RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	corticosteroid intravitreal implants
Policy Number:	RxA.569
Drug(s) Applied:	Iluvien®, Ozurdex®, Retisert®, Yutiq®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Dexamethasone (Ozurdex®) and fluocinolone acetonide (Iluvien®, Retisert®, Yutiq®) intravitreal implants contain a corticosteroid.

Iluvien® is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Ozurdex® is indicated for the treatment of:
- Macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).
- Non-infectious uveitis affecting the posterior segment of the eye.
- Diabetic macular edema (DME).

Retisert® and Yutiq® are indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
Dexamethasone (Ozurdex®)	Macular edema, DME, uveitis	Inject the implant containing 0.7 mg dexamethasone intravitreally	One implant injection per eye every 6 months
Fluocinolone (Iluvien®)	DME	Inject the implant containing 0.19 mg fluocinolone intravitreally	One implant injection per eye every 12 months
Fluocinolone (Retisert®)	Uveitis	Inject the implant containing 0.59 mg fluocinolone intravitreally	One implant injection per eye every 30 months
Fluocinolone (Yutiq®)	Uveitis	Inject the implant containing 0.18 mg fluocinolone intravittreally	One implant injection per eye every 36 months

Dosage Forms

Drug Name	Availability
Dexamethasone (Ozurdex®)	Biodegradable intravitreal implant: 0.7 mg
Fluocinolone (Iluvien®)	Non-biodegradable intravitreal implant: 0.19 mg

Fluocinolone (Retisert®)	Non-biodegradable intravitreal implant: 0.59 mg
Fluocinolone (Yutiq®)	Non-biodegradable intravitreal implant: 0.18 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Macular Edema following BRVO or CRVO (must meet all):

1. Diagnosis of macular edema following BRVO or CRVO;
2. Request is for Ozurdex®;
3. Prescribed by or in consultation with an ophthalmologist;
4. Age ≥ 18 years;
5. Failure of both of the following (a and b) unless contraindicated or clinically significant adverse effects are experienced (see Appendix B):
   a. Intravitreal steroid injections;
   b. Intravitreal anti-VEGF agents;
6. Dose does not exceed 1 implant per eye.

Approval Duration
Commercial: 4 weeks (one implant per eye)
Medicaid: 4 weeks (one implant per eye)

B. Non-Infectious Uveitis (must meet all):

1. Diagnosis of non-infectious uveitis affecting the posterior segment of the eye;
2. Request is for Ozurdex®, Retisert®, or Yutiq®;
3. Prescribed by or in consultation with an ophthalmologist;
4. Member meets one of the following (a or b):
   a. For Ozurdex®, Yutiq®: Age ≥ 18 years;
   b. For Retisert®: Age ≥ 12 years;
5. Failure of ALL the following (a, b, and c) unless contraindicated or clinically significant adverse effects are experienced (see Appendix B):
   a. Intravitreal steroid injections;
   b. Systemic corticosteroid;
   c. Non-biologic immunosuppressive therapy;
6. Dose does not exceed 1 implant per eye.

Approval Duration
Commercial: 4 weeks (one implant per eye)
Medicaid: 4 weeks (one implant per eye)

C. Diabetic Macular Edema (must meet all):

1. Diagnosis of DME;
2. Request is for Ozurdex® or Iluvien®;
3. Prescribed by or in consultation with an ophthalmologist;
4. Age ≥ 18 years;
5. Failure of both of the following (a and b) unless contraindicated or clinically significant adverse effects are experienced (see Appendix B):

a. Intravitreal steroid injections;
b. Intravitreal anti-VEGF agents;

6. Dose does not exceed 1 implant per eye.

Approval Duration
Commercial: 4 weeks (one implant per eye)
Medicaid: 4 weeks (one implant per eye)

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.
2. Member is responding positively to therapy;
3. Member meets one of the following (a, b, c or d)
   a. At least 6 months have passed since last treatment with Ozurdex®;
   b. At least 12 months have passed since last treatment with Iluvien®;
   c. At least 30 months have passed since last treatment with Retisert®;
   d. At least 36 months have passed since last treatment with Yutiq®;
4. Dose does not exceed 1 implant per eye.

Approval Duration
Commercial: 4 weeks (one implant per eye)
Medicaid: 4 weeks (one implant per eye)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
BRVO: branch retinal vein occlusion
CRVO: central retinal vein occlusion
DME: diabetic macular edema
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
Anti-VEGF agents (e.g., bevacizumab, Lucentis®, Eylea®)	**Macular Edema** Refer to prescribing information	Refer to prescribing information
Intravitreal steroid injections [e.g., triamcinolone (Triesence®), dexamethasone, fluocinolone, etc.]	**Macular Edema and Uveitis** Refer to prescribing information	Refer to prescribing information
Systemic corticosteroids (e.g., prednisone)	**Uveitis** prednisone 5 – 60 mg/day PO in 1 – 4 divided doses	Varies

Drug Name	Dosing Regimen	Maximum Dose
azathioprine (Azasan®, Imuran®)	**Uveitis** 1.5 – 2 mg/kg/day PO	2.5 mg/kg/day
chlorambucil (Leukeran®)	**Uveitis** 0.2 mg/kg PO once daily, then taper to 0.1 mg/kg PO once daily or less	0.2 mg/kg/day
cyclophosphamide	**Uveitis** 1 – 2 mg/kg/day PO	N/A
cyclosporine (Sandimmune®, Neoral®)	**Uveitis** 2.5 – 5 mg/kg/day PO in divided doses	5 mg/kg/day
methotrexate	**Uveitis** 7.5 – 20 mg/week PO	30 mg/week
mycophenolate mofetil (Cellcept®)	**Uveitis** 500 – 1,000 mg PO twice daily	3 g/day
tacrolimus (Prograf®)	**Uveitis**	N/A

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Iluvien®, Ozurdex®, Retisert®, Yutiq® are contraindicated in patients with active or suspected ocular or periocular infections of the eye. Also in those with known hypersensitivity.
  - Iluvien®, Ozurdex® are contraindicated in patients with glaucoma with cup to disc rations of greater than 0.8.
  - Ozurdex® is contraindicated in patients with posterior lens capsules that is torn or ruptured because of the risk of migration into the anterior chamber.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Based on clinical trials with Retisert®:
  - Within 3 years post-implantation, approximately 77% of patients will require intraocular pressure (IOP) lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure.
  - Following implantation of Retisert®, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately one to four weeks post-operatively.

