs. 0% - all respectively). In patients who
were retreated with the 0.7 mg dexamethasone implant after the initial 180-day study, 25% of patients had an increase in intraocular pressure.

In the open-label extension phase, patients in both the implant and sham-control groups who completed the 6-month double-masked phase could receive a 0.7 mg dexamethasone implant if BCVA was less than 84 letters or retinal thickness was greater than 250 microns. At day 180, 997 patients received a dexamethasone implant, of which 341 received a second implant. Another 199 patients entered into the open-label phase of the study for follow-up without receiving further treatment. The primary outcome at 12 months was safety and results were analyzed for all patients according to the treatment received. Cataract progression over the 12 months occurred in 90 of 302 phakic eyes (29.8%) that received 2 implants in comparison with 31 of 296 eyes (10.5%) that received a single implant and 5 of 88 sham-treated phakic eyes (5.7%). Increases in IOP tended to be transient but increased to 35 mm Hg or more in about 15% of eyes at 60 days after implantation. A 15-letter or more improvement in BCVA was found in 30% of patients at 60 days after the first implant and 32% of patients at 60 days after the second dexamethasone implant. With the exception of cataract progression, the efficacy and safety of receiving 2 implants was similar to the efficacy and safety of 1 dexamethasone implant.

The dexamethasone intravitreal implant (0.35 or 0.7 mg) has been compared with observation for the treatment of persistent macular edema in patients with diabetic retinopathy, BRVO and CRVO, uveitis, or Irvine-Gass Syndrome (postcataract surgery macular edema) in a U.S. Phase II multicenter trial. The primary inclusion criteria was that the patient had persistent macular edema that had persisted for 90 days or more after laser treatment or medical therapy; randomization was stratified by the underlying cause of the macular edema. The study included 172 patients with diabetic retinopathy, 60 patients with BRVO, 42 patients with CRVO, 14 patients with uveitis, and 27 patients with Irvine-Gass Syndrome. Both the 0.35 mg and 0.7 mg dexamethasone implants increased the proportion of patients meeting the primary outcome of an improvement in visual acuity of equal to or greater than 10 letters at 90 days (24.3% and 35.2%, respectively) versus 13.3% of patients in the observation group. As in the FDA trial described above, the effect was reduced at 180 days (24.3% and 32.4% with the 0.35 mg and 0.7 mg dexamethasone implants vs. 21% for observation, respectively; p=0.06). Anterior chamber flare and increased intraocular pressure were more frequent in the dexamethasone implant group. Subgroup analysis indicated that the efficacy results were similar across the different diseases. Additional subgroup analysis from the 2007 trial was reported in 2009 and 2010. Additional

In a randomized trial from 2014, Pichi et al. found that the combination of an Ozurdex implant plus macular grid laser increased both visual acuity and the time interval between repeated Ozurdex injections. In other small trials, Maturi et al found no benefit for visual acuity with a combination of dexamethasone plus bevacizumab, while Gado et al found similar visual acuity outcomes when testing Ozurdex® versus bevacizumab.

Section Summary: Macular Edema Following Retinal Vein Occlusion
No RCTs were identified with fluocinolone acetonide implants. Ozurdex is approved for the treatment of macular edema following BRVO and CRVO. Evidence for these indications includes 3 RCTs, 2 of which were sham-controlled. The time to improved vision was faster with the implant, which met the prespecified outcome, but there were no differences between treatment groups at the 6-month time point.

