Clinical Policy Bulletin: Fluocinolone Acetonide Intra-vitreal Implant (Retisert and Iluvien)

Number: 0719

Policy

Aetna considers the Retisert (fluocinolone acetonide intravitreal implant) medically necessary for the treatment of chronic non-infectious uveitis (including birdshot chorioretinopathy) affecting the posterior segment of the eye in persons who do not respond to or are intolerant to conventional treatment (i.e., failed corticosteroid or immunosuppressive therapy).

Aetna considers Iluvien (fluocinolone acetonide intravitreal implant) medically necessary for the treatment of diabetic macular edema in persons who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Aetna considers fluocinolone acetonide intravitreal implant experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Anterior uveitis
- Inflammatory vitreoretinopathy
- Intermediate (pars planitis) uveitis
- central retinal vein occlusion
- Serpiginous choroiditis
- Sympathetic ophthalmia

See also CPB 0795 - Ozurdex (Dexamethasone Intravitreal Implant)

Background
Uveitis, an intra-ocular inflammatory disease, entails a large group of inflammatory diseases involving the iris, the ciliary body and the uvea. It is a significant cause of visual impairment. Multiple causes can be responsible for ocular inflammation that can result either from infectious or autoimmune disease. Uveitis can be classified by the location of inflammation: (i) anterior uveitis, (ii) posterior uveitis, (iii) intermediate uveitis, and (iv) panuveitis (diffused). The most common causes of posterior uveitis or panuveitis are Behcet's disease, toxoplasmosis, and Vogt-Koyanagi-Harada syndrome (Chung and Choi, 1989; Khairallah et al, 2004).

The incidence of uveitis varies from 14 to 28 per 100,000. According to the anatomical classification, about 30 to 60 % (average 47 %) are related to anterior uveitis; 6 to 30 % (average 21 %) are posterior uveitis; 7 to 15 % (average 12 %) are intermediate uveitis; and 7 to 69 % (average 20 %) are panuveitis. A specific diagnosis can be established in more than 70 % in most series (Guex-Crosier, 1999).

Corticosteroids represent the mainstay of short-term medical therapy for ocular inflammation, especially in children (Hesselink et al, 2004). They can be administered systemically or via periocular injections. Song (2004) noted that corticosteroids are usually included in 1st-line therapy for the treatment of posterior uveitis because of its rapid onset of action and favorable safety profile; and systemic immunosuppressive agents also play an important role in the management of this condition. Immunosuppressive agents take several weeks for their full effect and are considered when long-term therapy is anticipated. When long-term therapy is anticipated, immunosuppressants may be added. This approach allows for the reduction and eventual discontinuation of treatment with corticosteroids. Combination therapy of various immunosuppressive agents may decrease relapse rate, however, immunosuppressants can be associated with serious side effects, and requires careful monitoring. Moreover, the role of new therapeutic approaches in the treatment of uveitis such as anti-tumor necrosis factor alpha treatment or immunosuppression with drugs including tacrolimus, sirolimus, and interleukin-2 receptor antibodies is being investigated (Efthimiou and Markenson, 2005). Furthermore, chlorambucil, a cytotoxic alkylating anti-neoplastic agent, has been reported to be a safe and effective alternative for preserving vision in patients with otherwise treatment resistant (i.e., systemic steroids and immunomodulatory therapy) uveitis (Miserocchi et al, 2002).

Uveitis often requires long-term medical therapy. In a pilot study, Tanner et al (1998) examined the safety and effectiveness of posterior, sub-Tenon's steroid injections (PSTSI) in the treatment of posterior and intermediate uveitis. A total of 28 PSTSI injections (40 mg triamcinolone) were given and the results analyzed with a 6 month prospective follow-up in 13 cases. These investigators concluded that PSTSI significantly decreases cystoid macular edema, with a corresponding increase in visual acuity, in patients with posterior uveitis. Also, systemic immunosuppression may be reduced or discontinued with the avoidance of associated systemic side effects, and the technique has a high level of patient acceptability. This is in agreement with the findings of Lafranco Dafflon et al (1999) who reported that PSTSI (n = 53 with 162 injections of 40 mg triamcinolone) are very effective in restoring visual acuity in patients with chronic uveitis of the posterior segment, without systemic complications. However, this
benefit was attained at the expense of intra-ocular hypertension, a complication that was found more frequently than expected. Mean duration of follow-up was 448 +/- 57 days.

