Subject: Intravitreal corticosteroid implants: Retisert, Yutiq (fluocinolone acetonide intravitreal implants)	**Original Effective Date:** 12/13/2017
Policy Number: MCP-302	**Revision Date(s):** 2/2019; 05/29/2019
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DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq)** for the treatment of adult patients with **chronic non-infectious uveitis affecting the posterior segment of the eye** when appropriate criteria are met.

The intent of the **Fluocinolone Acetonide Intravitreal Implant (Retisert, Yutiq)** policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

*****Fluocinolone Acetonide Intravitreal Implant (Iluvien) is addressed in MCP-301*****
**Significant differences between Retisert and Iluvien include: different dosages of the drug being delivered to different areas of the eye. Retisert is a 0.59 mg sterile implant designed to release fluocinolone acetate to the posterior segment of the eye over approximately 30 months, while Iluvien is a 0.19 mg sterile implant in a 36-month drug delivery system injected directly into the vitreous*

- **Uveitis** is inflammation of any component of the uveal tract, which includes the iris, ciliary body, and choroid. Causes of uveitis can include autoimmune disorders, infection, and toxin exposure, although, in many cases, the cause is unknown. Posterior uveitis is the least common form of uveitis and affects the back portion of the uveal tract and primarily involves the choroid and frequently causes floaters and vision loss from scarring on the choroid and retina. Signs include cells in the vitreous humor, white or yellow lesions in the retina and/or underlying choroid, exudative retinal detachments, retinal vasculitis, and optic nerve edema. There are many infectious and non-infectious causes of posterior uveitis.

- **Chronic non-infectious posterior segment uveitis**
  The goals of therapy in non-infectious uveitis are to control inflammation, minimize recurrences, and prevent the occurrence of sight-threatening complications secondary to the disease or the therapy itself. The sight-threatening complications of chronic noninfectious uveitis include cystoid macular edema (CME) and choroidal neovascularization (CNV), with CME being the most common. (Tan et al. 2016)

- **Retisert (fluocinolone acetonide implant 0.59 mg)**
  Retisert intravitreal implant is designed to release fluocinolone acetonide locally to the posterior segment of the eye. Fluocinolone acetonide is a synthetic corticosteroid. Its potential value in the treatment of uveitis is a direct function of its anti-inflammatory action. The initial rate of release of the fluocinolone acetonide from the intravitreal implant is 0.6 mcg/day. This decreases over the first month to a steady state between 0.3 and 0.4 mcg/day over approximately 30 months.

  FDA approved as an orphan drug for the single indication of chronic non-infectious uveitis affecting the posterior segment of the eye. FDA approval of Retisert was based in part on the results of two randomized double-masked multicenter clinical trials including 224 individuals with chronic (persisting for at least 1 year) non-infectious uveitis affecting the posterior segment of one or both eyes. The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the study eye in the 34-week period post implantation compared to the rate of recurrence in the 34-week period pre implantation. The rates of recurrence ranged from approximately 7% to 14% for the 34-week period post implantation as compared to approximately 40-54% for the 34-week period pre implantation. Current evidence supporting the safety and efficacy of the fluocinolone acetonide intravitreal implant for this indication includes the results of several multicenter, randomized, controlled clinical trials (Callanan, 2008; Pavesio, 2010).

  Fluocinolone acetonide intravitreal implant effectively controlled intraocular inflammation, significantly reducing uveitis recurrence rates in patients with noninfectious posterior uveitis over a 3-year follow-up period, but is also associated with significant ocular adverse effects, including elevated intraocular pressure, glaucoma, and cataracts (Callanan DG, Jaffe GJ, et al. 2008). **Therefore it is recommended to reserve therapy for patients with non-infectious posterior uveitis whose 1) symptoms are not adequately controlled with injectable or systemic corticosteroids, 2) experiencing substantial side effects from chronic systemic corticosteroid therapy, 3) or use of other immune modulators may be particularly problematic.**

- **Yutiq (fluocinolone acetonide intravitreal implant 0.18 mg)**
  Yutiq is a sterile non-bioerodible intravitreal implant containing fluocinolone acetonide 0.18mg in a 36-month sustained-release drug delivery system. It is designed to release fluocinolone acetonide, a corticosteroid, at an initial rate of 0.25mcg/day.

