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

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SUMMARY OF EVIDENCE/POSITION

This policy addresses **Ozurdex (dexamethasone intravitreal implant),** solid polymer sustained-release drug-delivery system (DDS) a drug delivery system, is surgically implanted in the vitreous of the eye for sustained release of a corticosteroid when appropriate criteria are met.

Dexamethasone intravitreal implant (Ozurdex) incorporates a potent corticosteroid that suppresses inflammation in the eye by inhibiting edema, fibrin deposition, capillary leakage and phagocytic migration. Corticosteroids inhibit the expression of vascular endothelial growth factor (VEGF), a cytokine that is expressed at increased concentrations in macular edema and is a potent promoter of vascular permeability. Corticosteroids also prevent the release of prostaglandins, some of which are mediators of cystoid macular edema.

Ozurdex (dexamethasone intravitreal implant) is a dexamethasone implant using a solid polymer delivery system, in which 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.

Ozurdex is FDA-approved for various ocular etiologies:

1) Macular edema due to branch or central retinal vein occlusion (BRVO/CRVO) in June 2009;
2) Non-infectious posterior uveitis in September 2010; AND
3) Diabetic macular edema (DME) in 2014, first 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. Later in 2014, the FDA broadened the approval to all patients with DME.
4) Diabetic macular edema (DME) approved in 2014 for patients who are pseudophakic or are phakic and scheduled for cataract surgery. This indication was expanded to include the general DME patient population in September 2014. Approval was based on 2 randomized, multicenter, masked, placebo-controlled, phase III clinical trials with identical protocols. Data from 1048 patients were pooled for analysis. The percentage of patients with ≥15-letter improvement in best-corrected visual acuity (BCVA) from baseline was greater with dexamethasone intravitreal implant 0.7 mg (22.2%) than with placebo implant (12%).

An intravitreal implant may be 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. The goal of therapy is to reduce the inflammatory process in the eye while minimizing the adverse effects of the therapeutic regimen.

Five studies evaluated the safety of the dexamethasone implant compared with intravitreal injection of anti-VEGF agents, including bevacizumab (3 studies) (Gillies et al., 2014; Moisseiev et al., 2014; Shah et al., 2016) and ranibizumab (2 studies) (Callanan et al., 2016; Thomas et al., 2016). Two studies found significantly increased IOP in dexamethasone-treated eyes compared with either intravitreal bevacizumab injection (P=0.049) (Shah et al., 2016) or intravitreal ranibizumab injection (P<0.001) (Callanan et al., 2016). One study reported a greater incidence of cataract (P<0.001), ocular hypertension (P=0.018), vitreous floaters (P=0.011), and vitreous hemorrhage (P=0.007) in dexamethasone-treated eyes compared with intravitreal ranibizumab injection (Callanan et al., 2016). No differences between groups were noted for pain or serious ocular or systemic AEs in any study. (Hayes 2016)

A total of three phase II trials studied the effects of dexamethasone compared with anti- VEGF drugs (ranibizumab, bevacizumab) in adult patients with DME who are pseudophakic (RAN study, BEVORDEX study and the COMB study). [Callanan et al. 2016; Gillies et al. 2014; Fraser-Bell et al. 2016; Maturi et al. 2017]

- All trials were multi-center; however, only two were multinational. One study was a non-inferiority study that compared 700 mcg dexamethasone injections to 0.5 mg ranibizumab injections (RAN study), and another superiority study compared 700 mcg dexamethasone injections to 1.25 mg bevacizumab injections (BEVORDEX). In addition to 0.3 mg ranibizumab, the other superiority study compared 700 mcg dexamethasone injections to sham (COMB Study).
- Compared with bevacizumab, dexamethasone implant achieved similar improvement in visual acuity, with greater decrease in central macular thickness at 12 months, and fewer injections, but with elevations in intraocular pressure [Fraser-Bell S, et al; Gillies MC, et al: (BEVORDEX)].

Kiddee et al (2013) conducted a systematic review of IOP following intravitreal corticosteroid administration. The review included 7 studies on the fluocinolone intravitreal implant and 6 studies on the dexamethasone implant. Meta-analysis of ocular hypertension with intravitreal corticosteroid implants was conducted using a threshold of a 10 mm Hg rise from baseline or an IOP greater than 21 mm Hg for fluocinolone or 25 mm Hg or more for dexamethasone. Pooled analysis found a rise in IOP in 65.9% of patients with a fluocinolone 0.59-mg implant and 10.9% of patients with a dexamethasone 0.7-mg implant. Most cases of ocular hypertension can be controlled medically.

FDA INDICATIONS

The covered FDA-approved indications are conditions that are considered medically necessary; however it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria. 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.

- **Macular Edema** *[FDA approved: June 17, 2009]*
  Treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)

- **Noninfectious uveitis** *[FDA approved: September 24, 2010]*
  Treatment of non-infectious uveitis affecting the posterior segment of the eye

- **Diabetic macular edema** *[FDA approved: June 2014 and updated indication on September 2014 for DME]*
  Treatment of diabetic macular edema

Available as: Ozurdex 0.7 mg (700 µg) biodegradable dexamethasone intravitreal implant
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.

