Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

Plan: Aetna Better Health
Policy Number: 0719
Policy Name: Fluocinolone Acetonide Intra-vitreal Implant (Retisert, Yutiq and Iluvien)

Type of Submission – Check all that apply:

☐ New Policy
☒ Revised Policy*
☐ Annual Review – No Revisions
☐ Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

CPB 0719 Fluocinolone Acetonide Intra-vitreal Implant (Retisert, Yutiq and Iluvien)

This CPB has been revised to state that Yutiq (fluocinolone acetonide 0.18 mg intravitreal implant) is considered medically necessary for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. The CPB title has been updated to include Yutiq.

Name of Authorized Individual (Please type or print):
Dr. Bernard Lewin, M.D.

Signature of Authorized Individual:

Revised July 22, 2019

Proprietary
Fluocinolone Acetonide Intra-vitreal Implant (Retisert, Yutiq and Iluvien)

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers Retisert (fluocinolone acetonide intravitreal 0.59 mg implant) and Yutiq (fluocinolone acetonide intravitreal 0.18 mg 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).

Retisert and Yutiq (fluocinolone acetonide intravitreal implant) are contraindicated and considered not medically necessary for members with active ocular or periocular infections.

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.

Iluvien (fluocinolone acetonide intravitreal implant) therapy is not considered...
medically necessary for members with the following contraindications:

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

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
- Uveitic glaucoma

See also CPB 0795 - Ozurdex (Dexamethasone Intravitreal Implant) (0795.html).

**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 an intravitreal 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. Retisert is available at a 0.59 mg fluocinolone acetonide intravitreal implant.

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.

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 diabetic macular edema (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 triamcinolone 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.
On October 16, 2018, the FDA approved Yutiq, an intravitreal 0.18 mg fluocinolone acetonide implant for patients with chronic noninfectious posterior uveitis by EyePoint Pharmaceuticals. The implant is supplied in a sterile single-dose preloaded injector that can be administered in an office setting. Yutiq is intended to prevent uveitis flares by releasing 0.18 mg of fluocinolone acetonide over a period of 3 years. The drug is housed within proprietary nonbioerodible drug delivery technology (i.e., Durasert) that has also been utilized Iluvien, Retisert and Vitrasert. The approval was based on data from 2 randomized, multicenter, sham-controlled, double-masked phase 3 clinical trials with up to 3 years of follow-up (NCT01694186 and NCT02746991). Both studies met primary endpoints, demonstrating significantly lower rates of uveitis recurrence compared with sham at 6 and 12 months. Overall, the insert was well tolerated. Mean IOP increased by 2 mmHg in the treatment group, and did not change within the sham group. Cataract surgery was performed in 18% of patients receiving Yutiq and 8.6% for sham.

Jaffe et al (2019; NCT01694186) state to assess the safety and efficacy of an intravitreal fluocinolone acetonide (FA) insert to manage inflammation associated with chronic noninfectious posterior uveitis. Multicenter, randomized, prospective, doubled-masked, sham-controlled, 3-year phase 3 clinical trial. One hundred twenty-nine participants with recurrent noninfectious posterior uveitis were assigned randomly to FA insert (n = 87) or sham injection (n = 42). The more severely affected eye in participants with bilateral disease was designated as the study eye. The insert (FA, 0.18 mg) was injected into the vitreous cavity; sham injection mimicked the insert delivery procedure. Ophthalmic examinations, OCT, and ocular tolerability and discomfort assessments were conducted; study visits were on days 7 and 28 and months 2, 3, 6, 9, and 12. Uveitis recurrence was treated as needed. The 6-month recurrence rate was the primary outcome measure. The 6-month (28% and 91%) and 12-month (38% and 98%) uveitis recurrence rates were significantly lower (P < 0.001) with FA insert vs. sham, respectively. Fewer recurrences per study eye (mean, 0.7 vs. 2.5), lower incidence of 15-letter or more decrease in best-corrected visual acuity (14% vs. 31%), and reduced systemic (19% vs. 40%) and local (7% vs. 62%) uveitis adjunctive treatments were observed with FA insert vs. sham, respectively. Of the 42 FA study eyes that were phakic at baseline, 14 (33%) required cataract surgery during the first 12 months of the study. Over the same period, 1 phakic sham injection eye (5%) required cataract surgery. Post hoc analysis showed a significant increased risk for cataract development among study eyes treated with FA insert compared with those treated with sham injection (33% vs. 12%, respectively; odds ratio, 3.7; P < 0.01). Intraocular
pressure-lowering treatment use was similar between groups. No deaths, treatment-related study discontinuations, or unanticipated safety signals were observed through 12 months. The authors concluded that chronic noninfectious posterior uveitis was managed successfully in this study population; FA insert eyes experienced fewer uveitis recurrence episodes, required fewer adjunctive treatments, and demonstrated less visual acuity loss compared with sham eyes. The FA insert treatment group showed higher rates of cataract; delivery by injection was not associated with an increase in ocular adverse events or any other safety measures not typically associated with local steroid use, suggesting the procedure is appropriate for an office setting. Study limitations include enrollment of participants without severe active inflammation at the time of the initial study treatment and lack of stratification by uveitis etiology. Evaluation of the therapeutic effect of FA insert in uveitic eyes with more significant active ocular inflammation than that included in the current study and in the uveitis subset stratified by anatomic location, cause, or both likely would yield additional useful information to the practicing clinician, particularly considering the ceiling effect for possible visual acuity improvements based on BCVA letters gained, a constraint that likely disproportionately affected the FA insert treatment group.

