Policy: Ozurdex (dexamethasone intravitreal implant)	**Original Effective Date:** 10/24/2016
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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.

The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available. The information outlined in the MCP includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). 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.

RECOMMENDATION

This policy addresses the FDA approved indications of **Ozurdex (dexamethasone intravitreal implant)** for treatment of patients with non-infectious uveitis, macular edema following retinal vein occlusion, and diabetic macular edema when appropriate criteria are met.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

SUMMARY OF EVIDENCE/POSITION

Uveitis is a group of intraocular inflammatory disorders affecting the middle layer of the eye (the uvea) which can cause significant visual impairment, causing partial or complete loss of vision. **Non-infectious uveitis** may be due to an underlying inflammatory condition, an autoimmune disorder or as a result of trauma to the eye. In many cases the cause remains uncertain. It is estimated that only 10 in 100,000 adults and 3 in 100,000 children are diagnosed with noninfectious posterior uveitis (Thorne et al. 2016). The goals of therapy in noninfectious posterior uveitis is to eliminate intraocular inflammation, relieve discomfort, prevent visually significant complications, minimize recurrences, and prevent the occurrence of sight-threatening complications secondary to the disease or the therapy itself. The mainstay of treatment of intermediate and posterior uveitis is systemic or local corticosteroids. Posterior uveitis is challenging to treat and often unresponsive to topical administration of steroids due to inadequate therapeutic drug penetration to the posterior ocular tissues. (Tan et al. 2016). Long-term systemic steroid therapy, although highly effective, is associated with various serious adverse effects and intolerance. Immunosuppressive drugs and biological agents such as tumor necrosis factor inhibitors may be used as 'steroid sparing' treatments; however, most of these treatments also are present adverse effect profiles. While topical corticosteroids administered as eye drops are generally better tolerated than systemic corticosteroids, it is generally more effective for anterior uveitis than with posterior uveitis. Side effects of local ophthalmic corticosteroids include a high rate of cataract and complications due to increased intraocular pressure (IOP). Other forms of local therapy for corticosteroid include local injection (sub-Tenon's or intravitreal) and intraocular drug implants [i.e. dexamethasone intravitreal implant (Ozurdex), fluocinolone acetonide intravitreal implant (Retisert, Iluvien)].

Diabetic macular edema (DME) is macular thickening secondary to DR that may be present in any of the stages of this disease. DME can be present in all stages of DR and is the most common cause of vision loss in patients with DR with an increasing prevalence tied to type 2 diabetes mellitus. Inflammation plays an important role in the pathogenesis of DME. The breakdown of the blood–retinal barrier involves the expression of inflammatory cytokines and growth factors, including vascular endothelial growth factor (VEGF). Although the exact mechanism of corticosteroid on ocular tissues is not fully understood, steroids have demonstrated efficacy in the treatment of DME by inhibiting many of the processes known to be involved in the progression of DME, through anti-inflammatory properties and VEGF inhibition. Visual acuity and macular thickness are two central parameters in the follow-up of patients with DME. Three synthetic corticosteroids (dexamethasone, fluocinolone, and triamcinolone) have been used mainly in the treatment of DME. Corticosteroids have a broad spectrum of biologic action and noted to inhibit some of the processes known to be involved in the progression

of DME through anti-inflammatory properties and VEGF inhibition which results in anti-vascular permeability and antiangiogenic effects and stabilizes retinal capillaries (Daruich et al. 2018). Ozurdex (dexamethasone intravitreal implant) is the first intravitreally injectable drug implant approved for the treatment of DME.

Other treatment options for DME include intravitreal anti-VEGF and photocoagulation (laser therapy). Macular laser photocoagulation is effective in preserving vision by slowing the progression of retinopathy and reducing visual loss but has a limited effect in restoring lost vision. Although first-line treatment of DME with anti-VEGF agents, with or without laser, have become the standard treatment for DME, there is no consensus on the treatment of patients who do not respond, or are contraindicated to anti-VEGF agents. Focal photocoagulation is an established treatment for DME and can be used as initial therapy in poorly compliant patients with DME, who may not return for follow-up appointments, or as adjunctive therapy for patients who do not respond or have an incomplete response to anti-VEGF therapy (UTD 2021). The efficacy of intravitreal injection of anti-VEGF has been proven in several randomized clinical trials, which reported better outcomes compared to macular laser photocoagulation in DME (Blinder et al. 2017; Lazic et al. 2014).