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

REMS: *None at the time of this writing*

Warnings and precautions in the product label include the following (Allergan Inc., 2019):

- *Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased IOP, and retinal detachments. Patients should be monitored following the intravitreal injection.*
- *Use of corticosteroids may produce posterior subcapsular cataracts, increased IOP, and glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.*
- *The implant may migrate into the anterior chamber if the posterior lens capsule is not intact.*

Pharmacologic Category: 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 diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]

❒ Diagnosis of ONE (1) of the following: [ONE: A, B, C, OR D]

A. Diabetic Macular Edema (DME) [ALL]
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 (≤ 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 Branch Retinal Vein Occlusion (BRVO) or central retinal vein occlusion (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) noted in member's profile to review for reauthorization of treatment

  Informational Note
  - *Refer to 'Summary of Evidence' section discussing DME for additional information on the diagnosis of DME.*
  - *The evaluation of RVO includes a history and a complete ophthalmic examination. Important components of the ophthalmic examination include visual acuity and dilated fundus examination looking for hemorrhage, edema, and dilatation of the retinal veins. Other testing such as fluorescein angiogram and coherence tomography may be performed to confirm the diagnosis and follow disease progression or response to treatment (Covert, Douglas J.; UpToDate)*

  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) will NOT be concurrently prescribed or administered with other intravitreal implants [i.e. fluocinolone acetonide intravitreal implant (Iluvien® and Retisert®)]

  NOTE: Molina staff: Verify medical/pharmacy claims data for the above drug therapies or implants within the last 30 days, OR for new members to Molina Healthcare, confirm above mentioned therapies in medical chart history

  AND
- ❒ Previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure

AND

❒ Condition-specific criteria as applicable to member's diagnosis **[ONE: A, B, OR C]**

A. Diabetic Macular Edema (DME) [ALL]

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); triamcinolone acetonide 80 mg/mL (Trivaris, Allergan); TA 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 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.*

AND

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

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

AND

❒ Laser Photocoagulation

B. <u>Macular Edema due to BRVO and CRVO</u> [ALL]
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]

❒ Vascular Endothelial Growth Factor (VEGF) Inhibitors [ONE]
- ❍ **bevacizumab (Avastin): PREFERRED/NO PA REQUIRED**
- ❍ ranibizumab (Lucentis)
- ❍ pegaptanib (Macugen)
- ❍ aflibercept (Eylea)

Informational Note: Grid laser photocoagulation was the gold standard therapy for BRVO; however, intravitreal pharmacotherapy has largely replaced laser as the intervention of choice for both BRVO and CRVO. Intravitreal injection of anti-VEGF agents has become first-line therapy for ME secondary to RVO since numerous prospective studies revealed their remarkable therapeutic effects. [Covert, Douglas J. (In: UpToDate)]

<u>AND</u>

❒ Triamcinolone acetonide, intravitreal injection [FOR CRVO ONLY (BRVO not required)]

<u>Informational Note</u>
- *Based on safety and efficacy findings from the SCORE-CRVO trial, administering intravitreal triamcinolone in a 1-mg dose and following the retreatment criteria applied in the SCORE study should be considered for up to 1 year, and possibly 2 years, in patients with vision loss associated with macular edema secondary to CRVO.*
- *In the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) trial for BRVO, intravitreal triamcinolone in doses of 1 or 4 mg were compared with macular grid laser photocoagulation in 411 patients with visual acuity loss from BRVO-related macular edema.[19] There was no difference in visual acuity between the treatment arms. Increasing intraocular pressure and cataract formation were more common in the triamcinolone arms, particularly the 4 mg treatment group. Given these complications, other therapies such as intravitreal anti-VEGF agents or macular grid laser photocoagulation are preferred options for patients with persistent vision loss secondary to BRVO-related macular edema. Therefore, triamcinolone is not a criterion for BRVO.*
- *The Ophthalmic Technology Assessment Committee Retina/Vitreous panel of the AAO evaluated available literature regarding efficacy of available pharmacotherapies in the treatment of macular edema due to CRVO. The panel reported that intravitreal anti-VEGF therapy is safe and effective over 2 years for macular edema and that delayed treatment is associated with worse visual outcomes. Intravitreal corticosteroid therapy yielded short-term efficacy but was associated with a higher frequency of adverse events. Yeh S, Kim SJ, et al. 2015)*

AND

❒ Laser Photocoagulation [*AS APPLICABLE ONLY]
*Generally not suitable due to macular hemorrhage (NICE 2011)

NOTE: For the treatment of macular edema from RVO, grid laser photocoagulation is generally considered to be second-line to anti-VEGF and intravitreal glucocorticoid therapies and often reserved for patients who are averse to intravitreal injections

Informational Note: *In patients with BRVO and visual loss who are averse to intravitreal injection treatments, macular grid laser photocoagulation treatment rather than observation is recommended. [SCORE Study Research Group; Covert, Douglas J. in UpToDate]*

C. Non-infectious Posterior Segment Uveitis ONLY

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. **[BOTH: 1 AND 2]**

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

- ❒ Injectable or systemic corticosteroids
  OR
- ❒ Immunosuppressives, *including but not limited to*:
  - ❍ Antimetabolites: azathioprine, mycophenolate mofetil (CellCept; Myfortic), or methotrexate; OR
  - ❍ Calcineurin inhibitors: cyclosporine or tacrolimus

AND

2) Triamcinolone acetonide injection

Informational Note: Currently, systemic immunomodulation with oral corticosteroids is the mainstay of treatment to control the inflammation. Periocular or intravitreal corticosteroid therapy is indicated for noninfectious unilateral ocular inflammation or when systemic corticosteroids contraindicated. [Dynamed 2019] 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 Ozurdex (dexamethasone intravitreal implant) 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®)]

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

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 continues to meet initial coverage criteria AND member's continued need for Ozurdex 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]

- ❒ 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, Optical Coherence Tomography (OCT) or Scanning Computerized Ophthalmic Diagnostic Imaging (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) values

- ❒ Severely raised intraocular pressure (IOP) occurs in the treated eye, or moderately raised IOP in the treated eye is related to Ozurdex

- ❒ Limited clinically meaningful benefit of treatment: 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.