Menezo et al (2005) evaluated the visual outcome and corticosteroid dose requirement in patients with non-infectious uveitis affecting the posterior segment treated with corticosteroids and additional second-line immunosuppression. Seventy-two patients (141 eyes) with uncontrolled non-infectious uveitis on systemic prednisolone were treated with at least one second-line immunosuppressive agent in addition to systemic prednisolone and followed for at least 3 months. At the end of the follow-up period (mean of 55.5 months), 70 eyes (49.6 %) had visual acuity of 6/9 or better. There was a reduction in the mean maintenance dose of prednisolone required before the introduction of the second-line agent (19 mg/day +/- 2 SE) when compared to the mean maintenance dose of prednisolone at the end of the data collection (9 mg/day +/- 1 SE; p < 0.001). There was also a significant reduction in the number of disease relapses requiring an increase in prednisolone dose after starting the second-line agents as compared to the year before (p < 0.02). These investigators concluded that in patients with uveitis affecting the posterior segment, the addition of all second-line immunosuppressive therapy was effective in allowing reduction of the dose of systemic prednisolone to 10 mg/day or less, in controlling intraocular inflammation, reducing the number of relapses and in maintaining vision. Because of their side-effects, immunosuppressive treatment should be individualized and monitored closely but its addition is beneficial in the short and longer term.

An intra-vitreal implant that can deliver fluocinolone acetonide to posterior eye tissue for up to 3 years has been developed recently (Retisert, Bausch & Lomb Inc., Rochester, NY). Retisert is the world's first intra-vitreal drug implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye, which affects an estimated 175,000 people in the United States. This sight-threatening inflammatory disease primarily affects people between the ages of 20 and 50. In May 2000, the Retisert was granted fast-track status by the United States Food and Drug Administration (FDA) and in July 2000 it received Orphan Drug designation from the FDA for posterior uveitis. On April 11, 2005, the FDA approved the single-indication orphan drug Retisert (fluocinolone acetonide intra-vitreal implant) for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

The FDA’s approval of Retisert was based on results from two randomized, double-masked, multi-center clinical studies demonstrating that in eyes treated with Retisert there was: (i) a statistically significant decrease in the recurrence of uveitis from approximately 40 to 54 % for the 34-week period pre-implantation to approximately 7 to 14 % for the 34-week period post-implantation; (ii) a statistically significant decrease in the use of adjunctive therapy including systemic corticosteroid and/or immunosuppressive therapy from approximately 47 to 63 % at the time of implantation to approximately 5 to 10 % at 34 weeks post-implantation, (iii) a statistically significant decrease in patients needing periocular corticosteroid injections from about 50 to 65 % for the 34 week period pre-implantation to approximately 3 to 6 % for the 34 week period post-implantation; and (iv) statistically significant improvement of 3 or more lines of visual acuity in approximately 19 to 21 % of treated eyes at 34 weeks post-implantation.
In a randomized controlled trial (n = 32), Jaffe et al (2005) examined the safety and effectiveness of a fluocinolone acetonide intra-vitreal implant in the treatment of patients with a history of recurrent non-infectious posterior uveitis. Patients were randomized to receive either a 0.59-mg or a 2.1-mg fluocinolone acetonide intra-vitreal implant. They were observed every 4 to 6 weeks for the first 3 months and then every 3 months thereafter. Main outcome measures were pre-operative and post-operative ocular inflammation, visual acuity (VA), anti-inflammatory medication use, and safety. Mean follow-up duration was 683 +/- 461 days (range of 204 to 1,817). The average number of recurrences in the 12 months before implantation was 2.5 episodes per eye. None of these eyes experienced a recurrence for the first 2 years after implantation. There was a reduction in systemic and local therapy use in the device-implanted eyes. Of the patients who remained on systemic medication after implantation, nearly 70% had a reduced dosage by the 1st year of study, and 85% by 2nd year (reduced dosage is defined as a reduction of dosage and/or a discontinuation of a medication for patients on combination therapy). The posterior sub-Tenon's capsule injection rate significantly decreased from a mean of 2.2 injections per eye per year to 0.07 injections per eye per year (p < 0.0001). The most common adverse event was increases in intra-ocular pressure (IOP). At baseline, 11.0% of eyes used pressure-lowering agents, versus 56.1% over the follow-up period (p = 0.005). There were no device explantations or patients lost to follow-up during the investigation. These investigators concluded that the fluocinolone acetonide intra-vitreal implant effectively controlled intra-ocular inflammation in the studied population. Elevated IOP and cataracts that occurred in fluocinolone device-implanted eyes were managed by standard means. The fluocinolone acetonide sustained drug delivery implant seems to be promising in patients with posterior uveitis who do not respond to or are intolerant to conventional treatment.