**Diabetic macular edema**

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. Diabetic macular edema occurs when blood vessels in the retina of patients with diabetes begin to leak into the macula, the part of the eye responsible for detailed central vision. These leaks cause the macula to thicken and swell, progressively distorting acute vision. 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.
Diabetic macular edema occurs when blood vessels in the retina of patients with diabetes begin to leak into the macula, the part of the eye responsible for detailed central vision. These leaks cause the macula to thicken and swell, progressively distorting acute vision.

Diabetic macular edema is classified into 2 types:

- **Focal macular edema**: caused by vascular abnormalities (primarily microaneurysms), which tend to leak fluid.
- **Diffuse macular edema**: caused by dilated capillaries in the retina.

Treatment options currently available for the treatment of diabetic macular edema include photocoagulation (laser therapy), intravitreal corticosteroid injections, intravitreal anti-vascular endothelial growth factor agents (VEGF) and intravitreal corticosteroid implants.

Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg is a sustained release intravitreal implant approved by the FDA to treat 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 available as a non-bioerodable intravitreal implant containing 0.19 mg fluocinolone acetonide in a sustained-release drug delivery system. 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. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. The implant may migrate into the anterior chamber if the posterior lens capsule is not intact. Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber. The labeling advises patients to have follow-up eye examinations at appropriate intervals following treatment with Iluvien.

Safety and effectiveness of Iluvien in pediatric patients has not been established. Iluvien is contraindicated in patients with ocular or periocular infections, glaucoma with a cup to disc ratio of greater than 0.8 and known hypersensitivity to fluocinolone acetonide or any components of the product.

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 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.”

Kempen and colleagues (2017) noted that a randomized clinical trial comparing fluocinolone acetonide implant versus systemic corticosteroids and immunosuppression for treatment of severe non-infectious intermediate, posterior, and panuveitides did not result in a significant difference in VA at 2 and 4.5 years; longer-term outcomes are not known. These researchers compared the association between intra-vitreous fluocinolone acetonide implant versus systemic therapy and long-term visual and other outcomes in patients with uveitis. This study was a no pre-specified 7-year observational follow-up of the Multicenter Uveitis Steroid Treatment (MUST) randomized clinical trial. Follow-up was conducted in tertiary uveitis sub-specialty practices in the United States (21), the United Kingdom (1), and Australia (1). Of 255 patients 13 years or older with intermediate, posterior, or panuveitis (active within less than or equal to 60 days) enrolled in the MUST trial between December 6, 2005, and December 9, 2008, 215 consented to ongoing follow-up through at least 7 years post-randomization (last visit, February 10, 2016). Participants had been randomized to receive a surgically placed intra-vitreous fluocinolone acetonide implant or systemic corticosteroids supplemented by immunosuppression. When both eyes required treatment, both eyes were treated. Primary outcome was change from baseline in BCVA in uveitic eyes (5 letters = 1 VA chart line; potential range of change in letters read, -121 to +101; minimal clinically important difference, 7 letters), analyzed by treatment
assignment accounting for non-independence of eyes when patients had 2 uveitic eyes. Secondary outcomes included potential systemic toxicities of corticosteroid and immunosuppressive therapy and death; 7-year data were obtained for 161 uveitic eyes (70 % of 90 patients assigned to implant) and 167 uveitic eyes (71 % of 90 patients assigned to systemic therapy) (77 % women; median age at enrollment, 48 [interquartile range [IQR], 36 to 56] years). Change in mean VA from baseline (implant, 61.7; systemic therapy, 65.0) through 7 years (implant, 55.8; systemic therapy, 66.2) favored systemic therapy by 7.2 (95 % confidence interval [CI]: 2.1 to 12) letters. Among protocol-specified, prospectively collected systemic adverse outcomes, the cumulative 7-year incidence in the implant and systemic therapy groups, respectively, was less than 10 %, with the exceptions of hyperlipidemia (6.1 % versus 11.2 %), hypertension (9.8 % versus 18.4 %), osteopenia (41.5 % versus 43.1 %), fractures (11.3 % versus 18.6 %), hospitalization (47.6 % versus 42.3 %), and antibiotic-treated infection (57.4 % versus 72.3 %). The authors concluded that in 7-year extended follow-up of a randomized trial of patients with severe intermediate, posterior, or panuveitis, those randomized to receive systemic therapy had better VA than those randomized to receive intra-vitreous fluocinolone acetonide implants. Study interpretation was limited by loss to follow-up.