  FDA approval of Yutiq was based on clinical data from two randomized, sham injection-controlled, double-masked Phase 3 clinical trials with patient follow-up continuing for three years (study 1, n=129; study 2; n=153). After six and 12 months, both clinical trials achieved the primary efficacy endpoint of prevention of recurrent uveitis flares. The proportion of patients who experienced a recurrence of uveitis in the treated eye within 6 months was significantly lower with fluocinolone acetonide intravitreal implant versus sham injection (recurrence rate, 18% vs 79% in study 1 and 22% vs 54% in study 2). Within 12 months, the recurrence rate was 28% versus 86% in study 1 and 33% versus 60% in study 2 for active treatment compared with sham injection, respectively. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis or need for rescue medications. In both trials, Yutiq was generally well tolerated. The most common adverse reactions were cataract development and an increase in intraocular pressure.
  - The first Phase 3 clinical trial (n=129) met its primary efficacy endpoint at six months with statistical significance ($p < 0.01$, intent-to-treat analysis; recurrence of 18.4% for Yutiq versus 78.6% for control). This trial yielded similar efficacy through 12 months of follow-up ($p < 0.01$, intent-to-treat analysis; recurrence of 27.6% for Yutiq versus 85.7% for control). Yutiq was generally well tolerated through 12 months of follow-up

with a mean IOP elevation of 1.3 mmHg compared to 0.2 mmHg in the sham. Cataract surgeries were performed in 33.3% of patients receiving Yutiq compared to 4.8% for sham. (ClinicalTrials.gov Identifier: NCT01694186)

- The second Phase 3 clinical trial also met its primary efficacy endpoint of prevention of recurrence of uveitis flares at six months with statistical significance ($p < 0.01$, intent-to-treat analysis; recurrence of 21.8% for Yutiq versus 53.8% for control). 12-month recurrence occurred in 32.7% of patients receiving Yutiq and 59.6% of those receiving sham injection ($p<0.01$, intent-to-treat analysis). As observed in the first Phase 3 clinical trial, Yutiq was well tolerated with a mean IOP elevation of 2.0 mmHg compared to no change in the sham. Cataract surgeries were performed in 18.0% of patients receiving YUTIQ compared to 8.6% for sham. (ClinicalTrials.gov Identifier: NCT01694186 and NCT02746991)

NOTE: At the time of this review in February 2019, the two pivotal phase III trials which FDA approval was based on (NCT01694186 and NCT02746991) has not been published.

Summary: An intravitreal implant may an appropriate treatment alternative in members/individuals who are intolerant or refractory to other therapies or in patients who are judged likely to experience severe adverse events from systemic corticosteroids. Selection of the route of corticosteroid administration (topical, systemic, periocular or intraocular injection) is based on the cause, location, and severity of the disease. Due to the differing benefits and risks of each therapeutic approach, individuals 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. Fluocinolone acetonide intravitreal implants (Retisert and Yutiq) are indicated for treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. Fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq) significantly reduced the proportion of adult patients experiencing recurrence of uveitis at 6 months and the 0.59-mg intravitreal implant (Retisert) effectively controlled intraocular inflammation and significantly reduced uveitis recurrence rates in adult and pediatric patients over a 3-year follow-up period; however, there were significant increased incidents of intraocular hypertension and cataract formation (Callanan DG, et al).

CLASSIFICATION: Anti-inflammatory Agent, Corticosteroid, Ophthalmic

FDA INDICATIONS

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

Available As:
Retisert: 0.59 mg intravitreal implant release of fluocinolone acetonide over approximately 30 months
Yutiq: 0.18 mg intravitreal implant release of fluocinolone acetonide over approximately 36 months

FDA Approved:
Retisert: April 2005
Yutiq: October 2018

Black Box Warnings: None at the time of this writing

REMS: No REMS at the time of this writing

Warnings/Precautions in labeling: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure and retinal detachment. Monitor carefully after intravitreal injection. Complications may also include cataract formation, choroidal detachment, hypotony, vitreous hemorrhage, vitreous loss, and wound dehiscence. Procedure may cause optic nerve injury. Visual defects in acuity and field of vision may occur (lasting 1 to 4 weeks postoperatively). Late-onset endophthalmitis has been observed, often associated with surgical site integrity.

*****Fluocinolone Acetonide Intravitreal Implant (Iluvien) is addressed in MCP-301*****

RECOMMENDATIONS/COVERAGE CRITERIA

Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by board-certified ophthalmologists or retinal specialist experienced in the administration of intravitreal injections. Treatment and monitoring must be retained by the specialist.