In a randomized, controlled, phase IIb/III, open-label, multi-center trial, Pavesio et al (2010) assessed the safety and effectiveness of Retisert compared with standard therapy in subjects with non-infectious posterior uveitis (NIPU). Subjects with unilateral or bilateral NIPU (n = 140) received either a 0.59 mg Retisert (n = 66) or standard of care (SOC; n = 74) with either systemic prednisolone or equivalent corticosteroid as monotherapy (greater than or equal to 0.2 mg/kg daily) or, if judged necessary by the investigator, combination therapy with an immunosuppressive agent plus a lower dose of prednisolone or equivalent corticosteroid (greater than or equal to 0.1 mg/kg daily). Main outcome measure was time to first recurrence of uveitis. Eyes that received Retisert experienced delayed onset of observed recurrence of uveitis (p < 0.01) and a lower rate of recurrence of uveitis (18.2% versus 63.5%; p < or = 0.01) compared with SOC study eyes. Adverse events frequently observed in implanted eyes included elevated IOP requiring IOP-lowering surgery (occurring in 21.2% of implanted eyes) and cataracts requiring extraction (occurring in 87.8% of phakic implanted eyes). No treatment-related non-ocular adverse events were observed in the implant group, whereas such events occurred in 25.7% of subjects in the SOC group. The authors concluded that Retisert provided better control of inflammation in patients with uveitis compared with systemic therapy.

In a retrospective, non-comparative case series, Mahajan et al (2009) examined if the Retisert implant can achieve control of inflammation and a reduced need for
oral corticosteroids or immunosuppressives in patients with sympathetic ophthalmia (SO). A total of 8 patients with active SO were included in this study, and were followed-up for a period of 6 months to 2 years. Main outcome measures included presence or absence of intra-ocular inflammation, VA, IOP, need for further surgery, and the need for additional use of oral or locally injected corticosteroids and/or immunosuppressives. All patients demonstrated a significant reduction in the systemic medication needed to maintain control of inflammation. Two patients had recurrent inflammatory episodes requiring the resumption of an oral immunosuppressive. Vision was improved or stabilized in all 8 patients. The authors concluded that the fluocinolone acetonide implant provides inflammatory control and reduces the dependence on systemic immunosuppression in patients with SO. These findings need to be validated by well-designed studies.

Vogt-Koyanagi-Harada (VKH) disease is a multi-system disorder, characterized by the T-cell-mediated autoimmune process directed against melanocytic antigens in the ocular, nervous, auditory and integumentary systems. The ocular hallmarks of the disease involve severe bilateral panuveitis associated with exudative retinal detachment. In an interventional case series study, Khalifa and colleagues (2009) described the use of Retisert in 2 patients with VKH disease requiring high-dose systemic corticosteroid therapy to control their inflammation and bilateral serous retinal detachments. Upon tapering of systemic corticosteroids, 1 patient had recurrent serous retinal detachments and the other patient's anterior chamber and vitreous inflammation returned. The authors concluded that their experience with Retisert in VKH has been mixed with an inability to fully taper off of systemic corticosteroids.