- ❒ <u>Contraindications/Exclusions to therapy</u>
  Discontinue treatment if ANY of the following conditions applies: [ANY]
  - ❍ Hypersensitivity to dexamethasone or any component of the formulation
    - *Documentation of allergenic cross-reactivity for corticosteroids is limited. However, because of 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
    - *Ozurdex is 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 <u>not</u> a contraindication for use.*
  - ❍ 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
  - *The implant provides intravitreal dexamethasone for up to 6 months. 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.*
  - *In the efficacy DME studies discussed in the FDA-approved labeling, subjects were to be evaluated for retreatment eligibility every three months starting from Month 6; however, received successive treatments at least 6 months apart.*
  - *GENEVA trial patients with macular edema associated with BRVO and CRVO: A retreatment was not allowed before 6 months after the initial implantation according to the protocol of this trial. (Haller JA, et al.; GENEVA Study Group)*
  - *According to NICE (TA349; 2015), 'The summary of product characteristics states that, after initial treatment, retreatment can be performed after approximately 6 months if the patient experiences decreased vision with or without an increase in retinal thickness with recurrent or worsening diabetic macular edema.' NICE Appraisal Committee noted that 'dexamethasone intravitreal implant is licensed for use every 6 months in line with the MEAD trials, however noted from physician experts that it is often given more frequently than this in practice (every 4 months).' Over a 3-year period, the mean number of injections reported in the MEAD trial was 4.1, but given the duration of action being reported to be anywhere between 3 and 6 months, therefore the injection number is expected to be higher in real-world clinical usage.*

- ❒ 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 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 only addresses the FDA approved indications of Ozurdex (Dexamethasone Intravitreal Implant) when appropriate criteria are met.

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)
    - *Molina Healthcare considers combined cataract surgery and Ozurdex experimental and investigational for the treatment of cataract and macular edema 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.*
        - *Demographic data, BCVA, CMT, (IOP, surgical time, and complications were recorded.*
        - *Twelve eyes had DME and 12 eyes had RVO (10 central RVO and 2 branch RVO). Median baseline logMAR BCVA was 1.0 (Snellen 20/200) and mean baseline CMT was 530.2 ± 218.9 µm. Median follow-up duration was 13 months. At last follow-up, median VA improved significantly to 0.523 (Snellen 20/66) ($p = 0.003$) and CMT decreased to 300.7 ± 78.1 µm ($p = 0.000$). Median surgical time was 23 minutes.*
        - *There were no intraoperative complications. However, in 12 eyes, ME recurred, requiring further treatment, and median time to recurrences was 21 weeks. One eye had raised IOP after second dexamethasone implant for recurrent ME. No major complication such as vitreous hemorrhage, retinal detachment, or endophthalmitis occurred.*
        - *The investigators of the study concluded that combined cataract surgery with intra-vitreal 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 (2015) 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.[10] All patients (n=243) in this industry-sponsored 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 (p=0.016). A small, but statistically significant percentage of patients did not require rescue ranibizumab over the 6-month study period (8.3% vs 2.5%, p=0.048). 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%; p=0.014), but there were no differences between the groups in cataract-related events.*

BACKGROUND/CLINICAL STUDIES/SUMMARY OF EVIDENCE

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

Noninfectious uveitis (NIU) is a serious, sight-threatening intraocular inflammatory condition characterized by inflammation of the uvea (iris, ciliary body, and choroid). For physicians caring for patients with uveitis, inflammatory eye disease involving adjacent structures (e.g., scleritis, retinitis) is also included in the definition of uveitis. Inflammation in NIU is driven by a T cell–mediated autoimmune process and perpetuated by pro-inflammatory cytokines. NIU of the posterior segment of the eye, which includes intermediate, posterior, and panuveitis, is more difficult to treat than anterior uveitis and requires more complex therapeutic modalities (Pan J, et al. 2014)

In most cases, the initial treatment for non-infectious uveitis affecting the posterior segment (NIU-PS) is corticosteroids. For uveitis, these may be administered locally or systemically. Current local options for corticosteroid administration include ophthalmic drops, local injection (sub-Tenon's or intravitreal) and implants (the dexamethasone intravitreal implant [Ozurdex, Allergan] and the fluocinolone acetonide intravitreal implant [Retisert, Bausch + Lomb]). In addition to risks from the individual form of administration (such as globe perforation for sub-Tenon's injection and endophthalmitis for intravitreal injection), side effects of local ophthalmic corticosteroids include a high rate of cataract and complications due to increased intraocular pressure.

