

CADTH RAPID RESPONSE REPORT: REFERENCE LIST

Ozurdex for Diabetic Macular Edema: Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Research Questions

1. What is the clinical effectiveness of dexamethasone intravitreal injection for patients with diabetic macular edema?
2. What is the clinical evidence regarding the safety of dexamethasone intravitreal injection for patients with diabetic macular edema?
3. What is the cost-effectiveness of dexamethasone intravitreal injection for patients with diabetic macular edema?
4. What are the evidence-based guidelines regarding dexamethasone intravitreal injection for the treatment of patients with diabetic macular edema?

Key Findings

Two systematic reviews (one with meta-analyses), two randomized controlled trials, and thirteen non-randomized studies were identified regarding the clinical effectiveness and safety of dexamethasone intravitreal injection for patients with diabetic macular edema. Additionally, three evidence-based guidelines were identified regarding dexamethasone intravitreal injection for the treatment of patients with diabetic macular edema.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ozurdex (dexamethasone) and diabetic macular edema. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and February 19, 2020. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-4: Adults with diabetic macular edema (DME) subgroups: people who are pseudophakic or who have natural lenses; patients unresponsive to or unable to receive anti-VEGF agents
Intervention	Q1-4: Dexamethasone 0.7 mg intravitreal injection; any number of implants (e.g., a single implant or two implants with approximately 6 months between doses, or continual treatment (i.e., 3 or more implants) or implants at intervals of less than every 6 months)
Comparator	Q1-3: - laser photocoagulation therapy - triamcinolone acetonide - anti-VEGF drugs (e.g., bevacizumab, ranibizumab, aflibercept) - any other treatment for patients who have failed anti-VEGFs - placebo or sham treatment - dexamethasone 0.7 mg intravitreal injections with a different number of implants Q2: no comparator Q4: not applicable
Outcomes	Q1. Clinical effectiveness (e.g., vision related function, health-related quality of life) Q2. Safety (e.g., glaucoma, eye inflammation, eye infections) Q3. Cost-effectiveness (e.g., cost per benefit gained, cost per QALY) Q4. Recommendations regarding the use of dexamethasone intravitreal injection for the treatment of patients with DME
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

Note: Studies addressing questions 1 and 2 prior to 2018 were excluded

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports and systematic reviews are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

Two systematic reviews¹⁻² (one with meta-analyses), two randomized controlled trials,³⁻⁴ and seven non-randomized studies^{5-9,14-15} were identified regarding the clinical effectiveness of dexamethasone intravitreal injection for patients with diabetic macular edema. Six non-randomized studies^{10-13,16-17} were identified regarding the safety of dexamethasone intravitreal injection for patients with diabetic macular edema. Furthermore, three evidence-based guidelines¹⁸⁻²⁰ were identified regarding dexamethasone intravitreal injection for the treatment of patients with diabetic macular edema. However, no relevant health technology assessments or economic evaluations were identified.

Additional references of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Bucolo C, Gozzo L, Longo L, Mansueto S, Vitale DC, Drago F. Long-term efficacy and safety profile of multiple injections of intravitreal dexamethasone implant to manage diabetic macular edema: A systematic review of real-world studies. *J Pharmacol Sci*.

2018 Dec;138(4):219-232.

[PubMed: PM30503676](#)

2. He Y, Ren XJ, Hu BJ, Lam WC, Li XR. A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema. *BMC Ophthalmol.* 2018 May 21;18(1):121.

[PubMed: PM29784048](#)

Randomized Controlled Trials

3. Sharma A, Bellala K, Dongre P, Reddy P. Anti-VEGF versus dexamethasone implant (Ozurdex) for the management of Centre involved Diabetic macular Edema (CiDME): a randomized study. *Int Ophthalmol.* 2020 Jan;40(1):67-72.

[PubMed: PM31377905](#)

4. Ozsaygili C, Duru N. Comparison Of Intravitreal Dexamethasone Implant And Aflibercept In Patients With Treatment-Naive Diabetic Macular Edema With Serous Retinal Detachment. *Retina.* 2019 Apr 2.

[PubMed: PM30950970](#)

Non-Randomized Studies

5. Bolukbasi S, Cakir A, Erden B, Karaca G. Comparison of the short-term effect of aflibercept and dexamethasone implant on serous retinal detachment in the treatment of naive diabetic macular edema. *Cutan Ocul Toxicol.* 2019 Dec;38(4):401-405.

[PubMed: PM31438736](#)

6. Busch C, Fraser-Bell S, Iglicki M, et al. Real-world outcomes of non-responding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results. *Acta Diabetol.* 2019 Dec;56(12):1341-1350.

[PubMed: PM31541334](#)

7. Cakir A, Erden B, Bolukbasi S, et al. Comparison of the effect of ranibizumab and dexamethasone implant in diabetic macular edema with concurrent epiretinal membrane. *J Fr Ophthalmol.* 2019 Sep;42(7):683-689.

[PubMed: PM31088741](#)

8. Coelho J, Malheiro L, Melo Beirao J, Meireles A, Pessoa B. Real-world retrospective comparison of 0.19 mg fluocinolone acetonide and 0.7 mg dexamethasone intravitreal implants for the treatment of diabetic macular edema in vitrectomized eyes. *Clin Ophthalmol.* 2019;13:1751-1759.