Retinal vein occlusion (RVO) is a blockage of a portion of the venous circulation that drains the retina and is classified according to where the occlusion is located. Pressure builds up in the capillaries and result in hemorrhage and leakage of fluid and blood which can lead to macular edema with leakage near the macula. Central retinal vein occlusion (CRVO) occurs when the blockage is in the main vein in the retina. Branch retinal vein occlusion (BRVO) occurs when the blockage is one of the smaller veins attached to the main vein in the retina. The prognosis of RVOs varies according to the site of the occlusion and the type of occlusion (ischemic or nonischemic). In general, more-distal RVOs with less occlusion have a better prognosis than more-proximal RVOs with greater ischemia. VEGF increases vessel permeability by increasing the phosphorylation of tight junction proteins and thus an important mediator of the blood-retinal barrier breakdown leading to vascular leakage and macular edema (EURETINA 2019). Therefore, therapy that inhibits VEGF is an effective therapeutic modality targeting the underlying pathogenesis of macular edema. Pharmacologic treatment with intravitreal anti-VEGF agents is first-line therapy for macular edema (Fraser, C et al. 2021). Intravitreal glucocorticoid therapy is considered an alternative for patients with edema refractory to anti-VEGF monotherapy. Corticosteroids inhibit the expression of VEGF, a cytokine that is expressed at increased concentrations in macular edema and is a potent promoter of vascular permeability.

Ozurdex is the first FDA-approved treatment for macular edema secondary to BRVO and CRVO. Ozurdex is a sustained-release intravitreal implant of 0.7mg dexamethasone designed to release over a 6-month period. Dexamethasone is combined with biodegradable material in the form of a small rod, which is injected into the vitreous cavity using a customized, single-use, 22-gauge applicator. Dexamethasone is released in a biphasic manner over 6 months, with higher concentrations released for the first 6 weeks, followed by lower concentrations for the following months. After this time, the implant dissolves to CO2 and H2O leaving no residue within the eye. The mean number of Ozurdex injections reported in the literature is 4.2 injections per year, and more than 6 consecutive injections have been reported (Haller et al. 2010, 2011). Ozurdex is indicated for the treatment of DME, macular edema associated with RVO, and non-infectious posterior uveitis.

Dexamethasone intravitreal implant (Ozurdex) received FDA approval based on MEAD trial results, in which administration was every 6 months and injections mean number over 3 years was 4.1 (Boyer et al. 2014).

For patient intolerant or refractory to other therapies, or likely to experience severe adverse events from systemic corticosteroids, an intravitreal implant delivering sustained-release corticosteroid is a therapeutic option. The continuous local release of steroid with an implant may reduce or eliminate long-term systemic therapy or frequent intravitreal injections; however, it should be noted that insertion or surgical implantation of the device also carries risks such as endophthalmitis, ocular inflammation, and retinal detachments. Furthermore, prolonged use of ophthalmic dexamethasone include increased IOP, glaucoma with possible damage to the optic nerve, defects in visual acuity and visual field, posterior subcapsular cataract formation, secondary ocular infection from pathogens (including herpes simplex), and perforation of the globe where there is thinning of the cornea or sclera. Cataracts are a frequent complication of long-term corticosteroid therapy and should be considered regardless of the route of administration.

FDA INDICATIONS

FDA-approved indication does not alone 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.

Macular Edema: Treatment of macular edema following BRVO or CRVO

Non-infectious uveitis: Treatment of non-infectious uveitis affecting the posterior segment of the eye

Diabetic Macular Edema (DME): Treatment of diabetic macular edema

Available as: Biodegradable intravitreal implant containing dexamethasone 0.7 mg
Ozurdex employs the Novadur™ solid polymer drug delivery system. Each implant comes preloaded in a specially designed, single-use applicator. The implant provides intravitreal dexamethasone for up to 6 months.

FDA Approval

- Macular Edema following BRVO/CRVO: June 17, 2009
- Noninfectious Posterior Uveitis: September 24, 2010
- DME: June 2014; updated indication on September 2014 for DME
    DME indication first approved with restrictions to patients who are pseudophakic or are phakic (have an artificial lens or have a cataract requiring removal and placement of an artificial lens) and scheduled for cataract surgery. This indication was expanded to include the all patients with DME.