The primary goal of therapy for uveitis is to preserve vision. Noninfectious uveitis typically responds well to corticosteroid treatment. Immunosuppressive therapy (e.g., antimetabolites, alkylating agents, T-cell inhibitors, tumor necrosis factor inhibitors) may also be used to control severe uveitis. Immunosuppressive therapy is usually reserved for patients who require chronic high-dose systemic steroids to control their disease. Immunosuppressants, while effective, may have serious and potentially life-threatening adverse effects, including renal and hepatic failure and bone marrow suppression**.**

Ozurdex (Dexamethasone Intravitreal Implant) is indicated for the treatment of non-infectious ocular inflammation affecting the posterior segment of the eye. This dexamethasone implant has been studied in a single, multicenter, double-masked RCT in patients with intermediate or posterior uveitis, which showed a significant increase in the percentage of patients who gained 15 or more letters compared with sham treatment.

HURON (cHronic Uveitis evaluation of the intRavitreal dexamethasone implant)

FDA approval Ozurdex is primarily based on HURON, a Phase III posterior segment uveitis study (Lowder et al. 2011) was a double-masked, randomized, controlled trial that compared the effect of two implant doses (0.7 mg and 0.35 mg) with sham injection.

- HURON study group (46 study sites in 18 countries) reported safety and efficacy outcomes of a double-masked RCT of the dexamethasone intravitreal implant in 229 participants (mean age 45 years) with uveitis (non-infectious intermediate or posterior uveitis)
- Patients were randomized to dexamethasone 0.7 mg intravitreal implant (n=77) vs. dexamethasone 0.35 mg intravitreal implant (n=76) vs. sham and followed for 26 weeks (n=76)
- Patients continued on existing medication regimens, including nonsteroidal anti-inflammatory agents, systemic corticosteroids, and systemic immunosuppressants
- Key exclusion criteria: Active ocular disease or infection; uveitis unresponsive to prior corticosteroid treatment; the use of IOP-lowering medications within the last month and a history of glaucoma, ocular hypertension, or clinically significant IOP elevation in response to corticosteroid treatment; IOP more than 21 mm Hg at baseline; BCVA less than 34 letters in the non-study eye; or any uncontrolled systemic disease.
- Conclusion:
    - In this study a single dose of the DEX implant was well-tolerated and produced significant improvements in intraocular inflammation and visual acuity that persisted for 6 months. The implant was still effective at the 6-month time point.
    - Ozurdex was found to be safe with a low incidence of cataract reported over the 26-week period (15% of patients developed clinically evident lens opacity, but none sufficient to require surgery). The key potential side effect of raised intraocular pressure (IOP) was also low with IOP >25 mmHg occurring in less than 10% of patients.
    - The 0.7 mg DEX implant demonstrated greater efficacy than the 0.35 implant, with similar safety. Both implant doses proved effective in controlling vitreous inflammation and improving visual acuity with reduction in cystoid macular edema, but the higher-dose implant (0.7 mg DEX implant) had a longer duration of action without a significant increase in side effects.
    - The 0.35-mg implant group showed significant improvement compared with sham at 8 weeks (p=0.012) but not at 26 weeks. Interpretation of these results is limited by the higher baseline scores for the sham group.
    - No significant difference was seen in cataract progression or in the proportion of patients with an IOP > 25 mmHg between the groups. The duration of the study was 6 months and no repeat injections were performed.

MACULAR EDEMA (ME) FOLLOWING RETINAL VEIN OCCLUSION (BRVO or CRVO)

Retinal vein occlusions (RVO) are the second most common cause of retinal vascular disease after diabetic retinopathy.1 Occlusions can involve the central retinal vein (CRVO) or hemicentral or branch retinal veins (BRVO). Though not completely understood, occlusions likely lead to a combination of increased venous pressure, production of cytokines such as interleukin-6 (IL-6), and production of vascular permeability factors including vascular endothelial growth factor (VEGF). These processes result in destruction of the blood-retinal barrier. Macular edema (ME) is just one of several devastating complications of RVO that can cause vision loss.

Ozurdex is the first FDA-approved treatment for macular edema secondary to BRVO and CRVO.

Macular edema (ME) is one of the prominent treatable causes of decreased visual acuity in patients with CRVO.

- The exact mechanism of macular edema is unclear; however multiple factors involved include increased venous pressure, elevated levels of VEGF, and deregulation of multiple inflammatory mediators leading to increased capillary permeability and leakage.
- No known effective medical treatment is available for either the prevention of or the treatment of CRVO. Identifying and treating any systemic medical problems to reduce further complications is important. Since the exact pathogenesis of the CRVO is not known, various medical modalities of treatment have been advocated by multiple authors with varying success in preventing complications and in preserving vision.
- There is no cure for this condition, thus the primary goal of treatment is to improve or prevent further loss of visual acuity and reduce macular edema.

Intraocular steroid injection has been shown to be effective in decreasing macular edema. Although the exact mechanism of action is unknown, steroids work by targeting various inflammatory pathways and decreasing expression of VEGF, reducing vascular permeability, stabilizing endothelial tight junctions, and decreasing macular edema.

American Academy of Ophthalmology (AAO)
The Ophthalmic Technology Assessment Committee Retina/Vitreous Panel of the AAO
The technology assessment (AAO 2015) found that intravitreal anti-VEGF treatment was safe and effective for treatment of macular edema associated with CRVO, and that earlier treatment was associated with improved visual outcomes. Studies included treatment with ranibizumab, aflibercept, and bevacizumab.