The most common adverse events associated with the implantation of Retisert include eye pain, procedural complications, cataract progression, which is managed by standard cataract surgery, and IOP, which is managed with the use of IOP-lowering eye drops or filtering surgery. Contraindications for Retisert include viral diseases of the cornea and conjunctiva, ocular mycobacterial and fungal infections of the eye, and hypersensitivity to ingredients or other corticosteroids.

In a retrospective, multi-center, interventional case study, Rush and colleagues (2011) assessed outcomes in birdshot chorioretinopathy following intra-vitreal implantation of a fluocinolone acetonide-containing drug delivery device. A total of 22 HLA-A29+ birdshot patients (36 eyes) were implanted with a sustained-release corticosteroid device and followed for up to 3 years. Main outcome measures were Snellen acuity, intra-ocular inflammation, adjunctive therapy, cataract, ocular hypertension, or glaucoma. Paired Wilcoxon statistics were used to analyze VA; paired McNemar statistics were employed to analyze presence or absence of other outcomes. Nineteen of 22 patients (32 eyes) completed 12 months of follow-up with improvement in median VA (p = 0.015). Prior to implantation, 18 of 22 patients (82 %) received immunosuppressive therapy versus 1 of 19 (5 %) by 12 months (p < 0.001). Eyes with zero vitreous haze increased from 7 of 27 scored eyes (26 %) at baseline to 30 of 30 eyes (100 %) by 12 months (p < 0.001). Cystoid macular edema was reduced from 13 of 36 eyes (36 %) at baseline to 2 of 32 eyes (6 %) at 12 months (p = 0.006). Five of 24 phakic eyes at baseline exited the study before surgery; all other eyes received cataract surgery. One hundred
percent of study eyes had ocular hypertension, required IOP-lowering therapy, or had glaucoma surgery by 12 months. The authors concluded that implantation of a fluocinolone acetonide-containing intra-ocular device in patients with birdshot chorioretinopathy can improve vision, control inflammation, and eliminate systemic therapy.

In an interventional case-series study, Hu and colleagues (2011) reported their experience of using Retisert in the treatment cystoid macular edema (CME) resulting from immune recovery uveitis (IRU) in 2 acquired immunodeficiency syndrome (AIDS) patients with a history of cytomegalovirus (CMV) retinitis. Medical records were reviewed of 2 patients who received Retisert implantation in 3 eyes for IRU-associated inflammation and CME. Suppression of CMV disease was achieved with oral medication in 1 patient and with simultaneous implantation of a ganciclovir implant in the other patient. Following Retisert implantation in 3 eyes in AIDS patients on HAART, improvement in CME was seen in 2 eyes. No CMV re-activation was detected during the several-month follow-up period. The authors concluded that Retisert may be an effective treatment for CME in AIDS patients with IRU re-activation and a history of CMV retinitis. Results of this case-series study need to be validated by further investigation.

Jain et al (2012) evaluated long-term visual outcomes and adverse events from a FA sustained drug delivery implant in eyes with chronic macular edema from central retinal vein occlusion (CRVO). A total of 24 eyes of 23 subjects with vision loss associated with chronic macular edema from CRVO. The primary outcome measure was mean Early Treatment of Diabetic Retinopathy Study (ETDRS) VA letter score at 36 months after implantation. Secondary outcome measures included number of subjects with greater than or equal to 10-letter improvement in ETDRS letter score, central foveal thickness (CFT), total macular volume, and IOP. At 1, 2, and 3 years after implantation, mean VA showed gains of 4.5 (p = 0.52), 8.2 (p = 0.07), and 3.4 (p = 0.64) letters, respectively, and 32 %, 56 %, and 50 % of study eyes, respectively, showed at least a 10-letter gain in ETDRS score. At these same time points, mean CFT improved by 247 (44 %; p = 0.002), 212 (38 %; p < 0.001), and 250 μm (45 %; p < 0.001), respectively. During the study period, all phakic eyes ultimately underwent cataract extraction, and 5 eyes underwent glaucoma surgery. The authors concluded that the FA drug delivery system provided sustained VA and anatomic benefit in patients with macular edema from CRVO, and it has promise as a therapeutic option for selected patients with this condition. The main complications were cataract and elevated IOP.

