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CADTH Reimbursement Recommendation

Dexamethasone Intravitreal Implant (Ozurdex)

Indication: For the treatment of adult patients with diabetic macular edema who are pseudophakic and have had an inadequate response to prior anti–vascular endothelial growth factor therapy

Sponsor: Allergan, an AbbVie Company

Final recommendation: Do not reimburse

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Ozurdex?

CADTH recommends that Ozurdex not be reimbursed by public drug plans for the treatment of adult patients with diabetic macular edema (DME) who are pseudophakic and have had an inadequate response to prior anti–vascular endothelial growth factor (VEGF) therapy.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial and 2 observational studies was insufficient to demonstrate a benefit with Ozurdex treatment over other available treatment options in the relevant patient population. It was highly uncertain how Ozurdex compared with anti-VEGF therapy in terms of improving clearness or sharpness of vision due to many limitations in the 3 studies, and there was no evidence comparing Ozurdex with triamcinolone acetonide.
- Patients identified a need for new treatments that are less invasive and/or require fewer injections, but Ozurdex is administered the same way as other drugs for DME and there was not enough strong clinical evidence to show that patients would experience a tangible benefit from reduced treatment frequency with Ozurdex.

Additional Information

What Is DME?

DME is an eye disease that can occur in people living with diabetes. It is caused by blood vessels leaking fluid into a part of the eye called the macula, which is responsible for sharp central vision and seeing fine detail. Untreated DME is a leading cause of visual loss, visual disability, and legal blindness in people with diabetes. It is estimated that 60,000 adults with DME in Canada experience vision impairment requiring treatment.

Unmet Needs in DME

Patients with DME expressed a need for new treatments that prevent the worsening of or improve vision and are less invasive and/or require fewer injections.

How Much Does Ozurdex Cost?

Treatment with Ozurdex is expected to cost approximately $2,892 to $5,784 for 2 to 4 injections, respectively, per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dexamethasone intravitreal implant not be reimbursed for the treatment of adult patients with DME who are pseudophakic and have had an inadequate response to prior anti-VEGF therapy.

The CADTH CDEC recommendation for dexamethasone intravitreal implant for the indication of adult patients with DME who are pseudophakic dated October 24, 2018, continues to apply to patients who are not included in the population evaluated in the resubmission.

Rationale for the Recommendation

There was insufficient evidence that treatment with dexamethasone implant results in added clinical benefit for patients with diabetic macular edema (DME) who are pseudophakic and have had an inadequate response to prior anti–vascular endothelial growth factor (VEGF) therapy. Evidence from a randomized controlled trial (RCT) authored by Shah et al. (N = 50 eyes) in patients with persistent DME following at least 3 anti-VEGF injections in the previous 5 months suggested that mean improvement in visual acuity (VA) was similar between dexamethasone implant and bevacizumab, and that reduction in central subfield thickness (CST) was greater with dexamethasone implant versus bevacizumab after 7 months of treatment. However, the comparative efficacy was highly uncertain due to numerous limitations of the RCT, including: no clearly stated hypotheses, no adjustment for multiple outcomes, small sample size, a mixture of pseudophakic and phakic patients with no subgroup analyses by lens status, and potential confounding from imbalances in baseline characteristics.

Results from a case-control study authored by Busch et al. (N = 76 eyes) comparing a switch to dexamethasone implant with continued anti-VEGF therapy in eyes with persistent DME following at least 3 monthly anti-VEGF injections suggested improved VA and CST with dexamethasone implant versus anti-VEGF therapy. However, this study suffered from the same limitations as the RCT and had additional limitations due to its retrospective design and incomplete reporting of methods. A case series authored by Thomas et al. (22 eyes in 11 patients) comparing a switch to dexamethasone implant with continued ranibizumab treatment within each patient had the same limitations as the Busch et al. study, and the studied treatment duration (3 months) was too short to assess efficacy. Due to the identified limitations, it was not possible to draw conclusions on the comparative efficacy of dexamethasone implant versus anti-VEGF therapies from any of the reviewed studies.