Conclusion: Level I evidence indicates that intravitreal anti-VEGF pharmacotherapy is safe and effective over 2 years for ME associated with CRVO and that delay in treatment is associated with worse visual outcomes. In addition, level I evidence demonstrates short-term efficacy of intravitreal corticosteroid but also an association with a higher frequency of adverse events.

Efficacy and safety of intravitreal therapy in macular edema due to BRVO and CRVO
A systematic review (Pielen et al.) compared anti-VEGF agents (ranibizumab, bevacizumab, aflibercept) versus steroids (triamcinolone and Ozurdex) for macular edema in CRVO or BRVO
All anti-VEGF agents showed a better visual acuity gain compared to steroids at month 12. The downside was that anti-VEGF therapy requires more frequent injections (around 8 injections per year, compared to 2 injections in the steroid group). IOP increase and cataract progression were also significantly higher in the patients treated with steroids compared to patients treated with anti-VEGF agents. Prospective studies comparing ranibizumab versus Ozurdex are ongoing [COMO and COMRADE (http://www.clinicaltrials.gov)].

There were 2 publications identified that compared dexamethasone with sham treatment (Haller et al., 2010 and Sadda et al., 2013) and an associated open-label study (Haller et al., 2011):

- The Haller (2010) publication included 2 identical RCTs of people with CRVO or BRVO that compared dexamethasone with sham treatment in 1267 eyes. At 6 months, there were statistically significantly more eyes with an improvement of 15 or more letters and statistically significantly fewer eyes with a 15 or more letter loss in the dexamethasone group (both $p<0.001$). The time needed to achieve an improvement in BCVA of 15 letters or greater was statistically significantly less with dexamethasone than sham ($p<0.001$). At day 180 there was no significant difference in the percentage of patients with intraocular pressure or cataracts or needing cataract surgery.
- The Haller (2011) open label extension study of the trials reported in Haller (2010) concluded that single and repeated dexamethasone treatment had a favorable safety profile over 12 months. The Haller (2011) study provides longer-term treatment data than the GENEVA study used in TA229 and may help to provide additional safety evidence. However, it does not provide any additional efficacy evidence than was included in the TA229 appraisal. The Sadda publication[7] was a post hoc analysis of data from 2 phase 3 clinical trials that compared dexamethasone with sham treatment in 329 eyes with CRVO or BRVO. There were statistically significantly fewer unreadable assessments because of hemorrhage at day 180 with dexamethasone compared to sham ($p=0.029$). There was a statistically significant difference in rate of neovascularization between the groups by day 180 ($p=0.026$). There was no statistically significant difference in overall non-perfusion or mean area of macular capillary non-perfusion.

GENEVA trials: **G**lobal **E**valuation of Impla**N**table D**E**xamethasone in Retinal **V**ein Occlusion With Macular Edem**A** (Haller et al., 2010)

- The safety and efficacy of dexamethasone intravitreal implant for the treatment of macular edema (ME) after BRVO or CRVO was studied in two identical, randomized, prospective, multicenter, masked, sham-controlled, 6-month, phase 3 trials involving 853 patients with macular edema following branch or central retinal vein occlusion who received Ozurdex 0.7 mg or sham.
- Participants randomized to a single treatment with dexamethasone intravitreal implant (DEX implant) 0.7 mg (n=427), DEX implant 0.35 mg (n=414), or sham (n=426)
- Patients receiving the DEX implant had a statistically significant improvement in vision compared to the sham group.
- The primary outcome measure for the combined data from the two studies was time to achieve a greater than or equal to 15-letter improvement in BCVA.
- Central retinal thickness, BCVA and safety were the secondary endpoints
- The greatest improvement was seen at day 60 with the 700 mg implant, with 29% of patients achieving a 15-letter improvement in vision. The proportion of eyes achieving at least a 15-letter improvement from baseline was significantly greater in patients receiving the injection at months 1 and 3, but no difference was seen at 6 months.
- Cataracts were not increased in any group, and although 30% of eyes were treated with intraocular pressure (IOP) lowering medication, the IOP returned to baseline after 6 months of the procedure in all groups. After 6 months, all study patients were eligible to receive an implant if they experienced a drop in vision or persistent macular edema.
- The results of the study demonstrated that the DEX implant reduced the risk of further vision loss and increased the chance of improvement in visual acuity in eyes with CRVO. The same efficacy and a similar effect on the IOP were seen in the 997 patients who received an implant after 6 months. The only difference was seen in cataract progression, which occurred in 29.8% of patients who received two implants versus 5.7% in patients who had previously belonged to the sham group. However, only one patient required cataract surgery.

The **Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE)** Study (Scott, I.U., Ip, M.S.,)

- A National Eye Institute (NEI) at the National Institutes of Health (NIH) randomized controlled trial comparing 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone acetonide versus observation for visual acuity loss due to macular edema associated with perfused CRVO.

  A phase III clinical trial conducted at 84 clinical sites included participants with CRVO (n = 271) and BRVO (n = 411) in 2 separate trials [SCORE Study Report 5; SCORE Study Report 6]
- The SCORE study reported that intravitreal triamcinolone (both 1-mg and 4-mg dose groups) yielded better visual acuity outcomes over 12 months than observation alone. Beyond 12 months, the greater likelihood of visual acuity gain with triamcinolone persists, although there is a mild attenuation of the effect of triamcinolone with respect to mean change in visual acuity.
- Both triamcinolone groups had a similar change in mean visual acuity letter score compared with the observation group, but the 4-mg group had the highest rate of cataract formation, cataract surgery, and intraocular pressure (IOP) elevation. The risk factors for IOP-related events included higher treatment dose, younger age, and higher baseline IOP. IOP-related events may take several months from the time of first triamcinolone injection to occur, so it is recommended to assess the risks and benefits of triamcinolone therapy and to maintain long-term follow-up of patients at risk for this complication.
- Conclusion: Based on safety and efficacy findings from the SCORE-CRVO trial, administering intravitreal triamcinolone in a 1-mg dose and following the retreatment criteria applied in the SCORE study should be considered for up to 1 year, and possibly 2 years, in patients with vision loss associated with macular edema secondary to CRVO.