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

Retisert®

In 2011, Pearson et al. reported 3-year efficacy and safety results from an industry-sponsored study of the fluocinolone acetonide intravitreal implant in 196 eyes with persistent or recurrent diabetic macular edema. (24) All affected eyes had undergone focal/grid laser photocoagulation at least 12 weeks before enrollment. Patients were randomized 2:1 to receive the 0.59-mg Retisert implant or standard of care (SOC; additional laser as needed after 6 months, n=69). Follow-up by masked examiners was performed on day 2 and then on weeks 1, 3, 6, 12, 26, 39, and 52 and then every 13 weeks for 3 years. The primary efficacy outcome, a 15 letter or greater improvement in BCVA at 6 months (prior to any additional laser treatment), was achieved in 16.8% of implanted eyes versus 1.4% of SOC eyes. Between 6 and 24 months there was a trend toward a higher proportion improved in the implant group (did not attain statistical significance on some of the follow-up visits), and during the third year there was no significant difference between the groups (e.g., 31.1% of implanted eyes versus 20.0% of SOC eyes improved ≥15 letters at 3 years). The proportion of eyes with no evidence of retinal thickening was greater in the implant group through 2 years, but not at 3 years post-implantation (about 40% in both groups at 3 years). More patients in the implant group showed improvement of 1 grade on the 12-grade Diabetic Retinopathy Severity Scale (roughly 30% vs. 20% for SOC), but there were no significant differences in the proportion of patients who improved by more than 1 grade (about 10% in both groups). There was a higher rate of treatment-related ocular adverse events in the implant group (100% vs. 88.4%). The most frequent adverse events in implanted eyes were elevated IOP (69.3% vs. 11.6%), worsening cataract (55.9% vs. 21.7%), vitreous hemorrhage (40.2% vs. 18.8%), pruritis (38.6% vs. 21.7%), and abnormal sensation in the eye (37.0% vs. 11.6%). IOP of 30 mm Hg or more at any time during follow-up was recorded in 61.4% of implanted eyes versus 5.8% of SOC eyes, and 33.8% of implanted eyes required surgery for ocular hypertension. In 3 eyes (2.4%) the implant was removed to relieve IOP. Of phakic eyes, 20% of SOC eyes had cataract extraction compared to 91% with a fluocinolone acetonide implant.

Iluvien®

The FAME study group reported the efficacy and safety of 2 doses of fluocinolone acetonide intravitreal inserts (ILUVIEN®) in 2 pivotal industry-sponsored multicenter, double-masked, randomized sham-controlled trials. (25) A total of 956 patients with persistent DME (at least 1 previous macular laser treatment) were randomized 1:2:2 to sham injection (n=185), low-dose insert (0.2 mg/day, n=375), or high-dose insert (0.5 mg/day, n=393). Patients were eligible for rescue laser after 6 weeks and could be given additional study drug or sham injections after 1 year. Follow-up visits were performed at 1 week, 6 weeks, and 3 months, and then every 3 months thereafter. The primary outcome, the percentage of patients with improvement from baseline BCVA of 15 letters or more at 24 months, was significantly greater in the low- and high-dose insert groups (28.7% and 28.6%, respectively) compared with the sham group (16.2%). A final BCVA of 20/40 was achieved in 31% to 33% of patients in the insert groups compared with 22% in the sham group. Foveal thickness less than 250 μm was attained by a greater percentage of patients in the low- and high-dose groups (51% and 47%, respectively) compared with the sham group (40%), while more patients in the sham group received focal/grid laser therapy after study entry (58.9% vs 36.7% and 35.2%). The authors reported an increase in IOP (not defined) in 3.25% of the implant groups and 0% of the sham group. However, the package insert indicates that there was an IOP elevation of 10 mm Hg or more from baseline in 34% of patients who received an ILUVIEN® insert compared with 10% of controls. Surgery for glaucoma was performed in 3.7% and 7.6% of the low- and high-dose inserts, respectively, compared with 0.5% of the sham groups. More patients in the insert groups required cataract surgery. Of phakic eyes, 23.1% had cataract surgery compared with 74.9% and 84.5% in the low- and high-dose groups, respectively. The low dose insert has received FDA approval for the treatment of DME.

Three-year results from the FAME study were reported in 2012. (26) The percentage of patients who gained 15 letters or more using the last observation carried forward was 28.7% (low dose) and 27.8% (high dose) compared with 18.9% in the sham group. When only the patients who remained in the trial at
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36 months were included (about 70% follow-up), the percentage of patients who gained 15 letters or more was 33.0% and 31.9% (low and high dose, respectively) compared with 21.4% for controls. Masked grading of diabetic retinopathy showed improvement of 2 steps or more in the Early Treatment Diabetic Retinopathy Study retina of a similar percentage of patients in the high-dose group compared with the sham group (8.9% vs. 10.1%, respectively), with a slightly higher percentage (13.7%) in the low-dose group. At 36 months, there was no significant difference in mean foveal thickness between the high-dose and sham groups, and a statistically significant difference between the low-dose and sham patients (29 microns) of uncertain clinical significance. Cataract surgery was performed in 80.0% of phakic patients in the low-dose group and 87.2% of the high-dose group compared with 27.3% of the sham group. The occurrence of laser or incisional glaucoma surgery by 36 months was 6.1% in the low-dose group and 10.6% in the high-dose group compared with 0.5% of the sham group. Planned subgroup analysis showed greater efficacy in patients with chronic (≥3 years) compared with nonchronic (<3 years) DME. (27) Specifically, the percentage of patients with who gained 15 letters or more was significantly greater in patients with chronic DME compared with sham (34.0% vs 13.4%, p<0.001), but not in patients with nonchronic DME (22.3% vs 27.8%). The improvement in visual acuity was not associated with an improvement in anatomic measures in the chronic DME group. Adverse event rates did not differ between the chronic and subchronic groups.