Kiernan and Mieler (2012) noted that DME, CME, age-related macular degeneration (ARMD), retinal vascular occlusion (RVO) and uveitis are responsible for severe visual impairment worldwide. In some patients with these conditions, treatment with intra-ocular corticosteroids may be beneficial. Although off-label use of these agents has occurred for many years, novel agents including preservative-free and sustained-release intra-vitreal implants are currently being studied in clinical trials (CTs). These investigators reviewed the use of CTs for vitreo-retinal (VR) diseases including choroidal neovascularization, CME, DME, RVO and posterior uveitis. They also discussed the use of corticosteroids for treating VR disease, including dexamethasone, FA, intravitreal implants and
triamicinolone acetonide. Used alone, intra-vitreal corticosteroids may benefit disorders such as DME, RVO and uveitis compared with standard therapy. Cases of exudative ARMD non-responsive to standard treatment may benefit from combination therapy, including usage of intra-vitreal corticosteroid injections. Intra-operative use of these agents may aid visualization of retinal structures. Sustained-release intra-ocular implants have been approved for posterior uveitis and RVO associated with macular edema. In spite of this, most intra-ocular corticosteroids have a limited duration of action along with significant side effects, including cataract and glaucoma. Currently, intra-vitreal corticosteroid usage for DME is considered off-label.

Furthermore, an UpToDate review on "Prevention and treatment of diabetic retinopathy" (Fraser and D'Amico, 2012) states that "Intravitreal triamcinolone injection (IVTA) is an option for ME of any cause. Injection of 4 mg of triamcinolone acetonide produces a rapid reduction in macular thickness, often within days, and with a several line gain in visual acuity. However, the treatment response in diabetic ME is transient. As a result, repeated injections are necessary, but these responses are also transient and adverse effects may be seen .... Intravitreal and retinal implants have been designed to deliver glucocorticoids over an extended time frame. The use of these implants is associated with even higher rates of cataract formation and glaucoma than IVTA injection. In the aggregate, the above findings have diminished the enthusiasm for IVTA as monotherapy for chronic ME. IVTA in combination with photocoagulation has been associated with a higher rate of sustained visual improvement than IVTA alone in some studies, but not in others. Larger clinical trials are required to clarify whether there is a role for IVTA with photocoagulation for the management of diabetic macular edema".

Tlucek and associates (2012) reviewed the effect of the fluocinolone acetonide implant in subjects with autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV), an inherited autoimmune uveitis. A retrospective case series was assembled from patients with ADNIV who received fluocinolone acetonide implants. Visual acuity and features of ADNIV, including inflammatory cells, neovascularization, fibrosis, and CME, were reviewed. Nine eyes of 5 related patients with ADNIV with uncontrolled inflammation were reviewed. Follow-up ranged from 21.7 to 56.7 months. Visual acuity at implantation ranged from 20/40 to hand motion. Pre-operatively, 8 eyes had vitreous cells (a 9th had diffuse vitreous hemorrhage). Eight eyes had CME, 7 had an epi-retinal membrane, and 3 had retinal neovascularization. Following implantation, vitreous cells resolved in all eyes and neovascularization regressed or failed to develop. Central macular thickness improved in 4 eyes. During the post-operative course, however, VA continued to deteriorate, with VA at the most recent examination ranging from 20/60 to no light perception. There was also progressive intra-ocular fibrosis and phthisis in 1 case. Four eyes underwent cataract surgery. Six of the 7 eyes without previous glaucoma surgery had elevated IOP at some point, and 3 of these required glaucoma surgery. The authors concluded that the fluocinolone acetonide implant may inhibit specific features of ADNIV such as inflammatory cells and neovascularization, but does not stabilize long-term vision, retinal thickening, or fibrosis. All eyes in this series required cataract extraction, and more than 50 % required surgical intervention for glaucoma. They stated that
further studies may identify additional therapies and any benefit of earlier implantation.