  - During the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.
- In one study, intravitreal bevacizumab 1.25 mg and the dexamethasone (DEX) 0.7 mg implant were compared in a randomized, Phase II trial called the BEVORDEX study. Forty-two eyes received intravitreal bevacizumab every 4 weeks, and 46 eyes received an intravitreal DEX (0.7 mg) implant every 16 weeks, with a when necessary (PRN) regimen for 12 months. The primary outcome of the study was to gain ten or more letters in the best-corrected distance visual acuity (BCVA) at 12 months, which was achieved in 40% of the bevacizumab-treated eyes and 41% of the DEX implant-treated group (P=0.99). The mean corneal refractive therapy (CRT) decrease was statistically significant between the groups, and the reduction was 122 µm in the bevacizumab group and 187 µm in the DEX implant group (P=0.015). The mean number of injections over 1 year was 8.6 for the bevacizumab group and 2.7 for the DEX implant group. Finally, in the DEX implant-treated eyes, 11% lost ten or more letters of the BCVA, which was due to cataracts in 4 of 5 cases; none lost ten letters in the bevacizumab-treated eyes.
- According to Pommier et al., an average of 2.6 injections of Ozurdex® were needed to obtain a 58.6% of patients who gained more than 15 letters, and 51.1% of patients showed macular edema resolution.
- Ozurdex®: The main rationale behind the 6-month restriction is safety. The onset of improvement in BCVA with Ozurdex® occurs in the first 2 months after implantation, with a further duration of action of 1 to 3 months. However, one of the main clinically significant adverse effects of corticosteroid implants is increased intraocular pressure (IOP). During the clinical trials, the mean IOP measurement in the study subjects showed that it increased by an average of 4 mmHg at Month 1.5 and returned to baseline by Month 6. This data pattern was replicated for each cycle of 6 months. Given that this was an average increase, while about 28% of the subjects showed IOP elevation of ≥ 10 mmHg from baseline, 15% showed of ≥ 30 mmHg from baseline, and 3% of subjects required surgical procedures for management of elevated IOP, there is a significant safety concern for repeated implantation of Ozurdex® more frequently than 6 months. This is supported by the clinical trial design which also limited successive treatments with Ozurdex® to at least 6 months apart. Other safety concerns for more frequent implantation of Ozurdex® are cataracts and conjunctival hemorrhage.

References

1. Iluvien® Prescribing Information. Alpharetta, GA: Alimera Sciences, Inc. November 2016. Available at: www.iluvien.com. Accessed October 7, 2020.
2. Ozurdex® Prescribing Information. Irvine, CA: Allergan, Inc. May 2018. Available at: www.ozurdex.com. Accessed October 7, 2020.
3. Retisert® Prescribing Information. Bridgewater, NJ: Valeant Pharmaceuticals; May 2019. Available at: www.retisert.com. Accessed October 7, 2020.
4. Yutiq® Prescribing Information. Watertown, MA: EyePoint Pharmaceuticals US, Inc; October 2018. Available at: www.Yutiq.com Accessed October 7, 2020.
5. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetic Care 2017;40:412-418. Accessed October 7, 2020.
6. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions. San Francisco, CA: American Academy of Ophthalmology; November 2015. Available at: www.aao.org/ppp. Accessed October 7, 2020.
7. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; February 2016. Available at: www.aao.org/ppp. Accessed October 7, 2020.
8. Durrani K, Zakka FR, Ahmed M, Memon M, Siddique SS, Foster CS. Systemic therapy with conventional and novel immunomodulatory agents for ocular inflammatory disease. *Surv Ophthalmol*. 2011;56(6): 474–510. Accessed October 7, 2020.

9. Gillies MC, Lim LL, Campain A, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. Ophthalmology. 2014;121(12):247-324. Accessed October 7, 2020.
10. Lam WC, Albiani DA, Yoganathan P, et al. Real-world assessment of intravitreal dexamethasone implant (0.7 mg) in patients with macular edema: the CHROME study. Clin Ophthalmol. 2015 Jul 10;9:1255-68. doi: 10.2147/OPTH.S80500. eCollection 2015. Accessed October 7, 2020.
11. Pommier S, Meyer F, Guigou S, et al. Long-term real-life efficacy and safety of repeated Ozurdex® injections and factors associated with macular edema resolution after retinal vein occlusion: The REMIDO 2 Study. Ophthalmologica. 2016;236(4):186-192. Accessed October 7, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated. Line of business policy applies was updated to “all lines of business”. 2. Dosage forms section formatting was updated. 3. Wording for age requirements in all initial therapy updated for simplicity. 4. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 5. Approval duration section was updated to remove HIM from initial and continued approval criteria. 6. Appendix B standard verbiage has been changed and updated. Also updated to remove discontinued drugs. 7. Appendix C was updated to simplify wording. 8. References were updated.	10/07/2020	12/07/2020