Black Box Warnings/REMS: None at the time of this writing

CLASSIFICATION: Anti-inflammatory Agent, Corticosteroid, Ophthalmic

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Ozurdex (Dexamethasone Intravitreal Implant) for initial treatment of *each affected eye* may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. **Prescriber specialty [ALL]**

   ❒ 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]**
   Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information.

   ❒ Definitive diagnosis of ONE (1) of the following: **[A, B OR C]**

   A. Diabetic Macular Edema (DME*)
   **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 (≤ 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*

   OR

   B. Macular Edema due to BRVO or CRVO

   OR

   C. Chronic (duration of 1 year or more) Non-infectious **Posterior** Segment Uveitis
   NOTE: Ozurdex is not for use in anterior uveitis or in uveitis caused by infection

   AND

   ❒ 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 noted in member's profile to reference for review if reauthorization of treatment is requested

   AND

   ❒ Vision impairment (sight-threatening or sight-losing) caused by condition

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*

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

❒ Requested dexamethasone intravitreal implant (Ozurdex) is NOT intended for administration with other intravitreal implants (i.e. fluocinolone acetonide intravitreal implant [Iluvien/Retisert])

MOLINA REVIEWER: Verify medical/pharmacy claims data and medical history/chart notes for concurrent intravitreal implants

AND

❒ Member was previously treated with a course of corticosteroids and did *not* have a clinically significant rise in intraocular pressure

AND

❒ Documentation of an inadequate response, significant adverse effect(s), labeled contraindication(s), or clinical rationale supporting the inappropriateness of the following therapies as applicable to member's specific diagnosis (include date(s) of failed therapy or clinical events). **[A, B, OR C]**

A. Diabetic Macular Edema (DME)

❒ VEGF Inhibitors [ONE]: [bevacizumab (Avastin): PREFERRED/NO PA REQUIRED; aflibercept (Eylea), brolucizumab (Beovu); pegaptanib (Macugen), ranibizumab (Lucentis)]

AND

❒ Laser Photocoagulation
- *Focal photocoagulation is an established treatment for DME* [Fraser, CE; UTD 2021]

B. Macular Edema due to BRVO and CRVO

❒ VEGF Inhibitors [ONE]: [bevacizumab (Avastin): PREFERRED/NO PA REQUIRED; aflibercept (Eylea), brolucizumab (Beovu); pegaptanib (Macugen), ranibizumab (Lucentis)]

AND

❒ FOR CRVO ONLY (BRVO not required): Intravitreal glucocorticoids (e.g. Triamcinolone acetonide, intravitreal injection)
- *Randomized trials and cohort studies have found that intravitreal glucocorticoid injections may improve visual acuity in patients with BRVO (SCORE-BRVO) and with CRVO (SCORE-CRVO). The SCORE-CRVO trial suggests that patients with visual acuity loss from macular edema secondary to CRVO may benefit, relative to observation alone, from treatment with 1 mg of preservative-free triamcinolone at baseline and at four-month intervals as needed for one year.*

C. Non-infectious Posterior Segment Uveitis

❒ Systemic corticosteroid OR periocular or intravitreal corticosteroid therapy (i.e. Triamcinolone acetonide)

AND

❒ Non-Biologic Immunosuppressive Therapy [Antimetabolites (e.g. azathioprine, mycophenolate mofetil (CellCept; Myfortic), or methotrexate) OR Calcineurin inhibitors (e.g. cyclosporine or tacrolimus)]

5. Contraindications/Exclusions/Discontinuations

Authorization for Ozurdex will not be authorized if ANY of the following conditions apply [ANY]

❒ Hypersensitivity to dexamethasone 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

❒ Aphakic eyes with rupture of the posterior lens capsule

❒ ACIOL (Anterior Chamber Intraocular Lens) and Rupture of the Posterior Lens Capsule
- *Contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber.*
- *Laser posterior capsulotomy in pseudophakic patients is not a contraindication for use.*

❒ Concurrent treatment with other intravitreal implants (i.e. Fluocinolone acetonide intravitreal implant [Iluvien and Retisert])

AND

❒ 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.

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 are included.

   ❒ Prescriber to maintain record of administration of intravitreal therapy (recorded in the procedure or post-procedure note following the completion of treatments) with the following information: name of the medication, dose/amount of drug administered, and treated eye (Right eye, Left eye, or Both eyes). Submit with re-authorization requests.