There were no relevant studies found comparing dexamethasone implant with intravitreal triamcinolone acetonide. Although safety outcomes were not comprehensively assessed in the studies, the increases in intraocular pressure (IOP) and use of IOP-lowering medications reported in the RCT in the dexamethasone implant group only was consistent with the known safety profile of the drug. Patients indicated a need for treatments that prevent worsening of or improve VA and have less of a treatment burden, but there is insufficient evidence that dexamethasone implant meets any of these needs given its uncertain comparative efficacy, intravitreal administration route, and lack of evidence for reduced treatment frequency.

Discussion Points

- The key evidence gaps noted in the initial CADTH recommendation for Ozurdex for DME from 2018 were the lack of high-quality direct evidence comparing dexamethasone implant with other active treatments for DME in Canada, uncertainty regarding the magnitude of benefit in VA with dexamethasone implant in the pseudophakic population, and insufficient data to assess the safety and efficacy of dexamethasone in patients who would use dexamethasone implant as second-line therapy. Although the Shah et al. RCT compared dexamethasone implant directly with bevacizumab in patients with DME who had an inadequate response to prior anti-VEGF therapy, the comparative efficacy was highly uncertain due to many limitations and the lack of separate pseudophakic subgroup analyses. The 2 retrospective observational studies also had limitations that meant conclusions could not be drawn from them. Therefore, the new evidence provided by the sponsor for the resubmission does not adequately address the evidence gaps previously identified by CDEC.
- The comparators used in the studies may not have been the most clinically appropriate for the patient population in Canada. Patients may switch to another agent from the same drug class if there is an inadequate response to a specific anti-VEGF therapy. In the Busch et al. study, patients remained on their first anti-VEGF therapy despite an inadequate response. In the RCT and Thomas et al. study, treatment history with specific agents was not reported and it was unclear whether during the studies patients received an anti-VEGF therapy they had previously failed on. As another intravitreal corticosteroid therapy, triamcinolone acetonide is of particular relevance, but no relevant studies were found comparing it with dexamethasone implant.
- Patient input described impacts of DME related to health-related quality of life (HRQoL); however, HRQoL was not assessed in any of the studies.
- Increases in IOP related to treatment with dexamethasone implant occurred in approximately half of patients in the RCT. While increase in IOP can be managed with topical medications, this represents a potentially sight-threatening adverse event and treatment would carry an additional expense and inconvenience.

Background

DME is a vision-related, micro-vascular complication of diabetes mellitus (types 1 and 2). It is characterized by multifactorial pathophysiology, reportedly mediated by angiogenic VEGF and inflammatory pathways. Current estimates in Canada show that more than 4 million patients were diagnosed with type 1 and type 2 diabetes in 2022. A retrospective study conducted in Canada in 2012 assessing patient records from the Southwestern Ontario database estimated the prevalence of DME in adults with diabetes to be 15.7%, and the prevalence of vision loss due to DME to be 2.56%. DME manifests slowly as progressive vision loss of varying degrees, primarily dependent on severity and duration, as well as the location of intraretinal fluid, among other factors. Common signs and symptoms of DME include blurred vision, retinal hemorrhages, retinal detachment, colours appearing “washed out” or faded, changes in contrast sensitivity, impaired colour vision, gaps in vision, and potentially permanent vision loss.