2. Diagnosis/Indication [ALL]

Prescriber submit ALL supporting documentation and clinical rationale (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*):

- ❒ Diagnosis of chronic (duration of one year or greater) non-infectious uveitis affecting the posterior segment of the eye(s)
- ❒ Diagnosis and disease progression (*history of progressive visual loss or worsening of anatomic appearance*) as confirmed/determined by fluorescein angiography, Optical Coherence Tomography (OCT) or Scanning Computerized Ophthalmic Diagnostic Imaging (SCODI)

  MOLINA REVIEWER: Baseline labs (prior to treatment with requested implant) should be submitted and noted in member's profile to review for re-authorization of treatment

3. Age/Gender/Restrictions [ALL]

- ❒ Retisert: 12 years of age or older
  - *Safety and efficacy not established in pediatric patients 12 years of age and younger*
- ❒ Yutiq: 18 years of age or older

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

Documentation for ALL of the following must be submitted for review.

- ❒ Requested intravitreal implant will **NOT** be administered simultaneously (bilateral implantation) OR with other intravitreal implants at the same time [i.e. Ozurdex (dexamethasone intravitreal implant); Retisert (fluocinolone acetonide intravitreal Implant)]
  - *Simultaneous bilateral implantation should not be performed to limit the potential for bilateral post-operative infection (due to the risk of, and resistance to infections reduced by corticosteroids)*
- ❒ Previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure

❒ Non-infectious Posterior Segment Uveitis
Inadequate response (i.e. recurrent uveitis despite use of traditional therapy), clinically significant adverse effects associated with high dose systemic steroid or immunosuppressive therapy, labeled contraindication, or clinical rationale supporting the inappropriateness of the following, include date(s) of failed therapy or clinical event(s). Documentation required: **[BOTH: 1, 2, OR 3]**

1) ONE (1) of the following: [ONE]

   ❍ Injectable or systemic corticosteroids

   ❍ Immunosuppressives, *including but not limited to*: [ONE]

      o Antimetabolites: azathioprine, mycophenolate mofetil (CellCept; Myfortic), or methotrexate

      o Calcineurin inhibitors: cyclosporine or tacrolimus

      o Tumor Necrosis Factor (TNF) inhibitors (e.g. Humira)

OR

2) At least TWO administration of intra- or peri-ocular injection of corticosteroids for the management of uveitis (i.e. triamcinolone acetonide injection)

3) At least TWO (2) separate recurrences of uveitis requiring treatment with systemic corticosteroids or ocular injections of corticosteroids (intra- or peri-ocular injection of corticosteroid)

Commented [LTP1]: Yutiq Pivotal Trial; Safety and Efficacy of an Injectable Fluocinolone Acetonide Intravitreal Insert; ClinicalTrials.gov Identifier: NCT01694186

Commented [LTP2]: Yutiq Pivotal Trial; Safety and Efficacy of an Injectable Fluocinolone Acetonide Intravitreal Insert; ClinicalTrials.gov Identifier: NCT01694186

Informational Note: Currently, systemic immunomodulation with oral corticosteroids is the mainstay of treatment to control the inflammation. Systemic steroid sparing immunomodulators such as antimetabolites (methotrexate, azathioprine, and mycophenolate mofetil) and calcineurin inhibitors (cyclosporine and tacrolimus), among others, are often included in the treatment plan [Pasadhika, Rosenbaum 2014]

5. Contraindications/Exclusions/Discontinuations
Authorization for Fluocinolone Acetonide Intravitreal Implant (Retisert) will not be authorized if ANY of the following conditions apply [ANY]

❒ Hypersensitivity to fluocinolone, other corticosteroids, or any component of the formulation
- *Documentation of allergenic cross-reactivity for corticosteroids is limited. However, due to similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.*

❒ Ocular or periocular infections (viral, bacterial, or fungal): Active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, or fungal infections of the eye
- *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.*

❒ Advanced glaucoma: Glaucoma with cup to disc ratios of greater than 0.8

❒ Concurrent treatment with other intravitreal implants [i.e. Retisert (Fluocinolone acetonide intravitreal implant); Ozurdex (dexamethasone intravitreal implant)]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- ❒ Member has been 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.