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

REAUTHORIZATION/CONTINUATION OF THERAPY

Ozurdex (dexamethasone intravitreal implant) may be reauthorized if **ALL** the following criteria are met: **[ALL]**

1. **Initial Coverage Criteria [ALL]**

   ❒ Reauthorization request is for the **same eye** as initial authorization
   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 in accordance to 'Initial Coverage' criteria.

   AND
   ❒ Member's continued need for Ozurdex has been formally assessed and documented

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

   ❒ Initial positive response to treatment; however subsequently experience a loss in visual acuity, including but not limited to the following: [AS APPLICABLE]

      ❍ **Diabetic Macular Edema (DME):** Member experienced decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening DME

❍ **Non-infectious Posterior Segment Uveitis ONLY [ONE]**
- Greater than (>) 15 letters (3 lines) in BCVA from baseline *after 12 weeks following administration* or the patient achieves driving visual acuity; OR
- Visual acuity is maintained to at least 50% of the best recorded following diagnosis of uveitis

AND

❒ Response to treatment (including disease progression or history of progressive visual loss or worsening of anatomic appearance) as determined by fluorescein angiography, OCT or SCODI. Documentation required.

AND

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

NOTE: Retreatment is usually not necessary for patients that have maintained vision improvement. Exceptions may be reviewed on a case-by-case basis with relevant, supporting documentation from Prescriber.

NOTE: Ozurdex treatment should be discontinued (and patient monitored) in absence of macular edema or stable visual acuity. Treatment (and monitoring intervals) may be resumed at prescribing specialist's discretion and submission of authorization request with presence of macular edema or visual acuity is decreasing at any time.

4. Discontinuation of Treatment [ANY]

❒ Loss of visual acuity from baseline (pre-treatment with Ozurdex)

❒ Moderately or severely raised IOP in the treated eye is related to Ozurdex

❒ Limited clinically meaningful benefit of treatment, e.g. maximal gain in visual acuity is less than five letters on a standard sight chart in the presence of limited anti-inflammatory effect

❒ Absence of macular edema or stable visual acuity

NOTE: If absence of macular edema or stable visual acuity, Ozurdex treatment should be discontinued and patient monitored. Treatment and monitoring intervals may be resumed at prescribing specialist's discretion and submission of authorization request if there is presence of macular edema or visual acuity is decreasing at any time.

- ❒ Contraindications/Exclusions to Therapy
  Discontinue treatment if ANY of the following conditions applies: [ANY]
  - ❍ Hypersensitivity to dexamethasone or any component of the formulation
  - ❍ 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
  - ❍ Advanced glaucoma: Glaucoma with cup to disc ratios of greater than 0.8
  - ❍ Aphakic eyes with rupture of the posterior lens capsule
  - ❍ ACIOL (Anterior Chamber Intraocular Lens) and Rupture of the Posterior Lens Capsule
  - ❍ Concurrent treatment with other intravitreal implants [i.e. Fluocinolone acetonide intravitreal implant (Iluvien® and Retisert®)]

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]
Macular Edema, Noninfectious Uveitis, Diabetic Macular Edema

- ❒ Adults: 0.7 mg (700 µg) intravitreal implant injected intravitreally in affected eye
  - ◆ *Pediatric: Safety and efficacy in pediatric patients have not been established for Ozurdex*

2. Authorization Limit [ALL]

- ❒ **ONE (1)** dexamethasone intravitreal implant per affected eye every 4 to 6 months
  - ◆ *There is only very limited information on repeat dosing intervals less than 6 months; an interval of approximately 6 months should be allowed between the two injections.*

- ❒ Duration of authorization: 12 months

3. Route of Administration [ALL]

- ❒ Ozurdex (dexamethasone intravitreal implant) implantation is considered a **provider-administered** procedure performed under local anesthesia by an ophthalmologist experienced in intravitreal injections (*Allergan 2018*)
- ❒ Documentation of the following information required for review and submission of requests. Prescriber to maintain record of administration of intravitreal therapy (recorded in the procedure or post-procedure note following the completion of treatments):
  - ❍ Name of the intravitreal therapy
  - ❍ Dose and frequency
  - ❍ Treated eye: right eye, left eye, or both eyes

COVERAGE EXCLUSIONS

All other uses of Ozurdex (Dexamethasone Intravitreal Implant) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is 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.