<u>National Institute for Health and Clinical Excellence (NICE 2011)</u>

Technology Appraisal Guidance (TA229): Dexamethasone Intravitreal Implant for the Treatment of Macular Edema Secondary to Retinal Vein Occlusion [Published: July 2011. Evidence reviewed: January 2015 and no changes were made to guidance]

- Dexamethasone intravitreal implant is recommended as an option for the treatment of ME following CRVO.
- Dexamethasone intravitreal implant is also recommended as an option for the treatment of ME following BRVO when treatment with laser photocoagulation has not been beneficial, or treatment with laser photocoagulation is not considered suitable because of the extent of macular hemorrhage.

  *As of the MCP review: No new updates added to TA229

<u>American Academy of Ophthalmology (AAO)</u>

Evidence-based guideline: Therapies for Macular Edema Associated with Branch Retinal Vein Occlusion: A Report by the American Academy of Ophthalmology [updated in September 2017]

- Included 2 studies with a DEX implant (GENEVA trials; Haller et al. 2010 and 2011)
- The AAO concluded that intravitreal corticosteroids are safe and effective for the management of ME associated with BRVO. However, they are associated with increased potential ocular side effects.
- Multiple pharmacotherapies appear to be safe and effective treatments for ME secondary to BRVO. Level I evidence has shown anti-VEGF therapy, in particular, to result in significant VA improvement compared with laser or observation with a tolerable safety profile. Minimal data are currently available on the differential effectiveness of the various anti-VEGF inhibitors, switching between agents, and the optimal long-term dosing schedule (e.g., PRN, treat-and-extend).
- **On the basis of level I evidence, corticosteroid trials have exhibited favorable results. Dexamethasone implant trials have shown more rapid improvement in VA compared with sham injections and IVTA, demonstrating similar results to grid laser photocoagulation, but intravitreal corticosteroids are associated with more frequent ocular side effects (e.g., IOP increase, cataracts).**

DIABETIC MACULAR EDEMA (DME)

FDA approved: June 2014 for DME in persons who are pseudophakic or are phakic and scheduled for cataract surgery and FDA approved updated indication: September 2014 for DME without any additional qualifications.

Macular edema in diabetes, defined as retinal thickening within 2 disc diameters of the center of the macula, results from retinal microvascular changes that compromise the blood-retinal barrier, causing leakage of plasma constituents into the surrounding retina and, consequently, retinal edema.

Treatment options currently available for the treatment of DME include intravitreal anti-vascular endothelial growth factor agents (VEGF), intravitreal corticosteroids, and photocoagulation (laser therapy)

1) Tight glycemic and blood pressure control is the first line of treatment to control diabetic retinopathy, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss, it does not restore lost vision. Alternatives to intravitreal implants include intravitreal injection of triamcinolone acetonide, which is used as off-label adjunctive therapy for DME.
2) Intravitreal administration of anti-VEGF agents (bevacizumab, ranibizumab, aflibercept, and pegaptanib)
    - **Intravitreal anti-VEGF injections, with or without laser, have become first-line treatment for DME, corticosteroids are important second-line treatments**
    - Treatment with anti-VEGF agents is not effective for all patients with DME due to underlying mechanisms of pathogenesis. Cases of DME that do not respond well to regular anti-VEGF injections may be driven by pro-inflammatory cytokines other than VEGF.
    - The limitations of anti-VEGF injections include frequent injections, induction of resistance, and tachyphylaxis due to the long-term nature of the treatment.
3) Intravitreal administration of corticosteroids (dexamethasone, fluocinolone, and triamcinolone)
    - Corticosteroids are associated with substantial side effects, in particular, formation of cataracts and increases in intraocular pressure (IOP). The limitations of steroids for treatment of DME have led to the development of several types of long-acting, sustained-release, intravitreal implants that provide continuous delivery of a low dose of steroids without need for repeated intravitreal injections.
    - Three synthetic corticosteroids have been used mainly in the treatment of DME: triamcinolone acetonide (TA), DEX, and fluocinolone acetonide (FA)
    - Triamcinolone Acetonide (TA)
        - The use of intravitreal TA for DME has been investigated in multiple clinical trials. 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.
        - 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 (Elman MJ, et al). 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.
        - 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 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.

4) Laser photocoagulation
   - Laser photocoagulation is effective in some cases but may damage central and color vision, and is not indicated in eyes with perifoveal edema. Although the mechanism of action of corticosteroids is not fully understood, it is known that steroids suppress inflammation, reduce leukostasis, support the barrier function of retinal endothelial cells, and regulate proteins associated with transport of water out of the cell, thereby reducing edema.
   - 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.

Ozurdex was the first intravitreally injectable biodegradable implant drug approved for the treatment of DME.