Dexamethasone Intravitreal Implant

*Dexamethasone Intravitreal Implant Compared With Sham* Three-year results from 2 pivotal industry-sponsored, multicenter, double-masked Phase 3 trials (NCT00168389 and NCT00168337) with Ozurdex® were published in 2014. (28) A total of 1048 patients with DME were randomized to treatment with a 0.7 mg or 0.35 mg Ozurdex® 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. Patients with a loss of 15 letters or more in BCVA were exited from the study, with the last observation carried forward for the primary outcome measure of the percentage of patients with a 15-letter or greater improvement in BCVA. The 3-year completion rate was 57.9% of patients, with only 43.4% of patients in the sham group completing the study due to lack of efficacy. Completion rates for the dexamethasone groups were 64.1% and 66.3% for 0.7 and 0.35 mg, respectively.

Compared with sham treatment, the 0.7 mg and 0.35 mg dexamethasone implants led to improved visual acuity in a significantly higher percentage of patients, and a greater mean decrease in central retinal thickness (see Table). Notably, the difference in the percentage of Ozurdex® and sham treated patients who achieved greater than 15-letter improvement in BCVA ranged from about 6% to 10%, with a number needed to treat (NNT) of 9.8 patients to provide 1 patient with at least 15 letters of improvement with the 0.7 mg implant. IOP increased by 10 mm Hg or more in about 1/4 of patients treated with the corticosteroid implant. The occurrence of cataract surgery was more than 3-fold higher for Ozurdex® than sham, with about 2/3 of patients requiring cataract surgery. (Ozurdex® is indicated only for pseudophakic patients or phakic patients scheduled for cataract surgery).

<table>
<thead>
<tr>
<th>Treatments Received over 3 years</th>
<th>Ozurdex® 0.7 mg</th>
<th>Ozurdex® 0.35 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15-letter Improvement (percentage of patients)</td>
<td>22.2%**</td>
<td>18.4%*</td>
<td>12%</td>
</tr>
<tr>
<td>Baseline CRT (microns)</td>
<td>463.0</td>
<td>466.8</td>
<td>460.9</td>
</tr>
<tr>
<td>Reduction in CRT (microns)</td>
<td>-111.6**</td>
<td>-107.9**</td>
<td>-41.9</td>
</tr>
<tr>
<td>Increase in IOP ≥10 mm Hg (percentage of patients)</td>
<td>27.7%</td>
<td>24.8%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>
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| Cataract Adverse Events (percentage of patients) | 67.9% | 64.1% | 20.4% |

*p=0.018; **p<0.001; CRT: Central retinal thickness; IOP Intraocular pressure

Dexamethasone Intravitreal Implant Compared With Anti-VEGF

The BEVORDEX study was a Phase II randomized comparison of bevacizumab versus dexamethasone implant for the treatment of DME. (29) Forty-two eyes were randomized to bevacizumab every 4 weeks and 46 eyes were randomized to receive a dexamethasone implant every 16 weeks PRN (pro re nata). After 12 months of treatment, the improvement in BCVA of 10 letters or more was similar for the 2 groups (40% of the bevacizumab-treated eyes and 41% of the dexamethasone-treated eyes). The dexamethasone implant reduced central macular thickness to a greater extent than bevacizumab (187 vs 122 microns; p=0.015), but led to a greater number of adverse events including IOP elevation of 10 mm Hg or more (19.6% vs 0%), cataracts (13% vs 4.8%) and vision decrease of more than 10 letters (10.9% vs 0%) at 12 months. Other studies have shown an increase in cataracts predominantly in the second year of treatment with the dexamethasone implant. (28)

Dexamethasone Intravitreal Implant Plus Anti-VEGF

Maturi et al reported a small (N=40 eyes) single-masked, randomized trial of Ozurdex plus bevacizumab compared to bevacizumab alone. (30) At 12 months, there was no significant difference between the groups in visual acuity, with an improvement of 5.4 letters for the combined group and 4.9 letters for the monotherapy group. The monotherapy group received a mean of 9 injections of bevacizumab, which was similar to a mean of 6 injections of bevacizumab plus 2.1 injections with Ozurdex for the combined treatment group. Treatment with Ozurdex led to a greater mean reduction in central subfield thickness (difference, 69 μm; p=0.03). Drug-related adverse events were higher in the combined treatment group, with IOP elevation (>21 mm Hg) in 6 eyes and worsening of cataracts in 9 eyes. This compared with 1 instance of IOP elevation in the bevacizumab monotherapy group.