Ozurdex is considered investigational and experimental under the following condition(s)/indication(s) (not an all-inclusive list):

- ❒ Member does not meet policy criteria for Initial and Continuation of coverage
- ❒ Combined cataract surgery with intravitreal dexamethasone implant (Ozurdex)
  - *Combined cataract surgery and Ozurdex is considered experimental/investigational for the treatment of cataract and macular edema (ME) due to insufficient evidence of effectiveness of this approach. The safety and effectiveness of intravitreal dexamethasone implant in patients with cataract and ME undergoing phacoemulsification and intra-ocular lens (IOL) implantation was evaluated (Sze et al 2015). A total of 24 eyes with ME secondary to DME and RVO were retrospectively reviewed. These eyes underwent phacoemulsification with IOL implantation and intravitreal dexamethasone implant 0.7 mg at the same setting between September 2012 and September 2013. The authors of the study concluded that combined cataract surgery with intravitreal dexamethasone implant appeared to be safe and effective in treating patients with cataract and ME in this small case series. Furthermore, a larger prospective study with longer follow-up is required to demonstrate the long-term benefit of this combined procedure.*
- ❒ Coats' disease
- ❒ Macular edema secondary to idiopathic retinal vasculitis, Aneurysms, Neuroretinitis (IRVAN) syndrome, or retinitis Pigmentosa
- ❒ Non-arteritic anterior ischemic optic neuropathy
- ❒ Proliferative vitreoretinopathy
- ❒ Pseudophakic macular edema (Irvine-Gass syndrome) except for Pseudophakic persons with DME
- ❒ Radiation maculopathy
- ❒ Age-Related Macular Degeneration
  - *The ERIE Study Group published a single-masked, sham-controlled, multicenter trial on the use of a dexamethasone intravitreal implant as adjunctive therapy to treat age-related macular edema (Kuppermann et al. 2015) All patients (n=243) in this study received 2 ranibizumab injections, with the next injection given as needed based on established study criteria. The primary efficacy end point was the ranibizumab injection-free interval. Ozurdex increased the injection interval based on Kaplan-Meier survival analysis. A small, but statistically significant percentage of patients did not require rescue ranibizumab over the 6-month study period (8.3% vs 2.5%). There was a very small reduction in the mean number of as needed ranibizumab injections over the 6 months of the study (3.15 vs. 3.37), but patients in the Ozurdex group received an additional injection of the implant. There were no significant differences between the groups in mean change from baseline BCVA. More patients in the Ozurdex group had increased IOP (13.2% vs 4.2%), however no differences between the groups in cataract-related events.*

Dexamethasone Implant for DME

The MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study comprises of two multicenter, three-year, sham-controlled, masked, randomized clinical trials assessing the proportion of patients whose BCVA improved by 15 or more letters from baseline. The study evaluated 1,048 patients with DME who were randomized to receive a 0.7-mg implant (351 patients), a 0.35-mg implant (347 patients) or sham treatment (350 patients). Patients with BCVA between 34 and 68 ETDRS letters, and central subfield retinal thickness ≥300 mm by optical coherence tomography (OCT) were randomly assigned in a 1:1:1 ratio to treatment with dexamethasone implant 0.7 mg, dexamethasone implant 0.35 mg, or placebo procedure. Patients who met re-treatment eligibility criteria could be re-treated no more often than every 6 months. The primary endpoint was achievement of ≥15-letter improvement in BCVA from baseline at study end in the intent-to-treat population with last-observation-carried-forward for missing values. Safety measures included adverse events and IOP. A larger portion of patients treated with dexamethasone implant 0.7-mg achieved a significant improvement in BCVA (22.4%) than in the placebo group (12.0%) and a statistically significant reduction in central macular thickness (112 vs. 42 μm) compared to patients in the placebo group. Mean average reduction in central retinal thickness from baseline during the study was greater with dexamethasone implant 0.7 mg (–111.6 mm) and dexamethasone implant 0.35 mg (–107.9 mm) than placebo (–41.9 mm). The dexamethasone intravitreal implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA and **provided statistically and clinically significant improvement in BCVA and reduction in central subfield retinal thickness with an average of 4 to 5 injections over 3 years. Minimum treatment intervals between repeated dexamethasone implants were 6 months.** (NCT00168337 and NCT00168389 at ClinicalTrials.gov)

