

Subject: Intravitreal corticosteroid implants: Iluvien (fluocinolone acetonide intravitreal implant)	Original Effective Date: 12/13/2017
Policy Number: MCP-301	Revision Date(s):
Review Date:	

DISCLAIMER

This Molina Clinical Policy (MCP) 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 MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Fluocinolone Acetonide Intravitreal Implant (Iluvien)** for the treatment of adult patients with **treatment of diabetic macular edema** when appropriate criteria are met.

The intent of the **Fluocinolone Acetonide Intravitreal Implant (Iluvien)** 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 (Retisert) is addressed in MCP-302

**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.*

⌘ **Diabetic macular edema (DME)** is defined as retinal thickening within 2 disc diameters of the center of the macula, and results from retinal microvascular changes that compromise the blood-retinal barrier, causing leakage of plasma constituents into the surrounding retina and, consequently, retinal edema. Diabetes is a leading cause of new blindness in the United States, with clinically significant macular edema greatly contributing to this vision loss.

⌘ Treatment options

Laser photocoagulation, pharmacotherapy with intravitreal injection of corticosteroids or anti-vascular endothelial growth factor (VEGF) are options for treating DME.

- ⌘ **Iluvien (fluocinolone acetonide intravitreal implant)** is a small, non-biodegradable cylindrical tube with a central drug-polymer matrix that releases 0.19 mg of fluocinolone acetonide into the vitreous cavity. It is inserted intravitreally via a 25-gauge needle in the same manner as in intravitreal injection and can be done in the office setting. It releases small doses of fluocinolone acetonide for at least 3 years.

- ⌘ In September 2014, the U.S. Food and Drug Administration (FDA) approved Iluvien (fluocinolone acetonide implant) to treat diabetic macular edema in individuals who received previous treatment with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

- ⌘ FAME (Fluocinolone Acetonide for Diabetic Macular Edema) A and B Studies
(Campochiaro, 2011; Campochiaro, 2012)
The safety and efficacy of intravitreal fluocinolone acetonide implant (0.19 mg) was studied in two multi-center, randomized, sham-controlled, masked trials, FAME A and B studies.
 - ◆ A total of 956 subjects were randomized in a 1:2:2 ratio stratified by baseline BCVA and site, and enrolled in FAME A and FAME B.
 - ◆ Patients were randomly assigned to receive either sham injection or intravitreal injection of 0.2 µg/day or 0.5 µg/day FA implants: low-dose insert (n=375) or high-dose insert (n=393) or a sham group (n=185).
 - ◆ Subjects were stratified based on their BCVA at baseline (<49 and ≥49 ETDRS Letters).
 - ◆ The primary endpoint was the proportion of subjects with an improvement of ≥15 letters from baseline BCVA at Month 24 and the study continued through Month 36 to assess persistence of effect.
 - ◆ Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Implant-treated eyes showed in clinically meaningful improvements in vision at 2 and 3 years post-implant.
 - ◆ Results:
 - ◆ The percentage of patients who gained 15 letters or more was 28.7% in the implant group versus 18.9% in the sham group at 3 years. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic (difference in mean change in number of letters at 2 years from baseline was 5.6 letters in pseudophakic patients vs 1 letter in phakic patients).
 - ◆ Patients treated with the implant experienced a statistically significant improvement in visual acuity compared to the control group by week 3 of follow-up and maintained a statistically significant advantage over the control through completion of the trial at month 36.
 - ◆ A major limitation of these implants is that nearly 80% all phakic patients will develop cataracts and will require cataract surgery. Further, IOP was elevated in 34% of patients who received this implant compared with 10% of controls. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

- ⌘ 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, members/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.