In a comparative case-series study, Arcinue et al (2013) evaluated the safety and effectiveness of the fluocinolone acetonide (Retisert) implant compared with the dexamethasone (Ozurdex) implant in patients with non-infectious uveitis. A total of 27 eyes received either the fluocinolone acetonide (FA) (n = 16) or dexamethasone (n = 11) implant. Chart review of patients at the Massachusetts Eye Research and Surgery Institution (MERSI) was done and patients were selected and matched according to age, sex, and type of uveitis. Eyes that received either the FA or dexamethasone implant, with follow-up ranging from 6 months to 2 years, were included. Main outcome measure was the recurrence rate of uveitis after implantation. There were no significant differences in the baseline demographic characteristics. The majority of cases were idiopathic panuveitis, with 36.4 % and 31.3 % of eyes in the Ozurdex and Retisert groups, respectively. Recurrence rates of uveitis were 1.7 and 0.5 per 100 person-months in the Retisert and Ozurdex groups, respectively, with Retisert-implanted eyes 3.16 times more at risk of recurrence; however, this difference was not statistically significant (p = 0.41). No significant differences were seen in terms of improvement in inflammatory score and best-corrected visual acuity (BCVA). The median survival time for a 2nd implant was 13 and 28 months for the Ozurdex and Retisert groups, respectively (p = 0.0028). Eyes with the Ozurdex were 5 times more likely to receive a 2nd implant (p = 0.02). No eyes in the Ozurdex group needed additional glaucoma medications, surgery, or laser compared to 44 % of eyes in the Retisert group. Eyes with the Retisert implant had a statistically higher rate of having more glaucoma medications, surgery, or laser (p = 0.02). In the Ozurdex group, 50 % of phakic eyes at baseline had cataract progression and subsequent surgery compared with 100 % of Retisert phakic eyes. Eyes with the Retisert implant are 4.7 times more at risk of cataract progression (p = 0.04). The authors concluded that the dexamethasone (Ozurdex) implant seems comparable to the fluocinolone acetonide (Retisert) implant in preventing recurrence of non-infectious uveitis and in improving inflammation and BCVA. However, there were higher rates of cataract progression and need for glaucoma medications, laser, and surgery with the Retisert implant.

Diabetic macular edema, the primary cause of vision loss associated with diabetic retinopathy, is a disease affecting the macula, the part of the retina responsible for central vision (Alimera Sciences, 2014). When the blood vessel leakage of diabetic retinopathy causes swelling in the macula, the condition has progressed to diabetic macular edema. Duration of diabetes is the greatest risk factor for increased retinopathy and is associated with an increased prevalence of diabetic macular edema. The appearance of retinopathy is associated with an upregulation of vascular endothelial growth factor (VEGF) causing an increase in permeability of vessels leading to leakage of fluid. As retinopathy worsens, an up-regulation of multiple cytokines (inflammatory factors) takes place. Corticosteroids offer a broad effect on down regulation of multiple cytokines associated with diabetic macular edema that persists.

Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg is a sustained release intravitreal implant approved by the FDA to treat diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did
not have a clinically significant rise in intraocular pressure (Alimera Sciences, 2014). Each Iluvien implant is designed to release submicrogram levels of fluocinolone acetonide for 36 months. The Iluvien approval was based on clinical trial data that showed that at month 24 after receiving the Iluvien implant, 28.7 percent of patients (p value .002) experienced an improvement from baseline in their best corrected visual acuity on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart of 15 letters or more. Patients treated with Iluvien experienced a statistically significant improvement in visual acuity compared to the control group by week three of follow up, and maintained a statistically significant advantage over the control through completion of the trial at month 36.