Dexamethasone Implant for Noninfectious Posterior Uveitis

The HURON study established the efficacy and safety of dexamethasone intravitreal implants (Ozurdex) in the treatment of noninfectious uveitis affecting the posterior segment (Lowder et al. 2011). The study was a 26-week, multicenter, masked, randomized, sham-controlled trial of a dexamethasone intravitreal implant (n=229). Patients were randomized to 0.35-mg implants (n=76), 0.7-mg implants (n=77), or placebo procedure (n=76) and followed up for 8 weeks with an 18-week masked extension, for a total of 26 weeks. The primary outcome measure of the proportion of eyes with a vitreous haze score of 0 (0 = no inflammation) at week 8 and additional outcome measures were vitreous haze through week 26, BCVA, adverse events, IOP, and biomicroscopy/ophthalmoscopy. The results of the trial indicated that a single dexamethasone intravitreal implant was significantly more effective than placebo at eliminating vitreous haze. At the primary endpoint of week 8, approximately 4 times more eyes treated with the dexamethasone implant 0.7 mg had complete resolution of vitreous haze compared with sham; a total of 47% of patients treated with the 0.7 mg implant achieved the primary outcome measure (a vitreous haze score of 0 at 8 weeks) compared to 10% who received sham control. The incidences of elevated IOP (≥25 mm Hg) in phakic eyes were higher in 0.7-mg implant-treated eyes (7.1%) versus sham control eyes (4.2%). Over 26 weeks, 23% or less (n=77) of Ozurdex-treated patients required IOP-lowering medications, and 7.9% (n=76) of patients overall developed a pressure spike greater than or equal to 35 mm Hg. Cataract was observed in 15% of the phakic eyes treated with the implant compared with 7% of eyes in the control group, and only one eye required surgery; however, this difference was not statistically

significant. Treatment with the dexamethasone intravitreal implant also led to a significant improvement in BCVA by week 3 that persisted through week 26. Limitations of this study include a shorter follow-up period (6 months), and adverse effects such as cataract formation would not have been detected fully. The long-term efficacy and safety data for the dexamethasone 0.7-mg implant is not available and the trial had no information regarding the efficacy of repeated implantation of 0.7 mg dexamethasone.

Dexamethasone Implant for RVO

Two randomized, prospective, masked, sham-controlled studies evaluated the safety and efficacy of dexamethasone implant (0.7 mg and 0.35 mg to a sham procedure) over an initial 6-month period followed by a 6-month open-label extension (Haller et al. 2010, 2011; Ozurdex GENEVA Study Group). The study enrolled adult patients with macular edema secondary to BRVO or CRVO. Duration of macular edema between 6 weeks and 12 months for BRVO and 6 weeks to 9 months for CRVO was required for inclusion (Haller et al. 2010). The dexamethasone implant 0.7 mg and 0.35 mg were superior to sham procedure in reducing central retinal thickness and improving BCVS through 3 months after administration of a single implant. The proportion of eyes achieving an improvement of at least 15 letters of vision was greater in the treatment groups at month 1 and month 3. However, at month 6 this effect was no longer statistically significant. The reduction in mean OCT central retinal thickness was greater in the 0.7mg and 0.35mg groups than in the sham group at month 3, but not statistically significant at month 6. The dexamethasone intravitreal implant 0.7mg was FDA approved for treatment of patients with RVO-associated macular edema based on the GENEVA study results. In the open-label extension, the adverse events rate was similar between patients who received their first or second DEX implant, except for cataract (Haller et al. 2011). IOP increase in the groups treated with DEX implant was also noticed, which were usually transient and controlled with medications or observation. Also, 30% and 32% of the patients achieved an increase in 15 letters 60 days after the first and second DEX implant, respectively.

Comparative Studies

The BEVORDEX study was the first head-to-head randomized clinical trial of bevacizumab versus a slow-release intravitreal dexamethasone implant (Ozurdex) for DME (Fraser-Bell et al.). At 12 months, there was no difference between the groups in proportion of eyes achieving the primary endpoint of a 10-letter gain in visual acuity. There was significantly greater decrease in central macular thickness with fewer intravitreal injections in the dexamethasone implant compared with the bevacizumab group at 12 months. However, a greater number of eyes in the dexamethasone implant group lost vision, primarily due to cataract. Similarly, the 24-month results of the BEVORDEX study identified no significant difference in the proportion of eyes with a 10-letter gain in visual acuity between bevacizumab and dexamethasone implant treatment, with both agents providing good improvements (Fraser-Bell et al.). The burden of injections was significantly greater with bevacizumab (mean 9.1 vs. 2.8). However, the dexamethasone implant group had more cases of visual loss, mainly in eyes that were phakic at baseline. Elevated IOP in the dexamethasone implant group could largely be managed with topical therapy. Therefore, the dexamethasone implant could potentially be considered a first-line treatment option in pseudophakic patients and a second-line treatment option in phakic patients with DME.