Vogt-Koyanagi-Harada Disease

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.

Heo and colleagues (2016) examined the safety and effectiveness of fluocinolone acetonide intravitreal implant in patients with Vogt-Koyanagi-Harada disease. They carried out a post-hoc, subgroup analysis on patients with Vogt-Koyanagi-Harada using data sets from 2 multi-center randomized trials on fluocinolone acetonide

implant. Each subject received fluocinolone acetonide implantation in 1 eye and standard-of-care treatment in the fellow eye and was followed for 3 years. A total of 30 patients (mean age of 38.5 years) were included. The cumulative rate of uveitis recurrence for 3 years was significantly reduced in implanted eyes compared with fellow eyes (33 % versus 87 %; p < 0.001). The reduction of daily corticosteroid dose was well-maintained (12.8 mg before implantation versus 3.7 mg after implantation; p = 0.001), but final vision was similar to pre-operative vision in the implanted eyes (p = 0.082) and in the fellow eyes (p = 0.187). Post-operative elevation of IOP was more frequent in the implanted eyes than in the fellow eyes (70 % versus 20 %; p < 0.001). Cataract progression occurred in all phakic implanted eyes. The authors concluded that fluocinolone acetonide intravitreal implant reduced uveitis recurrence rate and the dosage of systemic corticosteroid and immunosuppressant requirement in patients with Vogt-Koyanagi-Harada. However, they stated that cataract and IOP elevation developed frequently. The clinical benefits of fluocinolone acetonide intravitreal implant in patients with Vogt-Koyanagi-Harada disease needs to be further investigated.

**Vitrectomized Eyes with Diabetic Macular Edema**

Meireles and colleagues (2017) stated that limited data are available on the effectiveness of the 0.2 μg/day fluocinolone acetonide (FAc) implant in eyes with prior vitrectomy. In a retrospective study involving 6 centers from 4 European countries, these researchers presented a collection of 26 vitrectomized eyes treated with the 0.2 μg/day FAc implant. They analyzed the safety and effectiveness data from patients (26 eyes from 25 patients) with DME and a prior vitrectomy that had been treated with one 0.2 μg/day FAc implant. Prior intravitreal therapies included anti-VEGF (mean of 3.8 injections) and steroids (mean of 1.9 injections). Pars plana vitrectomy (PPV) was performed in these eyes primarily for abnormalities of vitreo-retinal interface, followed by proliferative diabetic retinopathy and vitreous hemorrhage. The 0.2 μg/day FAc implant was injected 24.2 months, on average, after PPV and the mean duration of follow-up after injection was 255 days (range of 90 to 759 days). The mean change in BCVA was +11.7 ETDRS letters (range of -19 to +40 letters; p < 0.0004) and the mean change in CFT was -233.5 μm (range of -678 to 274 μm; p < 0.0001). The mean change in IOP from baseline at the last visit was +1.4 mm Hg (range of -9 to +8 mm Hg; p = 0.0090); 8 eyes initiated or continued IOP lowering medications. The authors concluded that these data suggested the 0.2 μg/day FAc implant is effective in vitrectomized
patients with an acceptable safety profile. Moreover, they stated that further studies are needed to confirm the current findings and to evaluate the effect of the 0.2 μg/day FAc implant over a longer period of follow-up.