- In July 2014, the FDA approved dexamethasone intravitreal implant (Ozurdex) for DME in patients who are pseudophakic or are phakic and scheduled for cataract surgery. This indication was expanded to include the general DME patient population in September 2014.
- Approval was based on 2 randomized, multicenter, masked, placebo-controlled, phase III clinical trials with identical protocols. Data from 1048 patients were pooled for analysis. The percentage of patients with ≥15-letter improvement in best-corrected visual acuity (BCVA) from baseline was greater with dexamethasone intravitreal implant 0.7 mg (22.2%) than with placebo implant (12%). (MEAD; Boyer et al. 2014)

MEAD: Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (Boyer et al. 2014)

3-year data

- Two randomized, multicenter, masked, sham-controlled, 3-year, phase III clinical trials (registered with the identifiers NCT00168337 and NCT00168389 at ClinicalTrials.gov) evaluated the efficacy and safety of the DEX implant for treatment of DME. Since the trials were identical in study design, the results were pooled for analysis.
- Patients (n = 1048) with DME, best-corrected visual acuity (BCVA) of 20/50 to 20/200 Snellen equivalent, and central retinal thickness (CRT) of ≥300 μm by optical coherence tomography
- Patients were randomized in a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or sham procedure and followed for 3 years (or 39 months for patients treated at month 36) at ≤40 scheduled visits. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months. Individuals who met re-treatment eligibility criteria could be retreated no more than every 6 months.

Results:

- The percentage of patients with ≥ 15-letter improvement (3 lines) in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%; P ≤ 0.018).
- Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg (-111.6 mm) and DEX implant 0.35 mg (-107.9 mm) than sham (-41.9 mm; P < 0.001).

- Rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively.
- Increases in IOP were usually controlled with medication or no therapy; only 2 patients (0.6%) in the DEX implant 0.7 mg group and 1 (0.3%) in the DEX implant 0.35 mg group required trabeculectomy.

Conclusions: The DEX implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA. The safety profile was acceptable and consistent with previous reports.

PLACID

12-month data

In the PLACID study (N = 253), patients with diffuse DME randomly received either 0.7 mg DEX implant (n = 126) or sham injection (n = 127), both followed by laser photocoagulation after 1 month. When necessary, a second DEX implant or sham injection was given 6 months after the initial injection, and in both groups up to 3 supplemental laser applications were done at 3-month intervals. The DEX implant and laser group showed a greater decrease in vascular leakage and retinal edema on angiography compared to the group treated with laser only. There were no significant differences between the groups in BCVA at 12 months. However, BCVA was significantly increased in the DEX implant group at 1 and 9 months. IOP elevation over 10 mmHg occurred in 15.2% of patients in the DEX implant group but was controlled without the need for glaucoma surgery. At 12 months, 3.2% of the patients had undergone cataract surgery

BEVORDEX trial [Gillies et al. 2014] [www.clinicaltrials.gov identifier; NCT01298076]

The first head-to-head clinical trial of bevacizumab versus Ozurdex for centre-involving DME either unresponsive or unlikely to benefit from macular laser. The BEVORDEX study reported the 12 month results of a randomized head-to-head clinical trial that compared bevacizumab (Avastin, Genentech) with the Ozurdex 0.7 mg dexamethasone implant.

- 88 eyes of 61 patients with center-involving DME enrolled; 42 eyes receiving bevacizumab up to every 4 weeks and 46 eyes receiving an Ozurdex implant up to every 16 weeks, both as necessary (PRN). The baseline bevacizumab and Ozurdex groups were well matched.
- Primary outcome: the proportion of eyes with improvement in BCVA by at least 10 logMAR letters. This was achieved in 40% of bevacizumab treated eyes and 41% of Ozurdex treated eyes (p = 0.83). Bevacizumab treated eyes received a mean of 8.6 injections over 12 months, compared with 2.7 injections for the Ozurdex group.
- A total of 26 of the 88 eyes (29.5%) were pseudophakic at baseline, 10 of which were treated with bevacizumab (24% of the bevacizumab treated eyes), whereas 16 were treated with the dexamethasone implant (35% of the dexamethasone implant eyes). There was no significant effect based on treatment received for the change in BCVA for the pseudophakic eyes, with a mean increase in BCVA for bevacizumab eyes of 7.7 letters and a mean increase in BCVA for dexamethasone treated eyes of 10.4 letters (p = 0.47)
- None of the 42 eyes treated with bevacizumab lost 10 or more letters, but 11% (5/46) of the eyes given the Ozurdex implant did. Of these, 4 cases were due to increase in cataract density, but 1 patient with undiagnosed secondary syphilis developed the rare complication of syphilitic chorioretinitis 1 week after administration of the dexamethasone implant with significant loss of vision. Increase in cataract density by ⩾2 grades from baseline was reported in 13% (6/46) of eyes in the dexamethasone implant group and in 4.8% (2/42) of eyes in the bevacizumab group. Most cataract progression is anticipated in the second year of steroid use and the effect on visual outcomes on the 24-month outcomes will be of interest.
- Over the initial year of the study, 12 eyes demonstrated an IOP of > 25 mmHg at least once during follow-up visits, all in the dexamethasone implant treatment group. These eyes were managed successfully with

either observation or topical IOP lowering medications. No eye required incisional glaucoma surgery in the first year of the BEVORDEX trial.