Efficacy of the Intravitreal Sustained-Release Dexamethasone Implant for DME Refractory to Anti-VEGF
A meta-analysis assessed the effect on BCVA and efficacy of 0.7 mg dexamethasone implant (Ozurdex) in 3,859 patients with refractory DME (Khan et al. 2017). Studies included adults undergoing treatment with Ozurdex for DME. At total of 15 studies were included in the final analysis. At a mean follow-up period of 6 months, dexamethasone intravitreal implant treatment in patients with DME refractory to anti-VEGF therapy is associated with a mean improvement of 20 ETDRS letters or a gain of 4 lines. The authors concluded that treatment with Ozurdex is associated with significant mean improvement in visual acuity. A multimodality approach to treating DME is recommended and clinicians should be informed of Ozurdex as a treatment option in patients who have a suboptimal response to anti-VEGF therapy.

Callanan et al. (2017) in a multicenter, open-label, 12-month, randomized, parallel-group, noninferiority study in 363 patients with DME. The study compared the dexamethasone intravitreal implant 0.7 mg to the anti-VEGF agent (ranibizumab) and evaluated whether dexamethasone every 5 months provides a similar average change in BCVA from baseline as ranibizumab 0.5 mg. Patients were treated with the dexamethasone implant at baseline, 5 and 10 months, and ranibizumab was given every 4 weeks until maximum visual acuity was achieved and stable over three visits. Treatments could then be suspended but allowed to recommence if a decrease in BCVA occurred. The mean average BCVA improvement over 1 year was 4.34 letters in the dexamethasone group and 7.60 letters in the ranibizumab group. Both dexamethasone implant and ranibizumab were well-tolerated and improved BCVA in patients with DME. Based on these results, it was concluded that the dexamethasone implant was non-inferior to ranibizumab; however, higher rates of raised IOP were reported in the dexamethasone group. Noninferiority was achieved with an average of 2.9 dexamethasone implant injections and 8.7 ranibizumab injections per patient with a more significant reduction in central macular thickness using dexamethasone implant (122 vs. 187 μm). Ocular adverse events in the study eye were more frequent in the dexamethasone implant group due to the occurrence of IOP increases and cataract. IOP increases were transient and generally managed with topical medication. Cataract surgery was performed on seven patients in the dexamethasone group and one patient in the ranibizumab group.

The Diabetic Retinopathy Clinical Research Network (DRCR Retina Network) conducted Protocol U, a phase 2, multicenter RCT evaluating a combination of dexamethasone implant (Ozurdex) and ranibizumab (Lucentis) versus ranibizumab monotherapy for the treatment of persistent DME. The study included 236 eyes with persistent DME despite receiving at least three anti-VEGF injections within 20 weeks of study enrollment. Patients were entered into a run-in phase to ensure that enrolled eyes truly had persistent DME. Patients in the run-in phase were treated with 3-month injections of ranibizumab and at the end of the run-in phase, there were Among the 129 eyes, 65 eyes underwent combination treatment and 64 had ranibizumab alone. Retreatment with ranibizumab occurred as often as every 4 weeks if the Snellen equivalent was 20/25 or worse or if there was persistent edema. The combination arm was eligible for a second dexamethasone implant beginning at 3rd month and patients were followed to week 24. The authors concluded no significant difference in visual acuity between the two treatment arms (Lucentis alone vs. combination therapy of Lucentis + dexamethasone implant) at 24 weeks. Both groups improved by approximately 3 additional letters in the 24th-week phase of the study. The addition of dexamethasone implant did not improve visual acuity at 24 weeks more than continued ranibizumab therapy alone. There was a significant improvement in macular thickness in the combination therapy with

dexamethasone implant, however this benefit is accompanied by the high incidence of IOP rise. It should be noted that some limitations in study design which might have affected the outcome (e.g. 'persistence of DME' was not formally defined; edema could have been improved significantly but still be defined as persistent). There was a subgroup of patients with baseline BCVA <20/50 who experienced a greater gain in vision with combination therapy compared to continued ranibizumab injections (+6.2 vs. +3.3 letters); however, there were only 27 patients in each group, the difference did not reach statistical significance.