Dexamethasone Intravitreal Implant Plus Laser Photocoagulation

The PLACID study group reported a multicenter, double-masked, RCT (N=253) that compared Ozurdex plus combination laser photocoagulation to sham plus laser photocoagulation for the treatment of diabetic macular edema. (31) The percentage of patients who gained 10 letters or more 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%). More patients in the laser-alone group discontinued the study due to lack of efficacy (8.7% vs 0.8%), which may have biased results. An increase in IOP of at least 10 mm Hg was observed in 15.2% of eyes treated with Ozurdex. In addition, cataract-related adverse events were more common after treatment with Ozurdex (22.2% vs 9.5%, p=0.017).

Section Summary: Diabetic Macular Edema

Retisert is not approved by FDA for this indication. This fluocinolone acetonide implant was compared with focal/grid laser photocoagulation in a single (investigator)-masked RCT. The primary efficacy outcome, at least a 15-letter improvement in BCVA at 6 months, was significantly improved, but there was no significant difference between the groups at 3 years. An IOP of 30 mm Hg or more was observed in 61.4% of implanted eyes versus 5.8% of eyes treated with SOC, and 33.8% of implanted eyes required surgery for ocular hypertension. Due to the marginal benefit and substantial increase in adverse events with this fluocinolone acetonide 0.59-mg implant, it is not indicated for DME.

ILUVIEN has been approved for DME in patients previously treated with corticosteroids who did not have a clinically significant rise in IOP. Approval of the ILUVIEN 0.19-mg implant was based on 2 multicenter,
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double-masked, RCTs with 2 doses of fluocinolone acetonide. As with the other indications, the benefit for vision was modest. The lower dose had similar efficacy to the high-dose implant, with a reduction in adverse events. There was an IOP elevation in 34% of patients who received this implant compared with 10% of controls, leading to the restricted indication.

Ozurdex has been approved for DME. Results from the pivotal FDA-regulated trials that evaluated the dexamethasone implant for DME showed modest benefit compared with sham (number needed to treat, 9.8) with a significant increase in adverse events. There was at least a 10 mm Hg increase in IOP in about 25% of study participants and a 3-fold increase in cataracts. Smaller trials comparing the dexamethasone implant to laser photocoagulation or bevacizumab also reported modest benefits for visual acuity, with an increase in adverse events.

Age-Related Macular Degeneration

Dexamethasone Intravitreal Implant

In 2015, the ERIE Study Group published a single-masked, sham-controlled, multicenter trial on the use of a dexamethasone intravitreal implant as adjunctive therapy to treat age-related macular edema. (32) All patients (n=243) in this industry-sponsored study received 2 ranibizumab injections, with the next injection given as needed based on established study criteria. The primary efficacy end point was the ranibizumab injection-free interval. Ozurdex increased the injection interval based on Kaplan-Meier survival analysis (p=0.016). A small, but statistically significant percentage of patients did not require rescue ranibizumab over the 6-month study period (8.3% vs 2.5%, p=0.048). There was a very small reduction in the mean number of as-needed ranibizumab injections over the 6 months of the study (3.15 vs. 3.37), but patients in the Ozurdex group received an additional injection of the implant. There were no significant differences between the groups in mean change from baseline BCVA. More patients in the Ozurdex group had increased IOP (13.2% vs 4.2%; p=0.014), but there were no differences between the groups in cataract-related events.