In Canadian practice, pharmacological and non-pharmacological therapeutic options are available for patients with DME. Anti-VEGFs are first-line options available in patients, administered intravitreally every month for up to 3 loading doses, and thereafter every 1 to 3 months. Health Canada–approved anti-VEGFs include ranibizumab and aflibercept, and recent additions such as brolucizumab and faricimab. Bevacizumab, an anti-VEGF agent, is also used in the first line in clinical practice but does not have Health Canada–approved indications for the treatment of DME and is reimbursed only in certain jurisdictions. Intravitreal corticosteroids, such as dexamethasone and triamcinolone, may be considered for patients who do not respond well to anti-VEGF treatment, especially for patients who have artificial lens implants (i.e., who are pseudophakic) because of the increased risk of cataract formation with corticosteroid treatment. In Canada, dexamethasone implants are indicated for use in DME patients who are pseudophakic. Focal laser, vitrectomy, and grid therapy are non-pharmacological treatment options available in later line settings, according to the clinician group input and the clinical expert consulted.

Dexamethasone implant received approval from Health Canada, with a notice of compliance (NOC) granted on April 15, 2015, for the treatment of adult patients with DME who are pseudophakic. Dexamethasone 0.7 mg biodegradable intravitreal implant (Ozurdex) is a sustained release, glucocorticoid receptor agonist. Dexamethasone is administered using the Dexamethasone Posterior Segment Drug Delivery System, which consists of a sterile, single-use system intended to deliver 1 implant into the vitreous cavity and was designed to prolong the duration of the dexamethasone effect in the eye. The product monograph notes that there is "very limited information on repeat dosing intervals less than 6 months" and highlights evidence from a 2-year observational study that "the use of more than two consecutive administrations is associated with increases in some adverse reactions; therefore, no more than two consecutive OZURDEX injections should be used, and an interval of approximately 6 months should be allowed between the two injections." However, clinical expert input to CADTH noted that, in practice, ophthalmologists readminister the dexamethasone implant approximately every 3 to 4 months, and treatment discontinuation is based on clinical considerations other than the maximum of 2 consecutive dexamethasone implants recommended in the product monograph.

Submission History

Dexamethasone implant (Ozurdex) has been reviewed previously by CADTH but received a negative recommendation from the CADTH Canadian Drug Expert Committee (CDEC) for the treatment of adult patients with DME who are pseudophakic. CDEC identified several gaps in the evidence presented by the sponsor during the submission. Key evidence gaps noted in the CDEC recommendation were the lack of high-quality direct evidence comparing dexamethasone implant with other active treatments used in Canada for the requested population, uncertainty regarding the magnitude of benefit with dexamethasone implant in the pseudophakic population, and insufficient data to assess the safety and efficacy of dexamethasone in patients who would use dexamethasone implants as second-line therapy. The sponsor has provided a resubmission to CADTH for dexamethasone implant for the treatment of patients with DME who are pseudophakic and have inadequate response to prior anti-VEGF therapies. The sponsor's reimbursement population differs from the Health Canada–approved indication in that it focuses on patients who have had an inadequate response to prior anti-VEGF therapies.

This resubmission is based on new evidence (1 RCT and 10 observational studies) submitted by the sponsor evaluating the use of dexamethasone implant in patients with DME, which was not available at the initial submission to CADTH in 2017.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of 1 RCT and 2 retrospective observational studies in patients with DME
- patients' perspectives gathered by 5 patient groups: Fighting Blindness Canada (FBC), the Canadian Council of the Blind (CCB), the Canadian National Institute for the Blind (CNIB), Vision Loss Rehabilitation Canada (VLRC), and Diabetes Canada (DC)
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating adult patients with DME
- input from 4 clinician groups: Eastern Canada Retina Specialists (ECRS), the Retina Society of Alberta, the Canadian Retina Society (CRS), and Retina Specialists From Western Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received a joint patient group submission of 5 organizations: FBC, CCB, CNIB, VLRC, and DC. FBC's goal is to understand why vision loss occurs, how it can be slowed, and how sight can be restored. CCB is a membership-based not-for-profit organization that brings together Canadians who are living with vision loss, including those who are blind, deafblind, or partially sighted, to promote a sense of purpose and self esteem along with enabling the efforts of each member to achieve an enhanced quality of life. CNIB is a non-profit organization that delivers programs and advocates to empower people impacted by blindness and remove barriers to inclusion. VLRC is a health services organization that provides training to enable people who are blind or partially sighted to develop or restore key daily living skills, helping to enhance their independence, safety, and mobility. DC is a national health charity representing millions of people living in Canada who are affected by diabetes. DC's mission is to provide education and services, advocate on behalf of people living with diabetes, support research and translate it into practical applications. Data were collected through an online survey made available to people in Canada living with DR or DME in January 2020, and shared across networks associated with the submitting organizations. A total of 67 patients living in Canada responded to the survey. In April 2020, CCB conducted a separate survey of 572 respondents on the impact of the COVID-19 pandemic on people living in Canada who are blind, deafblind, or partially sighted.