Iluvien is injected in the back of the patient's eye with an applicator that employs a 25-gauge needle, which allows for a self-sealing wound (Alimera Sciences, 2014). In the FAME Study, a phase 3 clinical study of Iluvien, the most frequently reported adverse drug reactions included cataract development and increased ocular pressure. Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. The labeling of Iluvien states that 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. The implant may migrate into the anterior chamber if the posterior lens capsule is not intact. The labeling advises patients to have follow-up eye examinations at appropriate intervals following treatment with Iluvien.

In 2 randomized, sham injection-controlled, double-masked, multi-center clinical trials, Campochiaro et al (2012) evaluated the long-term safety and effectiveness of intra-vitreal inserts releasing 0.2 μg/day (low-dose) or 0.5 μg/day (high-dose) fluocinolone acetonide (FAc) in patients with diabetic macular edema (DME). Subjects with persistent DME despite greater than or equal to 1 macular laser treatment were randomized 1:2:2 to sham injection (n = 185), low-dose insert (n = 375), or high-dose insert (n = 393). Subjects received study drug or sham injection and after 6 weeks were eligible for rescue laser. Based on re-treatment criteria, additional study drug or sham injections could be given after 1 year. Main outcome measures included percentage of patients with improvement of greater than or equal to 15 letters from baseline. Secondary outcomes included other parameters of visual function and foveal thickness. At month 36, the percentage of patients who gained greater than or equal to 15 in letter score using the last observation carried forward method was 28.7 % (low-dose) and 27.8 % (high-dose) in the FAc insert groups compared with 18.9 % (p = 0.018) in the sham group, and considering only those patients still in the trial at month 36, it was 33.0 % (low-dose) and 31.9 % (high-dose) compared with 21.4 % in the sham group (p = 0.030). Pre-planned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported duration of DME greater than or equal to 3 years at baseline; the percentage who gained greater than or equal to 15 in letter score at month 36 was 34.0 % (low- dose; p < 0.001) or 28.8 % (high-dose; p = 0.002) compared with 13.4 % (sham). An improvement greater than or equal to 2 steps in the Early Treatment Diabetic Retinopathy Study retinopathy scale occurred in 13.7 % (low-dose) and 10.1 % (high-dose) compared with 8.9 % in the sham group. Almost all phakic patients in the FAc insert groups developed cataract, but their visual benefit after cataract surgery was similar to
that in pseudophakic patients. The incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group and 8.1% in the high-dose insert group. The authors concluded that in patients with DME FAc inserts provide substantial visual benefit for up to 3 years and would provide a valuable addition to the options available for patients with DME.

The National Institute for Health and Clinical Excellence’s clinical practice guideline on “Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy” (NICE, 2013) stated that “Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema 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.”

CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

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

**HCPCS codes covered if selection criteria are met:**

J7311  Fluocinolone acetonide, intravitreal implant [Retisert]

**ICD-9 codes covered if selection criteria are met:**

363.00 - Focal chorioretinitis and focal retinochoroiditis
363.08

363.10 - Disseminated chorioretinitis and disseminated retinochoroiditis
363.15

363.20  Chorioretinitis, unspecified [birdshot chorioretinopathy]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

360.11  Sympathetic uveitis [sympathetic ophthalmia]
362.07  Diabetic macular edema
362.35  Central retinal vein occlusion
362.53  Cystoid macular degeneration
362.83  Retinal edema
363.54  Central choroidal atrophy, total [serpiginous choroiditis]
364.00  Acute and subacute iridocyclitis, unspecified
364.01 Primary iridocyclitis
364.02 Recurrent iridocyclitis
364.03 Secondary iridocyclitis, infectious
364.04 Secondary iridocyclitis, noninfectious
364.10 Chronic iridocyclitis, unspecified
364.11 Chronic iridocyclitis in diseases classified elsewhere
364.21 Fuchs' heterochromic cyclitis
364.23 Lens-induced iridocyclitis
364.24 Vogt-Koyanagi-Harada disease
364.3 Unspecified iridocyclitis [anterior uveitis]

Other ICD-9 codes related to the CPB:
360.12 Panuveitis

The above policy is based on the following references:


34. Alimera Sciences, Inc. Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg for intravitreal injection. Atlanta, GA: Alimera Sciences; revised September 2014.