- ❒ Requested intravitreal implant for use in affected eye: [APPLICABLE]
  - ❍ Right eye
  - ❍ Left eye

CONTINUATION OF THERAPY

Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Reauthorization request is for the **same eye** as initial authorization AND 30 months since the previous intravitreal implant

  NOTE: The continuation of therapy criteria is only for the same previously treated eye. If member has developed condition in an untreated eye, Prescriber must submit new request with Initial Coverage criteria.

  EXCEPTION: For requests more frequently than 30 months, clinical rationale and relevant supporting documentation must be submitted to Molina Medical Director for clinical review and may require a peer-to-peer.

- ❑ Member continues to meet initial coverage criteria AND member's continued need for treatment has been formally assessed and documented

2. Compliance: N/A

3. Labs/Reports/Documentation required [ALL APPLICABLE]
Prescriber submit ALL supporting documentation and clinical rationale [ALL APPLICABLE]

- ❒ Response to treatment as indicated by an improvement in uveitis and lack of recurrence within the preceding 30 months for Retisert OR 36 months for Yutiq

  EXCEPTIONS may be reviewed on a case-by-case basis with relevant, supporting documentation from Prescriber.

- ❒ Member is likely to benefit from re-treatment without being exposed to significant risk, according to Prescriber's clinical judgment

- ❒ Absence of unacceptable complications/toxicity to implant, e.g., eye pain, ocular/conjunctival hyperemia, reduced visual acuity (long term), conjunctival hemorrhage, headache

4. Discontinuation of Treatment [ANY]

Authorization for Fluocinolone Acetonide Intravitreal Implant (Retisert) will not be authorized if ANY of the following conditions apply [ANY]

- ❒ Loss of visual acuity from baseline (pre-treatment values)
- ❒ Severely increased intraocular pressure (IOP), or moderately raised IOP, in treated eye
- ❒ Limited clinically meaningful benefit of treatment
- ❒ Absence of unacceptable complications/toxicity to implant (e.g., eye pain, ocular/conjunctival hyperemia, reduced visual acuity (long term), conjunctival hemorrhage, headache)
- ❒ Contraindications/Exclusions to therapy

  Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq) will not be authorized if ANY of the following conditions apply [ANY]
  - ❍ Hypersensitivity to fluocinolone, other corticosteroids, or any component of the formulation
    - *Documentation of allergenic cross-reactivity for corticosteroids is limited. However, due to similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.*
  - ❍ Ocular or periocular infections (viral, bacterial, or fungal): Active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, or fungal infections of the eye
    - *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.*
  - ❍ Advanced glaucoma: Glaucoma with cup to disc ratios of greater than 0.8
  - ❍ Concurrent treatment with other intravitreal implants [i.e. Ozurdex (dexamethasone intravitreal implant)]
    - *The safety and efficacy of different fluocinolone acetonide intravitreal implants administered to both eyes concurrently have not been studied.*

- ❒ **EXCEPTIONS** to the above criteria may be reviewed on a case-by-case basis with relevant, supporting documentation from Prescriber

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ONE]

- ❒ Retisert (12 years of age or older): Fluocinolone acetonide is designed to be released from the implant initially at a rate of 0.6 mcg/day, decreasing over the first month to 0.3 to 0.4 mcg/day over approximately 30 months
  - *Pediatrics: Safety and efficacy have not been established in patients younger than 12 years of age*

- ❒ Yutiq: 0.18 mg (1 intravitreal implant) via intravitreal injection; provides initial drug release rate of 0.25 mcg/day and lasts for 36 months

2. Authorization Limit [ALL]

- ❒ Retisert: ONE (1) intravitreal implant over a duration of 30 months, per eye
  OR
  Yutiq: one intravitreal implant over a duration of 36 months, per eye

  EXCEPTION: For requests more frequently than 30 months, clinical rationale and relevant supporting documentation must be submitted to Molina Medical Director for clinical review and may require a peer-to-peer.

3. Route of Administration [ALL]

- ❒ Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq) is considered a **provider-administered** procedure to be performed in a **provider office, outpatient setting** by a qualified ophthalmologist experienced in intravitreal injections.

- ❒ Administration of intravitreal therapy (*record in the procedure or post-procedure note following the completion of treatments*). Documentation of the following information required for review and submission of requests for subsequent treatment(s):
  - ❍ Name of the intravitreal therapy
  - ❍ Dose and frequency
  - ❍ Treated eye: right eye, left eye, or both eyes

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq)** for the treatment of adult patients with **chronic non-infectious uveitis affecting the posterior segment of the eye** when appropriate criteria are met.