CLASSIFICATION: Anti-inflammatory Agent, Corticosteroid, Ophthalmic

FDA INDICATIONS

⌘ Diabetic macular edema (Iluvien)

Treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Available As: 0.19-mg intravitreal implant release FA at an initial rate of 0.25mcg/day and lasting 36 months

FDA Approved: April 8, 2005

Black Box Warnings: *None at the time of this writing*

REMS: No REMS at the time of this writing

Fluocinolone Acetonide Intravitreal Implant (Retisert) is addressed in MCP-302

Retisert: 0.59 mg intravitreal implant in a 30-month drug delivery system indicated for Chronic Non-infectious uveitis affecting the posterior segment of the eye

RECOMMENDATIONS/COVERAGE CRITERIA

Fluocinolone Acetonide Intravitreal Implant (Iluvien) 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 implants. 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*): [ALL]

- ☐ Diagnosis of Diabetic Macular Edema (DME)

NOTE: DME indicated by the presence of clinically significant macular edema as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS): Retinal thickening within 500 micrometers (µm) of the center of the fovea, OR Hard exudates within 500 µm (\leq 500 micrometers) of the fovea center with adjacent retinal thickening, OR At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea ^{Fraser CE}

- ☐ 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

Informational Note:

- ♦ Clinically significant macular edema as defined by the treatment ETDRS is appropriate for focal laser treatment. The terminology of clinically significant macular edema is less important for anti-vascular endothelial growth factor (VEGF) therapies or intravitreal steroid implants. ^{AMRRReview, Oct 2017}
- ♦ FAME A and FAME B Studies: DME based on investigator's clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and optical coherence tomography (OCT). FAME A and FAME B Studies: Mean foveal thickness of at least 250 µm by OCT in the study eye

3. Age/Gender/Restrictions [ALL]

- ☐ 18 years of age or older
 - ◆ *Safety and efficacy not established in pediatric patients 18 years of age and younger for the indication of diabetic macular edema*

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
- ☐ Inadequate response, clinically significant adverse effects, labeled contraindication, or clinical rationale supporting the inappropriateness of the following (include date(s) of failed therapy or clinical event). Documentation required: [ALL]

○ Triamcinolone acetonide, intravitreal injection

Informational Note

- ◆ *There is no current preparation of triamcinolone acetonide (TA) approved for the treatment of DME, although historically it has been studied and clinically used extensively for this purpose.*
- ◆ *Intravitreal TA is available in four preparations: TA injectable suspension 40 mg/mL (Triescence, Alcon); TA 80 mg/mL (Trivaris, Allergan); TA injectable suspension 40 mg/mL or 10 mg/mL (Kenalog, Bristol-Myers Squibb) formulated for intramuscular (IM) or intra-articular use; and preservative-free TA prepared by a compounding pharmacy. All formulations are used off-label for DME. The 40-mg/mL and 80-mg/mL formulations of TA have been approved for intravitreal injection and are prepackaged and preservative-free, thus avoiding potential sterile inflammatory reaction to preservative or to contaminants in compounded TA. The formulation of TA for IM or intra-articular use contains preservatives and is not approved by the FDA for intraocular use, but it is nevertheless commonly used by ophthalmologists off-label. Injections of intravitreal TA are generally repeated every 2 to 4 months to maintain effect.*

○ Vascular Endothelial Growth Factor (VEGF) Inhibitors [ONE]

- **bevacizumab (Avastin): PREFERRED/NO PA REQUIRED**
- ranibizumab (Lucentis)
- pegaptanib (Macugen)
- aflibercept (Eylea)

Informational Note

- ◆ *VEGF inhibitor therapy is indicated for DME [American Diabetes Association (ADA) Grade A].*
- ◆ *NICE Appraisal Committee recognizes that there are currently no clinical criteria for determining whether a treatment is unsuitable for a person with DME. However, clinical experts suggested that treatment with an anti-VEGF agent (i.e. ranibizumab) is likely to be unsuitable for individuals who cannot or unable to attend monthly appointments, individuals who have had a recent cardiovascular event or stroke, and individuals who have a phobia of needles. NICE 2015. Dexamethasone intravitreal implant for treating diabetic macular edema. 22 July 2015.*

○ Laser Photocoagulation

Informational Note

Reference: FAME Clinical Trials assessed patients with DME previously treated with laser photocoagulation. The FAME studies enrolled subjects with DME who had received prior laser photocoagulation who had increased central retinal thickness (≥ 250 microns per time-domain OCT) and baseline visual acuity of ≥ 19 and ≤ 68 ETDRS. By definition, these subjects were not responding adequately to the standard of care, laser photocoagulation, and are considered insufficiently responsive for the purposes of the study selection.