- Subgroup analysis of 25 of 34 patients who had one eye only enrolled in the BEVORDEX study and who had completed the Impact of Vision Impairment questionnaire at baseline and 12 months found no significant difference between the average improvement in scores between the dexamethasone implant and bevacizumab groups ($p > 0.1$). The 27 patients who had both eyes enrolled in the study were asked which treatment they preferred. A total of 25 responses were collected: 8 (33%) preferred bevacizumab, 11 (46%) preferred the dexamethasone implant, and 5 (21%) had no preference ($p > 0.1$). No significant difference in patient reported outcomes for the 2 drugs was noted at 12 months.
- The prospectively defined minimal time interval between Ozurdex implants was 16 weeks rather than the 6 months chosen in MEAD. Consequently, there was less recurrence of DME during the BEVORDEX trial. **The authors would not recommend regular retreatment intervals less than 4 months because of the potential risk of steroid-induced IOP rise.** The trial continues to 24 months for safety outcomes.

Summary

- Vascular endothelial growth factor (VEGF) (pegaptanib, bevacizumab, ranibizumab, aflibercept) is favored as initial therapy for the majority of patients with DME. VEGF inhibitors have been widely studied as a treatment for diabetic ME, and this therapy represents a major treatment advance (Fraser, CE)
- Focal photocoagulation is an established treatment for clinically significant ME and may be an option for initial therapy in poorly compliant patients with clinically significant ME, who may not return for follow-up appointments.
- The precise role for anti-VEGF therapy in combination with focal photocoagulation is unclear, and such treatment decisions should be made on an individual basis. The addition of focal laser photocoagulation to anti-VEGF therapy may be beneficial in eyes that do not respond to or have an incomplete response to anti-VEGF therapy.
- Intravitreal and retinal implants have been designed to deliver glucocorticoids over an extended time frame. The use of these implants is also associated with high rates of cataract formation and glaucoma (Kiddee W, et al.).
    - For eyes with persistent ME, adding dexamethasone 0.7 mg implant every three months to monthly ranibizumab 0.3 mg treatment did not reduce the number of ranibizumab injections needed. While retinal thickness decreased, intraocular pressure increased and visual acuity was similar to the ranibizumab alone group [Maturi RK, et al. 2018].

National Institute for Health and Clinical Excellence (NICE 2015)

Guidance: Dexamethasone Intravitreal Implant for Treating Diabetic Macular Edema (DME)
Technology Appraisal Guidance (TA349); 22 July 2015.

*As of the MCP review in June 2019: No new updates added to TA349

Dexamethasone intravitreal implant is recommended as an option for treating diabetic macular edema only if:

- the implant is to be used in an eye with an intraocular (pseudophakic) lens **AND**
- DME has not improved with non-corticosteroid treatment, or such treatment is unsuitable

The Appraisal Committee concluded that, based on current practice, the relevant comparators for dexamethasone intravitreal implant in the 4 subpopulations of people with DME are as follows and made the recommendations for each group ineligible for treatment with dexamethasone intravitreal implant :

- ranibizumab in people with a pseudophakic lens with a CRT of 400 micrometres or more
- laser photocoagulation or bevacizumab in people with a pseudophakic lens with a CRT less than 400 micrometres

- fluocinolone acetonide intravitreal implant in people with a pseudophakic lens and whose chronic DME does not respond to non-corticosteroid treatment
- watch-and-wait for people who do not have a pseudophakic lens and whose DME does not respond to non-corticosteroid treatment, or for whom such treatment is unsuitable.

DEFINITIONS

- Biodegradable: The Ozurdex implant uses a biodegradable* polymer implant that releases dexamethasone over an extended period of time to suppress inflammation, which plays a key role in the development of DME (Allergan, 2014). The most common adverse events in the studies of Ozurdex for DME included cataracts and elevated intraocular pressure. An increase in mean intra-ocular pressure (IOP) was seen with each treatment cycle; mean pressure generally returned to baseline between treatment cycles. The labeling states that Ozurdex should not be used in persons with glaucoma.
    - Corticosteroid implants may be either biodegradable or non-biodegradable. Non-biodegradable systems are thought to be preferable for treating chronic, long-term disease, while biodegradable products may be preferred for conditions that require short-term therapy.
    - Although the continuous local release of steroid with an implant may reduce or eliminate the need for intravitreal injections and/or long-term systemic therapy, surgical implantation of the device carries its own risks, and the implant could potentially increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration. With any route of administration, cataracts are a frequent complication of long-term corticosteroid therapy.
- Branch retinal vein occlusion (BRVO): An occlusion near the retina in a branch retinal vein
- Central retinal vein occlusion (CRVO): An occlusion of the central retinal vein where it enters the eye
- 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
- 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

<u>Uveitis</u>

- Anterior uveitis: Localized primarily to the anterior segment of the eye, includes iritis (inflammation in the anterior chamber alone) and iridocyclitis (inflammation in the anterior chamber and anterior vitreous)
- Intermediate uveitis: Localized to the vitreous cavity and/or pars plana
- Posterior uveitis: Any form of retinitis, choroiditis, or inflammation of the optic disk. Posterior uveitis is the rare form of the disorder and is the type of uveitis most associated with loss of vision.
- Panuveitis: Inflammation involving anterior, intermediate, and posterior structures

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.

HCPCS	Description
J7312	Injection, dexamethasone, intravitreal implant, 0.1 mg [Ozurdex]

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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

*NOTE: 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.