The authors noted that the main drawback of this study related to the collection and reporting of retrospective data with a relatively small number of patients (n = 25) and short period of follow-up (mean of 255 days) post-therapy with Iluvien. Another drawback was the reporting of non-standardized data, which were collected in real-life clinical practice. However, sustained, and statistically significant, therapeutic effects were observed in this small cohort over a 2-year period and appeared to be consistent with results reported in larger randomized controlled trials (RCTs). They stated that future studies should consider whether the difference in biochemical composition of the vitreous in vitrectomized eyes and non-vitrectomized eyes affects the pharmacokinetic profile of Iluvien and consequently its effectiveness. Another area of interest is to examine if PPV enhances the performance of Iluvien when performed after Iluvien, and therefore at any stage in the disease process, as has been described by Kumar et al. These investigators stated that this study described the most clinically significant cohort of vitrectomized eyes treated with a 0.2 μg/day FAc implant. Results showed there were statistically significant improvements in VA and a concurrent decrease of the macular edema. The current study is important as the FAME trial excluded patient eyes with prior vitrectomy and so the real-life data are now needed. This lack of the data and clinical need mean that there is no consensus on how to use DME therapies to manage vitrectomized eyes with DME, and there is no treatment pathway on to guide physicians. Hence, current real-life practice data are revealing how these eyes are being managed now but also informing future best practice.

Uveitic Glaucoma

Zivney and colleagues (2016) noted that glaucoma is a known complication of uveitis, and may require glaucoma tube shunt implantation for IOP control. The success of glaucoma tube shunt (Ahmed) implantation in the setting of a local ocular steroid depot in uveitic glaucoma remains unknown. These researchers examined if patients who underwent combined Ahmed implantation and fluocinolone acetonide (Retisert) implantation have superior outcomes compared to patients with Ahmed implants only in the setting of uveitic glaucoma. All participants were studied retrospectively and underwent Ahmed implantation alone or with existing/concurrent Retisert implantation (combined group) at a single
academic institution. The main outcome measures were IOP, VA, number of IOP-lowering medications, and adverse events (AEs) at 6 months after Ahmed implantation. Secondary outcome measures included AEs and surgical success at 6 months after Ahmed implantation. Mean IOP at 6 months after Ahmed implantation was 15.3 ± 4.8 and 15.1 ± 4.9 mm Hg in the Ahmed only group (n = 17) and the combined group (n = 17), respectively (p = 0.89). The mean number of IOP-lowering medications at 6 months after Ahmed implantation was 1.7 ± 1.0 and 1.8 ± 1.0 in the Ahmed only group and the combined group, respectively (p = 0.86). Mean VA at 6 months after Ahmed implantation was 0.35 ± 0.29 and 0.42 ± 0.33 log mean angle of resolution in the Ahmed only group and the combined group, respectively (p = 0.50). No significant differences in surgical success or AEs were noted between the 2 groups. The authors concluded that at 6 months, no significant differences in mean IOP, mean number of IOP-lowering medications, VA, surgical success, or AEs were noted between Ahmed implantation alone or combined Ahmed and Retisert implantation in patients with uveitic glaucoma. These investigators stated that further studies with larger sample sizes, longer follow-up, and prospective evaluation may provide more insight into patient outcomes after Ahmed implantation with or without the presence of a Retisert implant.

Appendix

For the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye:

Retisert (0.59 mg fluocinolone acetonide): Surgically insert 1 implant tablet into the posterior segment of the affected eye. The implant releases fluocinolone acetonide at an initial rate of 0.6 mcg/day, decreasing over the first month to 0.3 to 0.4 mcg/day at steady state, and lasting approximately 30 months. If there is a recurrence of uveitis after the implant is depleted, the implant may be replaced.

Yutiq (0.18 mg fluocinolone acetonide): Inject 1 implant intravitreally. Monitor the patient for elevated intraocular pressure and endophthalmitis. The implant is designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day, and lasting 36 months.