5. Contraindications/Exclusions/Discontinuations [ANY]

Authorization for Fluocinolone Acetonide Intravitreal Implant (Iluvien) 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)]
 - ◆ *The safety and efficacy of Iluvien administered to both eyes concurrently have not been studied.*

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 (Iluvien) 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 36 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 36 months, clinical rationale and relevant supporting documentation must be submitted to Molina Medical Director for 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 (including disease progression or history of progressive visual loss or worsening of anatomic appearance) as determined by fluorescein angiography, Optical Coherence Tomography (OCT) or Scanning Computerized Ophthalmic Diagnostic Imaging (SCODI)

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

INFORMATIONAL NOTE

At the end of the first 36 month treatment course, patients in the intervention arm are separated into two groups: those who are retreated with the FA implant and those who are not. In order to qualify for retreatment, patients must have gained ≥ 5 ETDRS letters of VA compared to baseline within the initial 36 months of treatment.

- ☐ Member is likely to benefit from re-treatment without being exposed to significant risk according to Prescriber

4. Discontinuation of Treatment [ANY]

Authorization for Fluocinolone Acetonide Intravitreal Implant (Iluvien) 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 (i.e. maximal gain in visual acuity is less than five letters on a standard sight chart in the presence of limited anti-inflammatory effect)

INFORMATIONAL NOTE: At the end of the first 36 month treatment course, patients in the intervention arm are separated into two groups: those who are retreated with the FA implant and those who are not. In order to qualify for retreatment, patients must have gained ≥ 5 ETDRS letters of VA compared to baseline within the initial 36 months of treatment.

- ☐ Absence of macular edema or stable visual acuity
 - ◆ *If absence of macular edema or stable visual acuity, treatment may be discontinued and patient monitored. Treatment and monitoring intervals may be resumed at the Prescriber's discretion and submission of authorization request if there is presence of macular edema or visual acuity is decreasing.*

☐ Contraindications/Exclusions to therapy

Fluocinolone acetonide intravitreal implant (Iluvien) 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)]
 - ◆ *The safety and efficacy of Iluvien 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]

- ☐ Adults: ONE (1) implant (0.19 mg) in the affected eye by intravitreal injection. The implant is designed to release fluocinolone at an initial rate of 0.25 mcg/day lasting 36 months.
- ☐ Pediatrics: Safety and efficacy in pediatric patients have not been established for Iluvien

2. Authorization Limit [ALL]

- ☐ ONE (1) implant (0.19 mg) over a duration of 36 months

EXCEPTION: For requests more frequently than 36 months, clinical rationale and relevant supporting documentation must be submitted to Molina Medical Director for review and may require a peer-to-peer.

Informational Note: From the two primary 36-month trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three year follow up period, approximately 75% of the Iluvien treated subjects received only one Iluvien implant.

3. Route of Administration [ALL]

- ☐ Fluocinolone Acetonide Intravitreal Implant (Iluvien) 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 (Iluvien)** for the treatment of adult patients with **diabetic macular edema** when appropriate criteria are met.

All other uses of **Fluocinolone Acetonide Intravitreal Implant (Iluvien)** 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: Iluvien is not FDA approved for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye at this time. However, Retisert, another brand of fluocinolone acetonide is indicated for diabetic macular edema.

*****Retisert (Fluocinolone Acetonide Intravitreal Implant) is addressed in MCP-302*****

*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

DIABETIC MACULAR EDEMA (DME)

FDA approved: September 2014, the U.S. Food and Drug Administration (FDA) approved Iluvien (fluocinolone acetonide implant) to treat diabetic macular edema in individuals who received previous treatment with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

⌘ DME is the result of chronic microvascular compromise and can develop by an inflammatory or ischemic mechanism. High plasma glucose levels cause the breakdown of the blood-retinal barrier through the loss of pericytes. This leads to loss of endothelial cell function and release of vascular endothelial growth factor (VEGF). This growth factor leads to capillary leakage, causing the accumulation of extracellular fluid in the macula. The goal of therapy in DME is to preserve retinal function by reducing vascular leakage causing edema (expressed as retinal thickening).