All other uses of **Fluocinolone Acetonide Intravitreal Implant (Retisert; Yutiq)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

NOTE: Retisert is not FDA approved for the treatment of diabetic macular edema (DME) at this time. However, Iluvien, another brand of fluocinolone acetonide is indicated for DME.
*****Iluvien (fluocinolone acetonide intravitreal implant) is addressed in MCP-301*****

- ❑ Macular Edema Following Retinal Vein Occlusion: No randomized controlled trials were identified with the fluocinolone acetonide implant for the treatment of macular edema following retinal vein occlusion.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF EVIDENCE/POSITION

NON-INFECTIOUS UVEITIS: *Treatment of non-infectious uveitis affecting the posterior segment of the eye*

In April 2005, Retisert (fluocinolone acetonide 0.59 mg intravitreal implant; Bausch & Lomb) was approved by FDA for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

- ⌘ **Uveitis** is a general term that refers to inflammation of the part of the eye known as the uvea. The uvea is a relatively thick, strong layer of fibrous tissue that encloses and protects the eyeball. It consists of three parts: the iris, the ciliary body, and the choroid. There are three types of uveitis, classified according to the part of the uvea that is affected. Anterior uveitis, which affects the front part of the eye, is also sometimes called iritis since the iris is part of the front of the eye. Intermediate uveitis, also known as pars planitis or cyclitis, refers to inflammation of tissues in the area just behind the iris and lens of the eye. Posterior uveitis, also known as choroiditis, refers to inflammation of the choroid, the back part of the uvea. **Posterior uveitis** may affect the retina and/or the optic nerve, and may lead to permanent loss of vision. Posterior uveitis is the rare form of the disorder and is the type of uveitis most associated with loss of vision.

  Uveitis encompasses a variety of conditions, of either infectious or non-infectious etiologies, that are characterized by inflammation of any part of the uveal tract of the eye (iris, ciliary body, choroid). Infectious etiologies include syphilis, toxoplasmosis, cytomegalovirus retinitis, and candidiasis. Non-infectious etiologies include sarcoidosis, Behcet's disease, and "white dot" syndromes such as multifocal choroiditis or "birdshot" chorioretinopathy. Uveitis may also be idiopathic, have a sudden or insidious onset, a duration that is limited (less than 3 months) or persistent, and a course that may be acute, recurrent, or chronic.

- ⌘ The goals of therapy are to reduce inflammation, prevent damage to ocular structures, and prevent long-term visual loss with the ultimate goal to preserve vision.

- **Corticosteroids** have been the mainstay of treatment for posterior segment uveitis Noninfectious uveitis typically responds well to corticosteroid treatment and are commonly administered systemically, or as periocular injections. Topical administration is seldom used to treat this form of disease as therapeutic drug levels do not reach the posterior segment of the eye. Periocular corticosteroid injections, which typically consist of triamcinolone acetonide, often need to be repeated at 2 to 4 month intervals in order to maintain adequate control. Complications of this form of treatment include globe perforation, orbital fibrosis, and ptosis.

- **Immunosuppressive therapy** [e.g., antimetabolites, alkylating agents, T-cell inhibitors, and tumor necrosis factor [TNF]-inhibitors] may also be utilized to control severe uveitis. Immunosupressive therapy is typically reserved for patients who require chronic high-dose systemic steroids to control their disease. While effective, immunosupressants may have serious and potentially life-threatening adverse effects, including renal and hepatic failure and bone marrow suppression.

- Two double-blind, randomized trials were conducted in patients with chronic (≥1-year history) non-infectious uveitis affecting the posterior segment of 1 or both eyes. The primary efficacy end point in both trials was the rate of recurrence of uveitis. These trials randomized patients to a fluocinolone acetonide 0.59-mg or to 2.1-mg implant. **In 2004, the FDA approved only the 0.59-mg dose and its approval was based on comparison of rates of recurrence of uveitis affecting the posterior segment of the study eye in the 34-week period post-implantation compared to the rates of recurrence in the 34-week period preimplantation.** Data from 224 patients were included. Subsequently, FDA reported recurrence rates 1, 2, and 3 years post-implantation.

PIVOTAL TRIALS

Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity.