For the treatment of diabetic macular edema:
Iluvien (0.19 mg fluocinolone acetonide): Inject 1 implant (containing 0.19 mg fluocinolone acetonide) intravitreally. Monitor the patient for elevated intraocular pressure and endophthalmitis. The implant is designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day, and lasting 36 months.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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### Fluocinolone Acetonide Intra-vitreal Implant (Retisert, Yutiq and Iluvien)

#### Medical Claims

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

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A54.30 - A54.39 | Gonococcal infection of eye                   |

A71.0 - A71.9  | Trachoma                                       |

B02.30 - B02.39 | Zoster oculardisease                         |

B30.0 - B30.9  | Viral conjunctivitis                         |

H00.011 - H00.19 | Hordeolum andchalazion                     |

H01.001 - H01.029 | Blepharitis                                  |

H01.00A - H01.02B | Unspecified blepharitis                     |

H01.01A - H01.01B | Ulcerative blepharitis                      |

H01.02A - H01.02B | Squamous blepharitis                        |

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H04.301 - H04.39 | Acute and unspecified inflammation of lacrimal passages |
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Iluvien:

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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]
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ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **H20.00** Unspecified acute and subacute iridocyclitis
- **H20.011** Primary iridocyclitis
- **H20.019** Primary iridocyclitis
- **H20.021** Recurrent acute iridocyclitis
- **H20.029** Recurrent acute iridocyclitis
- **H20.031** Secondary infectious iridocyclitis
- **H20.039** Secondary infectious iridocyclitis
- **H20.041** Secondary noninfectious iridocyclitis
- **H20.049** Secondary noninfectious iridocyclitis
- **H20.10 - H20.13** Chronic iridocyclitis
- **H20.20 - H20.23** Lens-induced iridocyclitis
- **H20.811** Fuchs' heterochromic cyclitis
- **H20.819** Fuchs' heterochromic cyclitis
- **H20.821** Vogt-Koyanagi syndrome
- **H20.829** Vogt-Koyanagi syndrome
- **H20.9** Unspecified iridocyclitis
- **H31.22** Choroidal dystrophy
- **H34.8110** Central retinal vein occlusion
- **H34.8192** Central retinal vein occlusion
- **H35.351** Cystoid macular degeneration
- **H35.359** Cystoid macular degeneration
- **H35.81** Retinal edema
- **H40.400** Glaucoma secondary to eye inflammation [Uveitic glaucoma]
- **H40.434** Glaucoma secondary to eye inflammation [Uveitic glaucoma]
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ICD-10 codes contraindicated for this CPB:

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- A54.30 - A54.39 Gonococcal infection of eye
- A71.0 - A71.9 Trachoma
- B02.30 - B02.39 Zoster ocular disease
- B30.0 - B30.9 Viral conjunctivitis
- H00.011 - Hordeolum and chalazion
- H00.19     
- H01.001 - Blepharitis
- H01.029     
- H04.001 - Dacryoadenitis
- H04.039     
- H04.301 - Acute and unspecified inflammation of lacrimal passages
- H04.339     
- H04.411 - Chronic inflammation of lacrimal passages
- H04.439     
- H05.00 - Acute inflammation of orbit
- H05.049     
- H10.011 - H10.9 Conjunctivitis
- H15.001 - Scleritis
- H15.009     
- H15.101 - Episcleritis
- H15.129     
- H16.001 - H16.9 Keratitis
- H40.001 - H40.9 Glaucoma [cup to disc ratio of greater than 0.8]
- H44.001 - Purulent endophthalmitis
- H44.029     
- H44.111 - Other endophthalmitis
- H44.129, H44.19
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.


47. EyePoint Pharmaceuticals US, Inc. Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection. Prescribing Information. Watertown, MA: EyePoint Pharmaceuticals; revised October 2018. Available at: https://yutiq.com/downloads/YUTIQ-USPI-20181120.pdf.
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Amendment to
Aetna Clinical Policy Bulletin Number: Fluocinolone Acetonide Intra-vitreal Implant (Retisert, Yutiq and Iluvien)

For the Pennsylvania Medical Assistance Plan, effective 1/1/20 medication coverage requests for medications on the statewide preferred drug list will be reviewed using the guidelines for determination of medical necessity developed by the Pennsylvania Department of Human Services.

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