⌘ DME is diagnosed by fundoscopic examination. The following studies can also be performed, to provide information for treatment and follow-up:

- Optical coherence tomography (OCT): Captures reflected light from retinal structures to create a cross-sectional image of the retina, which is comparable to histologic sections as seen with a light microscope; it can demonstrate 3 basic structural changes of the retina from diabetic macular edema: retinal swelling, cystoid edema, and serous retinal detachment
- Fluorescein angiography: Distinguishes and localizes areas of focal versus diffuse leakage, thereby guiding the placement of laser photocoagulation
- Color stereo fundus photographs: Can be used to evaluate long-term changes in the retina

Visual acuity should also be measured. Although it does not aid in the diagnosis of clinically significant macular edema (CSME) initially, at least, patients may have a visual acuity of 20/20—it is an essential parameter in following the progression of macular edema.

⌘ Currently, there are four evidence-based therapies for DME.^{Apte RS}

- 1) Focal and grid laser
- 2) Anti-VEGF injection, intravitreal
- 3) Steroid injection, intravitreal

4) Implant and surgical intervention^{Apte RS}

⌘ **Anti-VEGF** injections with or without laser photocoagulation has become first-line treatment of DME. However, the limitations of anti-VEGF injections include frequent injections, induction of resistance, and tachyphylaxis due to the long-term nature of the treatment. Cases of DME that do not respond well to regular anti-VEGF injections may be driven by pro-inflammatory cytokines other than VEGF.^{Abcouwer SF}

⌘ **Corticosteroids** act in multiple ways for the treatment of DME.¹⁵ They are potent anti-inflammatory agents and inhibit VEGF expression. The use of systemic or intravitreal corticosteroids inhibits leukocyte adhesion via the suppression of ICAM-1 gene expression, decreasing the protein levels and inhibiting the breakdown of the BRB by decreasing the VEGF levels. Mainly, three synthetic corticosteroids have been used in the treatment of DME: triamcinolone acetonide (TA), DEX, and fluocinolone acetonide (FA).¹⁵

➤ TRIAMCINOLONE ACETONIDE (TA)²²

The use of intravitreal TA for DME has been investigated in multiple clinical trials.²² Intravitreal triamcinolone has been shown to be more effective than placebo for improving vision in patients with refractory DME, and its efficacy has been studied in multiple clinical trials.^{i-vi} The Diabetic Retinopathy Clinical Research Network Protocol I trial reported that IVTA plus laser had efficacy similar to ranibizumab (Lucentis, Genentech) plus laser in pseudophakic patients at 2 years.^{vi} More recently, intravitreal triamcinolone combined with anti-VEGF injections has been shown to provide more benefit than anti-VEGF injections alone for some patients with DME.^{vii}

Intravitreal TA is available in four preparations: triamcinolone acetonide injectable suspension 40 mg/mL (Triescence, Alcon); triamcinolone acetonide 80 mg/mL (Trivaris, Allergan); triamcinolone acetonide injectable suspension 40 mg/mL or 10 mg/mL (Kenalog, Bristol-Myers Squibb) formulated for intramuscular or intra-articular use; and preservative-free TA prepared by a compounding pharmacy. All formulations are used off-label for DME. The 40-mg/mL and 80-mg/mL formulations of TA have been approved for intravitreal injection and are prepackaged and preservative-free, thus avoiding potential sterile inflammatory reaction to preservative or to contaminants in compounded TA. The formulation of TA for intramuscular or intra-articular use contains preservatives and is not approved by the US Food and Drug Administration for intraocular use, but it is nevertheless commonly used by ophthalmologists off-label.^{viii} Injections of intravitreal TA are generally repeated every 2 to 4 months to maintain effect.

⌘ **FAME STUDY GROUP** (Campochiaro PA et al. 2011, 2012)

The efficacy of Iluvien was assessed in two randomized, multicenter, double-masked, parallel studies enrolling subjects with diabetic macular edema who had previously been treated with laser photocoagulation at least once, each involving three years of follow-up. There were 74.4% of subjects treated with 1 implant, 21.6% with 2 implants, 3.5% with 3 implants and 0.5% with 4 implants and 0% > 4 implants. The primary efficacy endpoint in both trials was the proportion of subjects whose vision improved by 15 letters or greater after 24 months. In each of these trials, the primary endpoint was met for Iluvien.