Two of the 4 RCTs compared 2 doses of implants and 2 trials compared implants with systemic steroids (and immunosuppression when indicated).

- **Safety and Efficacy of Fluocinolone Acetonide Intravitreal Implants**
  A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety & Efficacy of Intravitreal Fluocinolone Acetonide (0.59 or 2.1 mg) Implant in Subjects with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye

  A multi-center, randomized, double-masked, controlled study to evaluate the safety and efficacy of fluocinolone acetonide (FA) intravitreal implants for the management of subjects with non-infectious uveitis affecting the posterior segment of the eye. An additional objective is to compare the safety and efficacy of two doses of fluocinolone acetonide.

  - **Callanan et al. (2008)**
    The safety and efficacy results of a 3-year study designed to evaluate the fluocinolone acetonide implant in individuals with non-infectious posterior uveitis. This study was done to evaluate the safety and efficacy and compare the two FA implants in noninfectious posterior uveitis. The main outcome measures were recurrence rate, vision, and complications.

    A 3-year, multicenter, randomized controlled trial for the treatment of posterior uveitis, of the 0.59-mg fluocinolone acetonide (FA) intravitreous implant in 110 patients and the 2.1-mg FA intravitreous implant in 168 patients.
    - Uveitis recurrence was reduced in implanted eyes from 62% (during the 1-year preimplantation period) to 4%, 10%, and 20% during the 1-, 2-, and 3-year post-implantation periods, respectively, for the 0.59-mg dose group ($P < .01$) and from 58% to 7%, 17%, and 41%, respectively, for the 2.1-mg dose group ($P < .01$). More implanted eyes than non-implanted eyes had improved visual acuity ($P < .01$).
    - Implanted eyes had higher incidences of intraocular pressure elevation (> or = 10 mm Hg) than non-implanted eyes ($P < .01$), and glaucoma surgery was required in 40% of implanted eyes vs 2% of non-

implanted eyes (P < .01). Cataracts were extracted in 93% of phakic implanted eyes vs 20% of phakic non-implanted eyes (P < .01).
- The FA implant significantly reduced uveitis recurrence and improved or stabilized visual acuity in subjects with noninfectious posterior uveitis.
- Most subjects required cataract extraction, and a significant proportion required intraocular pressure-lowering surgery.
- The FA implant provides an alternative therapy for prolonged control of inflammation in noninfectious posterior uveitis. ClinicalTrials.gov Identifier: NCT00407082.

- **Jaffe et al (2006)** reported the results of 1 of the 2 pivotal trials. These trials are not discussed in detailed because the comparator was a non-approved dose of fluocinolone acetonide.
  - The 2 trials randomized 278 patients and 239 patients to a fluocinolone acetonide 0.59-mg or 2.1-mg implant, respectively. Pooled data from both doses in the first trial showed a reduction in recurrence rates in implanted eyes compared with an increase in recurrence in non-implanted eyes.
  - An increase (approximately 6 mm Hg) in intraocular pressure (IOP) and cataracts were observed in implanted eyes compared to non-implanted eyes. The second trial was not published and results reported in FDA documents are similar to the first trial.

- **Pavesio and colleagues (2010)** evaluated the safety and efficacy of fluocinolone acetonide (FA) implant compared with standard therapy in individuals with unilateral or bilateral non-infectious posterior uveitis in a randomized, open-label, controlled, phase 2b/3, multicenter superiority trial.
  - The study was conducted from April 2002 through August 2005 at 37 centers across 10 countries.
  - Participants were individuals with unilateral or bilateral noninfectious posterior uveitis (NIPU). One hundred forty subjects received either a 0.59-mg FA intravitreal implant (n = 66) or standard of care (SOC; n = 74) with either systemic prednisolone or equivalent corticosteroid as monotherapy (> or =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 (> or =0.1 mg/kg daily).
  - A total of 140 individuals received either a 0.59 mg fluocinolone acetonide intravitreal implant (n=66) or standard of care (SOC; n=74) with either systemic prednisolone or equivalent corticosteroid as monotherapy or, if deemed necessary by the investigator, combination therapy with an immunosuppressive agent and a lower dose of prednisolone or equivalent corticosteroid.
  - The main outcome measure was the time to the first recurrence of uveitis. Eyes that received the FA intravitreal implant experienced delayed onset of observed recurrence of uveitis (P<0.01) and a lower rate of recurrence of uveitis (18.2% vs. 63.5%; P< or =0.01) compared with standard of care study eyes..
  - Adverse events frequently observed in implanted eyes included elevated intraocular pressure (IOP) requiring IOP-lowering surgery (occurring in 21.2% of implanted eyes) and cataracts requiring extraction (occurring in 87.8% of phakic implanted eyes).
  - Based on the results of this study, the authors concluded that the FA intravitreal implant seemed to be more effective than SOC therapy in controlling the intraocular inflammation in those with posterior uveitis. It was also noted that although increased rates of cataract development and elevated IOP were observed with the fluocinolone acetonide implant, these events were well managed by conventional surgical or medical treatment.
  - The FA intravitreal implant provided better control of inflammation in patients with uveitis compared with systemic therapy. Intraocular pressure and lens clarity of implanted eyes need close monitoring in patients receiving the FA intravitreal implant. (American Academy of Ophthalmology)