Other

There are reports of corticosteroid implants being investigated for a variety of other disorders of the eye, including radiation retinopathy, macular edema related to retinitis pigmentosa, vasoproliferative retinal tumors, idiopathic macular telangiectasia type 1, postoperative macular edema, Irvine-Gass Syndrome, Coat disease, circumscribed choroidal hemangioma, age-related macular degeneration, proliferative vitreoretinopathy, rhegmatogenous retinal detachment, and anterior scleritis. (33)

Adverse Events

In 2013, Kiddee et al conducted a systematic review of IOP following intravitreal corticosteroid administration. (34) The review included 7 studies on the fluocinolone intravitreal implant and 6 studies on the dexamethasone implant. Meta-analysis of ocular hypertension with intravitreal corticosteroid implants was conducted using a threshold of a 10 mm Hg rise from baseline or an IOP greater than 21 mm Hg for fluocinolone or 25 mm Hg or more for dexamethasone. Pooled analysis found a rise in IOP in 65.9% of patients with a fluocinolone 0.59-mg implant and 10.9% of patients with a dexamethasone 0.7-mg implant. Most cases of ocular hypertension can be controlled medically.

In addition to the common occurrence of an increase in IOP and development of cataracts, several rarer adverse events have been reported. These include fracture and/or desegmentation of the implant, implant migration into the anterior chamber, and inadvertent injection of the implant into the crystalline lens. Anterior chamber migration may be particularly problematic in vitrectomized eyes, and has led to corneal edema necessitating corneal transplantation. (33)

Summary of Evidence

The evidence for intravitreal corticosteroid implants in individuals who have inflammation or edema of the eye (eg, noninfectious uveitis, edema following retinal vein occlusion, diabetic macular edema) includes a number of high-quality trials submitted to U.S. Food and Drug Administration (FDA) in support of new
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Technologies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Overall, results have shown a modest improvement in visual outcomes in a relatively small number of patients, with a significantly higher rate of cataracts and increased intraocular pressure (IOP) compared with controls. As a result, one FDA-approved indication for a fluocinolone implant limits treatment to patients who have previously shown an improvement with corticosteroid treatment without an increase in IOP. Overall, intravitreal implants might be considered a reasonable alternative when patients are intolerant or refractory to topical or systemic therapy, in patients for whom systemic steroid-related adverse effects are expected to be more frequent and/or severe than ocular adverse effects, or in patients who have failed to respond to other intravitreal therapies. Given the modest improvement in vision and the potential for adverse events, patients should be informed about the potential for cataracts, increased IOP or hypotony, endophthalmitis, and risk of additional surgical procedures. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Ongoing and Unpublished Trials
An online search of ClinicalTrials.gov in March 2016 identified a large number of small trials with intravitreal corticosteroid implants.

Practice Guidelines and Position Statements
In 2011, the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) provided guidance on the use of the dexamethasone intravitreal implant for macular edema secondary to retinal vein occlusion. (35) The dexamethasone implant is recommended as an option for the treatment of macular edema following central retinal vein occlusion. It is recommended as an option for the treatment of macular edema following branch retinal vein occlusion when treatment with laser photocoagulation has not been beneficial, or if laser photocoagulation is not considered suitable because of the extent of macular hemorrhage.

In 2015, NICE provided guidance on the dexamethasone intravitreal implant for treating diabetic macular edema. (36) Ozurdex is recommended as a possible treatment for diabetic macular edema if there is an artificial lens and the edema either has not improved with non-corticosteroid treatment or non-corticosteroid treatment is not considered suitable.

In November 2013, NICE replaced technology appraisal (TA) guidance 271 (January 2013) with TA 301, concluding that the fluocinolone acetonide intravitreal implant (Iluvien) is recommended as an option for treating chronic diabetic macular edema that is insufficiently responsive to available therapies only if:

- The implant is to be used in an eye with an intraocular (pseudophakic) lens and
- The manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme. (37)

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

Medicare National Coverage
There is no national coverage decision.

REFERENCES
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POLICY HISTORY

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<th>Date</th>
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| June 2012  | New Policy | Policy updated with literature review, references added, Rewording of policy investigational policy statement and removal of Iluvien™:  
             |            | "All other uses of a corticosteroid intravitreal implant are considered investigational, including but not limited to the treatment of diabetic  
             |            | macular edema" from "The use of a corticosteroid intravitreal implant (i.e. Iluvien™) is considered investigational, for the treatment of diabetic 
             |            | macular edema.                                                                                                                                 |
| June 2013  | Update Policy | Policy updated with literature review, adding references 15, 20 and 22, Policy statements unchanged.                                             |
| June 2014  | Update Policy | Policy updated with literature review through September 18, 2014; references 16-17, 22-23, 25, and 27 added; policy statements updated to include medically necessary statements for Iluvien and Ozurdex for diabetic macular edema. |
| September 2016 | Update Policy | Policy updated with literature review; references 7-8, 11-13, 30-32, 34 and 36 added. Policy statements unchanged.                           |