[PubMed: PM31571814](#)

9. Mastropasqua L, Di Staso S, D'Aloisio R, et al. Anatomical and functional changes after dexamethasone implant and ranibizumab in diabetic macular edema: a retrospective cohort study. *Int J Ophthalmol.* 2019;12(10):1589-1597.

[PubMed: PM31637195](#)

10. Mello Filho P, Andrade G, Maia A, et al. Effectiveness and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic macular Edema: A Real-World Experience. *Ophthalmologica.* 2019;241(1):9-16.

[PubMed: PM30408801](#)

11. Nalcaci S, Akkin C, Afrashi F. Dexamethasone Implant in Patients with Diabetic macular Edema Resistant to Anti-VEGF Therapy. *Turk J Ophthalmol*. 2019 Apr 30;49(2):73-77.
[PubMed: PM31055891](#)
12. Singer MA, Dugel PU, Fine HF, Capone A, Jr., Maltman J. Real-World Assessment of Dexamethasone Intravitreal Implant in DME: Findings of the Prospective, Multicenter REINFORCE Study. *Ophthalmic Surg Lasers Imaging Retina*. 2018 Jun 1;49(6):425-435.
[PubMed: PM29927470](#)
13. Bahadorani S, Krambeer C, Wannamaker K, et al. The effects of repeated Ozurdex injections on ocular hypertension. *Clin Ophthalmol*. 2018;12:639-642.
[PubMed: PM29662300](#)
14. Busch C, Zur D, Fraser-Bell S, et al. Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol*. 2018 Aug;55(8):789-796.
[PubMed: PM29730822](#)
15. Demircan A, Ozkaya A, Alkin Z, Kemer B, Yesilkaya C, Demir G. Comparison of the effect of ranibizumab and dexamethasone implant on serous retinal detachment in diabetic macular edema. *J Fr Ophthalmol*. 2018 Oct;41(8):733-738.
[PubMed: PM30213609](#)
16. Hatz K, Ebnetter A, Tuerksever C, Prunte C, Zinkernagel M. Repeated Dexamethasone Intravitreal Implant for the Treatment of Diabetic macular Oedema Unresponsive to Anti-VEGF Therapy: Outcome and Predictive SD-OCT Features. *Ophthalmologica*. 2018;239(4):205-214.
[PubMed: PM29402873](#)
17. Pareja-Rios A, Ruiz-de la Fuente-Rodriguez P, Bonaque-Gonzalez S, Lopez-Galvez M, Lozano-Lopez V, Romero-Aroca P. Intravitreal dexamethasone implants for diabetic macular edema. *Int J Ophthalmol*. 2018;11(1):77-82.
[PubMed: PM29375995](#)

Economic Evaluations

No literature identified.

Guidelines and Recommendations

18. Diabetes Canada Clinical Practice Guidelines Expert Committee, Filiberto A, Kherani Am, Lovshin J. 2018 Clinical practice guidelines: Retinopathy. *Can J Diabetes*. 2018; 42: S210–S216. Accessed 2020 Feb 27
<https://guidelines.diabetes.ca/docs/cpg/Ch30-Retinopathy.pdf>
See: Local (intraocular) pharmacological intervention (p.S213)
19. Excerpt from the Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. *Can J Ophthalmol*. 2017;51 (S1):S45-74. Accessed 2020 Feb 27
[https://www.canadianjournalofophthalmology.ca/article/S0008-4182\(17\)31047-5/fulltext](https://www.canadianjournalofophthalmology.ca/article/S0008-4182(17)31047-5/fulltext)
See: Intraocular steroid (p.S57-S58)

20. Dexamethasone intravitreal implant for treating diabetic macular oedema. (*Technology appraisal guidance no. TA349*). London (GB): National Institute for Health and Care Excellence; 2015. <https://www.nice.org.uk/guidance/ta349> Accessed 2020 Feb 27
See: 1 Guidance (p.4)

Appendix — Further Information

Previous CADTH Reports

21. CADTH Common Drug Review (CDR) clinical review report: dexamethasone (Ozuredex – Allergan Inc.). Ottawa (ON): CADTH; 2018 Nov.
https://cadth.ca/sites/default/files/cdr/clinical/SR0535_Ozuredex%20CL_Report.pdf
Accessed 2020 Feb 27
22. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: dexamethasone (Ozuredex – Allergan Inc.). Ottawa (ON): CADTH; 2018 Oct.
https://cadth.ca/sites/default/files/cdr/complete/SR0535_Ozuredex_Oct-26-18.pdf
Accessed 2020 Feb 27
23. CADTH Common Drug Review (CDR) pharmacoeconomic review report: dexamethasone (Ozuredex – Allergan Inc.). Ottawa (ON): CADTH; 2018 Nov.
https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0535_Ozuredex_PE_Report%20.pdf Accessed 2020 Feb 27