- **Multicenter Uveitis Steroid Treatment (MUST) Trial**

The Multicenter Uveitis Steroid Treatment (MUST) trial is the largest randomized comparative trial to date regarding the efficacy, safety, and impact on quality of life of the FAi in comparison with systemic immunosuppression.
The MUST Trial, sponsored by the National Eye Institute, is a partially blind RCT (N=255) randomized comparison of the fluocinolone acetonide intravitreal implant versus systemic anti-inflammatory therapy for intermediate, posterior, and panuveitis in 2011.

- 479 uveitic eyes of 255 patients were observed over a period of 24 months 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. 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 ($p=0.01$).

DEFINITIONS

- Intravitreal: refers to that which is injected into the eye's vitreous humor between the lens and the retina
- Intravitreal implants deliver a continuous concentration of drug over a prolonged period of time. Intravitreal corticosteroid implants are being studied for a variety of eye conditions leading to macular edema, including uveitis, diabetic retinopathy, and retinal venous occlusions. The goal of therapy is to reduce the inflammatory process in the eye while minimizing the adverse effects of the therapeutic regimen.
- Phakic: An eye containing the natural lens
- Pseudophakic: An eye in which a natural lens is replaced with an artificial lens implant
- Retinopathy: Damage to the retina
- Vascular endothelial growth factor (VEGF): A chemical signal produced by the body's cells that stimulates growth of new blood vessels
- Uveitis: An inflammation of part or all of the uvea, the middle (vascular) tunic of the eye and commonly involving the other tunics (the sclera and cornea and the retina)

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
NA	

HCPCS	Description
J7311	0.59 mg fluocinolone acetonide intravitreal implant inserted into affected eye(s) once per 30 months
J3490	

REFERENCES

PACKAGE INSERT, FDA, DRUG COMPENDIA

Retisert [Product Information], Rochester, NY. Bausch and Lomb, Inc.; May 2012. Available at: http://www.bausch.com/Portals/107/-/m/BL/United%20States/USFiles/Package%20Inserts/Pharma/retisert-prescribing-information.pdf. Accessed on February 2019.

Yutiq intravitreal implant, fluocinolone acetonide intravitreal implant. EyePoint Pharmaceuticals US Inc (per manufacturer), Watertown, MA, 2018. Accessed on February 2019.

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at www.clinicalpharmacology.com. Accessed February 2019. [Available with subscription]

Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2019. Available from Wolters Kluwer Health, Inc. Accessed February 2019. [Available with subscription]

Fluocinolone Acetonide Monograph. American Hospital Formulary Service (AHFS) Online, Hudson, Ohio. Lexi-Comp., Inc. 2019. Accessed February 2019.

DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T908258, Fluocinolone acetonide; [updated 2018 Nov 06, cited February 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T908258. [Available with subscription]

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited February 2019]. Available from: http://clinicaltrials.gov/.

U.S. Food and Drug Administration. (2014, September). Center for Drug Evaluation and Research. *RETISERT (fluocinolone acetonide intravitreal implant).* Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021737s019.pdf. Accessed February 2019.

TREATMENT OPTIONS/CONVENTIONAL THERAPIES

Early Treatment Diabetic Retinopathy Study research group Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985;103(12):1796–1806.

Elman MJ, Aiello LP, Beck RW, et al; **Diabetic Retinopathy Clinical Research Network.** Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117(6):1064-1077.

Elman MJ, Bressler NM, Qin H, et al; **Diabetic Retinopathy Clinical Research Network.** Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011;118(4):609-614.