American Academy of Ophthalmology (AAO)
The AAO published its Preferred Practice Pattern for retinal vein occlusions in 2019: 'Macular edema may complicate both CRVOs and BRVOs. The first line of treatment for associated macular edema is anti-VEGFs. Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation surgery in BRVO has a potential role in treatment.'

National Institute for Health and Clinical Excellence (NICE)
Dexamethasone Intravitreal Implant for the Treatment of Macular Edema Secondary to RVO (2011; TA229)
NICE published guidance on the use of the dexamethasone intravitreal implant for macular edema secondary to retinal vein occlusion. The dexamethasone implant is recommended as an option for the treatment of macular edema following CRVO. It is recommended as an option for the treatment of macular edema following BRVO when treatment with laser photocoagulation has not been beneficial, or if laser photocoagulation is not considered suitable because of the extent of macular hemorrhage.

Dexamethasone Intravitreal Implant for Treating DME (2015; TA349)
NICE provided guidance on the dexamethasone intravitreal implant (Ozurdex) for treating DME in 2015. Dexamethasone intravitreal implant is recommended as an option for treating DME in the following case:

- The implant is to be used in an eye with an intraocular pseudophakic (artificial) lens **AND**
- DME does not respond to non-corticosteroid treatment, or such treatment is unsuitable

Adalimumab and Dexamethasone for Treating Noninfectious Uveitis (2017; TA460)
NICE released guidance in 2017 addressing the use of dexamethasone intravitreal implant (with adalimumab) for the treatment of noninfectious uveitis. NICE recommended the ddexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:

- Active disease (that is, current inflammation in the eye) and
- Worsening vision with a risk of blindness

DEFINITIONS

Intravitreal implant: A drug delivery system, injected or surgically implanted in the vitreous of the eye, for sustained release of a pharmacologic agent to the posterior and intermediate segments of the eye.

Phakic: An eye containing the natural lens

Pseudophakic: An eye in which a natural lens is replaced with an artificial lens implant
Retinal vein occlusion (RVO): A blockage of one or more veins that carry blood away from the retina. Central retinal vein occlusion (CRVO) occurs when the blockage is in the main vein in the retina. Branch retinal vein occlusion (BRVO) occurs when the blockage is one of the smaller veins attached to the main vein in the retina.
Retinopathy: Damage to the retina

APPENDIX

N/A

CODING INFORMATION

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive.

HCPCS	Description
J7312	Injection, dexamethasone, intravitreal implant, 0.1 mg [Ozurdex]
67028	Intravitreal injection of a pharmacologic agent (separate procedure)

KEO June 3, 2021

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Package Insert, FDA, Drug Compendia

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Policy History	MCPC
Policy Developed Peer Review: AMR Peer Review Network. 10/20/2016. Practicing Physician. Ophthalmology, Surgery Vitreoretina	12/15/2016
Revision* Peer Review: AMR Peer Review Network. 7/10/2019. Practicing Physician. Board certified ophthalmologist Notable revision: Revised authorization limit criterion from ONE (1) dexamethasone intravitreal implant per affected eye 'every 6 months' to 'every 4 to 6 months'	P&T Q3 2019
Annual Review* No coverage criteria changes or notable revisions with this annual review	P&T Q3 2020
Revision* Peer Review: IRO Peer Review Network. 5/19/2021. Practicing Physician. Board certified in ophthalmology Notable revisions: In the 'Initial Coverage Criteria' section: • Diabetic Macular Edema (DME) and Non-infectious Posterior Segment Uveitis: the requirement for 'Triamcinolone acetonide, intravitreal injection' was removed • Macular Edema due to BRVO and CRVO: In the criterion 'FOR CRVO ONLY (BRVO not required)'—previously 'Triamcinolone acetonide, intravitreal injection' replaced with 'Intravitreal glucocorticoids' AND removed: 'Laser Photocoagulation [AS APPLICABLE ONLY]' requirement	6/9/2021

Added criterion to #5: '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' Added criterion to #6 for congruency with existing continuation of treatment requirement): 'Prescriber to maintain record of administration of intravitreal therapy (recorded in the procedure or post-procedure note following the completion of treatments) with the following information: name of the medication, dose/amount of drug administered, and treated eye (Right eye, Left eye, or Both eyes). Submit with re-authorization requests.' Reauthorization/Continuation of Treatment section: Removed: 'Member continues to meet initial coverage criteria' from criteria #1	

**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context*.