The FAME Study, consisting of two double-blind, randomized, phase 3 pivotal clinical trials (Trial A and Trial B) **evaluated the long-term safety and effectiveness of intra-vitreous inserts releasing 0.2 µg/day (low-dose) or 0.5 µg/day (high-dose) fluocinolone acetonide (FA) in patients with diabetic macular edema (DME).**

- ◆ The FDA approval of FA was based on 2 trials (FAME) that were conducted under a single protocol.
- ◆ These trials were randomized, double-blind, double-dummy, and placebo-controlled. Randomization took place according to baseline best-corrected visual acuity (BCVA) letter score ≤40 and >40.
- ◆ Select Inclusion criteria for the trial were:
 - ◆ Patients with DME previously treated with laser photocoagulation. [Foveal thickness (FTH) at center point ≥250µm despite ≥1 prior focal/grid macular laser photocoagulation treatment]
 - ◆ BCVA letter score 19-68 (20/50-20/400)

- ◆ Exclusions included: glaucoma, ocular hypertension, intraocular pressure (IOP) >21mmHg, use of IOP-lowering drugs
- ◆ Demographic and mean baseline information was as follows: age 62.5 years, 59.4% males, time to diagnosis of DME 3.6 years, A1C 7.8%, pseudophakic 34.8%, BCVA 53.4 letters, center point thickness 469µm, IOP 15.2mmHg, cataract at baseline 47.1% (16.5% no cataract, 36.4% cannot grade or not applicable). In the 36-week study, 57.5% and 42.5% had chronic (≥3 years) and non-chronic (<3 years) DME respectively.
- ◆ Patients were randomized to FA 0.2mg, 0.5mg, or sham. Rescue focal/grid laser for persistent edema was allowed after 6 weeks and could be repeated as frequently as every 3 months. Retreatment with originally assigned drug was allowed after month 12 if there was a loss of ≥5 letters in BCVA or increase in FTH ≥50µm compared to patient's best status during previous 12 months.
- ◆ The primary outcome was the percentage of patients with improvement from baseline BCVA of 15 letters or more at month 24.

⌘ UpToDate

- ◆ Intravitreal VEGF inhibitors as initial therapy is favored for most patients with diabetic ME. (Fraser, CE)
- ◆ Focal laser photocoagulation is an option for initial therapy in poorly compliant patients with clinically significant ME, who may not return for follow-up appointments.

⌘ COCHRANE COLLABORATION

A 2008 Cochrane review evaluated the efficacy of intravitreal steroids for macular edema in diabetes (Grover D, et al. 2008)

- ◆ Seven studies, involving 632 eyes with diabetic macular edema (DME) were included.
- ◆ Three of the total seven trials examined intravitreal steroids implantation with either fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system (Kupperman 2007).
 - ◆ Two trials evaluated fluocinolone implant versus standard of care or observation. At 12 months, there was no evidence of effect on three or more lines improvement in visual acuity (RR 2.73, 95% CI 0.63 to 11.93). The other trial demonstrated a marginal statistically significant effect on three or more lines in visual acuity at 36 months (RR 1.93, 95% CI 1.02 to 3.66). Data was insufficient to combine for a meta-analysis and both trials had a high risk of bias.
 - ◆ The dexamethasone implant trial included participants with various underlying causes of macular edema. In a subgroup analysis of DME patients, 58% in the dexamethasone group showed a two-line improvement in vision compared to 21% in the observation group (RR 2.75, 95% CI 1.59 to 4.76) at 3 months. This suggests a beneficial effect from dexamethasone and possible evidence of benefit with the use of fluocinolone. There were many methodology limitations in the fluocinolone data, making it difficult to draw strong conclusions on the magnitude of effect.
- ◆ Conclusion: The authors concluded that evidence suggests that steroids administered either by intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DME. However, questions remained about whether intravitreal steroids could be of value in other (earlier) stages of DME or in combination with other therapies, such as laser photocoagulation.

⌘ NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

- ◆ Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular edema after an inadequate response to prior therapy (NICE, 2013)

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

- ◆ The implant is to be used in an eye with an intraocular (pseudophakic) lens

DEFINITIONS

- ◆ Diabetic macular edema (DME): The leakage of fluid from retinal blood vessels which in turn causes the macula to swell
- ◆ Diabetic retinopathy (DR): The progressive damage to the blood vessels in the back of the eye
- ◆ 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
J7313	Injection, fluocinolone acetonide intravitreal implant, 0.01 mg [Iluvien]

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