Jin E, Luo L, Bai Y, Zhao M. Comparative effectiveness of intravitreal bevacizumab with or without triamcinolone acetonide for treatment of diabetic macular edema. Ann Pharmacother. 2015;49(4):387-397.
Watanabe A, Tsuzuki A, Arai K, et al. Efficacy of intravitreal triamcinolone acetonide for diabetic macular edema after vitrectomy. J Ocul Pharmacol Ther. 2016;32(1):38-43.

CLINICAL TRIALS, DEFINITIONS, PEER-REVIEWED PUBLICATIONS

Definition of Uveitis

[DEFINITION] Jabs DA, Nussenblatt RB, Rosenbaum JT, et al: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 140(3):509-16, 2005.

United States National Library of Medicine. Medline Plus. Medical Encyclopedia. Uveitis. August 16, 2004. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/001005.htm. Accessed August 2017.

Retisert

Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results. Arch Ophthalmol. 2008 Sep;126(9):1191-201. doi: 10.1001/archopht.126.9.1191.

Pavesio C, Zierhut M, Bairi K, et al. Fluocinolone Acetonide Study Group. Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis. Ophthalmology. 2010; 117(3):567-575.

Multicenter Uveitis Steroid Treatment Trial Research Group. Kempen JH, Altaweel MM, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. Ophthalmology. 2011;118(10):1916–1926.

Multicenter Uveitis Steroid Treatment Trial Follow-up Study Research Group. Quality of life and risks associated with systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, or panuveitis: fifty-four-month results of the Multicenter Uveitis Steroid Treatment trial and follow-up study. Ophthalmology. Oct 2015;122(10):1976-1986. PMID 26298718

Multicenter Uveitis Steroid Treatment Trial Research Group. Benefits of systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, and panuveitis: fifty-four-month results of the Multicenter Uveitis Steroid Treatment (MUST) trial and follow-up study. Ophthalmology. Oct 2015;122(10):1967-1975. PMID 26298715

Multicenter Uveitis Steroid Treatment Trial Research Group. Kempen JH, Altaweel MM , Holbrook JT , et al: Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA 2017; 317(19):1993-2005.

Brady CJ, Villanti AC, Law HA, et al. Corticosteroid implants for chronic non-infectious uveitis. **Cochrane Database Syst Rev.** Feb 12 2016;2:CD010469. PMID 26866343

Tan HY, Agarwal A, Lee CS, et al. Management of noninfectious posterior uveitis with intravitreal drug therapy. *Clinical Ophthalmology (Auckland, NZ)*. 2016;10:1983-2020. doi:10.2147/OPTH.S89341.

Pasadhika S, Rosenbaum JT. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. Biologics. 2014;8:67–81.

GOVERNMENT AGENCIES, PROFESSIONAL SOCIETIES, GUIDELINES/CONSENSUS

American Optometric Association. Eye care of patient with diabetes mellitus. 2014. Accessed August 2017.

American Academy of Ophthalmology Retina Panel. Preferred Pattern Guidelines diabetic retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2014. Available at: www.aao.org/ppp. Accessed August 2017.

Dick AD, Rosenbaum JT, Al-Dhibi HA, et al. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. Ophthalmology 2018; 125:757.

Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology 2014; 121:785.

Mitchell P and Wong TY. Management paradigms for diabetic macular edema. AJO. 2013; 157(3):505-513e8

National Institute for Health and Care Excellence (NICE). Dexamethasone intravitreal implant for treating diabetic macular edema. 22 July 2015; Available at: www.nice.org.uk/guidance/ta349. https://www.nice.org.uk/guidance/ta349/chapter/2-The-technology Accessed August 2017.

Yeh S, Kim SJ, Ho AC, Schoenberger SD, Bakri SJ, Ehlers JP, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the **American Academy of Ophthalmology.** Ophthalmology. 2015 Apr. 122 (4):769-78. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25576994 Accessed October 2016.

Contents

Policy History	MCPC
Policy Developed *Peer Review: AMR Peer Review Network. 10/2/2017. Practicing Physician. Board certified in Ophthalmology, Surgery Vitreoretina*	12/13/2017
Annual Review	12/19/2018
Revision *Peer Review: AMR Peer Review Network. 2/5/2019. Practicing Physician. Board certified in Ophthalmology*	5/29/2019 P&T