Systematic Review – Mixed Intervention

24. Mehta H, Hennings C, Gillies MC, Nguyen V, Campain A, Fraser-Bell S. Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. *Cochrane Database Syst Rev*. 2018 Apr 18;4:Cd011599.
[PubMed: PM29669176](https://pubmed.ncbi.nlm.nih.gov/29669176/)

Randomized Controlled Trials

Alternative Dosing

25. Fonseca ALA, Panetta H, Nascimento MA, Lira RPC, Arieta CEL. Effect of intravitreal dexamethasone solution on the reduction of macular thickness in pseudophakic diabetic patients in a public hospital in Brazil: a randomized clinical trial. *Clin Ophthalmol*. 2019;13:1523-1531.
[PubMed: PM31496644](https://pubmed.ncbi.nlm.nih.gov/31496644/)

Alternative Population

26. Li X, Wang N, Liang X, et al. Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients: randomized, sham-controlled, multicenter study. *Graefes Arch Clin Exp Ophthalmol*. 2018 Jan;256(1):59-69.
[PubMed: PM29119239](https://pubmed.ncbi.nlm.nih.gov/29119239/)

Mixed Intervention

27. Maturi RK, Glassman AR, Liu D, et al. Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic macular Edema: A DRCR Network Phase 2 Randomized Clinical Trial. *JAMA Ophthalmol*. 2018 Jan 1;136(1):29-38.
[PubMed: PM29127949](https://pubmed.ncbi.nlm.nih.gov/29127949/)

Alternative Outcome

28. Mehta H, Fraser-Bell S, Nguyen V, Lim LL, Gillies MC. The Interval between Treatments of Bevacizumab and Dexamethasone Implants for Diabetic macular Edema Increased over Time in the BEVORDEX Trial. *Ophthalmology Retina*. 2018 Mar;2(3):231-234.
[PubMed: PM31047591](#)
29. Mehta H, Fraser-Bell S, Nguyen V, Lim LL, Gillies MC. Short-term vision gains at 12 weeks correlate with long-term vision gains at 2 years: results from the BEVORDEX randomised clinical trial of bevacizumab versus dexamethasone implants for diabetic macular oedema. *Br J Ophthalmol*. 2018 Apr;102(4):479-482.
[PubMed: PM28779007](#)

Non-Randomized Studies

Alternative Outcome

30. Demir G, Ozkaya A, Yuksel E, et al. Early and Late Switch from Ranibizumab to an Intravitreal Dexamethasone Implant in Patients with Diabetic macular Edema in the Event of a Poor Anatomical Response. *Clin Drug Investig*. 2020 Feb;40(2):119-128.
[PubMed: PM31768784](#)
31. Hernandez Martinez A, Pereira Delgado E, Silva Silva G, et al. Early versus late switch: How long should we extend the anti-vascular endothelial growth factor therapy in unresponsive diabetic macular edema patients? *Eur J Ophthalmol*. 2019 May 16:1120672119848257.
[PubMed: PM31096782](#)

Mixed Population

32. Rajesh B, Zarranz-Ventura J, Fung AT, et al. Safety of 6000 intravitreal dexamethasone implants. *Br J Ophthalmol*. 2020 Jan;104(1):39-46.
[PubMed: PM31040132](#)
33. Hemarat K, Kemmer JD, Porco TC, Eaton AM, Khurana RN, Stewart JM. Secondary Ocular Hypertension and the Risk of Glaucoma Surgery After Dexamethasone Intravitreal Implant in Routine Clinical Practice. *Ophthalmic Surg Lasers Imaging Retina*. 2018 Sep 1;49(9):680-685.
[PubMed: PM30222802](#)

Mixed Intervention

34. Hernandez-Bel L, Cervera-Taulet E, Navarro-Palop C, Castro-Navarro V, Chiarri-Toumit C, Montero-Hernandez J. Sequential Dexamethasone and Aflibercept Treatment in Patients with Diabetic macular Edema: Structural and Functional Outcomes at 52 Weeks. *Ophthalmologica*. 2019;241(2):98-104.
[PubMed: PM29996128](#)
35. Jung YH, Lee Y. Efficacy of vitrectomy combined with an intraoperative dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol*. 2019 Jun;56(6):691-696.
[PubMed: PM30824977](#)

36. Kim KT, Jang JW, Kang SW, Chae JB, Cho K, Bae K. Vitrectomy Combined with Intraoperative Dexamethasone Implant for the Management of Refractory Diabetic macular Edema. *Korean J Ophthalmol*. 2019 Jun;33(3):249-258.
[PubMed: PM31179656](#)
37. Calvo P, Ferreras A, Al Adel F, Dangboon W, Brent MH. Effect Of An Intravitreal Dexamethasone Implant On Diabetic Macular Edema After Cataract Surgery. *Retina*. 2018 Mar;38(3):490-496.
[PubMed: PM28196056](#)

Alternative Population

38. Rezkallah A, Malcles A, Dot C, et al. Evaluation of Efficacy and Safety of Dexamethasone Intravitreal Implants of Vitrectomized and Nonvitrectomized Eyes in a Real-World Study. *J Ocul Pharmacol Ther*. 2018 Oct;34(8):596-602.
[PubMed: PM30117755](#)