Overall, respondents indicated that both DR and DME had substantial and life-altering impacts, including: negative impact on the ability to perform daily activities such as reading, using a phone, and driving; anxiety over potential worsening of the condition; and increased

reliance on others. In addition, the CCB COVID-19 study showed that fear, anxiety, loneliness, and other psychosocial impacts were intensified for patients with age-related macular edema and DR during the pandemic. Respondents of the joint survey indicated that they had experience with a variety of DR or DME treatments, including anti-VEGF therapies and Ozurdex, and most indicated that intravitreal treatment prevented further loss of vision. When asked about the most difficult part of eye injection appointments, travel and waiting time were central concerns. The submission highlighted that the low number of respondents (4.5%) who received injections less than 3 months ago is disconcerting, potentially indicating low adherence to injections. Respondents indicated the following reasons for cancelling or delaying appointments: being too busy to attend the appointment, not feeling well, being unable to find someone to take them to the appointment, and being "scared to receive the injection."

Though the survey did not ask patients for their views on improving their experiences and outcomes, the submission highlighted that any treatment that reduces the physical, psychological, and logistical strain on patients would be preferred. A treatment that is less invasive, or one that is similarly invasive but that is administered less frequently, would be helpful in reducing this strain.

Clinician Input

Input From Clinical Expert Consulted By CADTH

According to the clinical expert consulted by CADTH for this review, the goal in treating patients with DME is to resolve macular edema and to improve vision while minimizing treatment-related complications. The expert highlighted that anti-VEGF therapies are available in the mainstay therapies in the first-line setting for patients with centre-involved DME, while steroids (dexamethasone implant or triamcinolone acetonide) are reserved for pseudophakic patients who have shown inadequate response while on anti-VEGF therapy, those with contraindication to anti-VEGF therapy (recent stroke, MI, or pregnancy), or those who cannot afford the cost of anti-VEGF therapies. The clinical expert noted that although anti-VEGFs have shown effectiveness in patients with DME, up to 40% of patients respond inadequately to repeated injections with anti-VEGFs; therefore, there is a need for other treatment options for these patients. In addition, the expert highlighted that treatment with anti-VEGFs requires monthly administration for up to 5 doses, which may be inconvenient for some patients. The expert also noted that anti-VEGFs are associated with high costs, concerns with the potential complications, and the possibility of no improvement with the vision despite treatment. The expert indicated that patients often mention the inconvenience of taking time off work to receive monthly treatments and discomfort associated with the injection.

The clinical expert consulted highlighted that the patients who are most likely to respond to treatment with dexamethasone implant are patients with chronic DME, because they are likely to have inflammation as part of the mechanism of DME. The clinical expert considered central retinal thickness (CRT) measured by optical coherence tomography (OCT) and VA to be important outcomes used in clinical practice. In the opinion of the clinical expert, a clinically meaningful response to treatment with dexamethasone would include a gain of 5 letters in Snellen acuity, or a reduction of CRT of 50 microns or more as measured by OCT. According to the expert, adverse events such as glaucoma, infection, migration of the implant to the anterior chamber, and lack of improvement in treatment would be considered when deciding to discontinue the dexamethasone implant.

The expert noted that dexamethasone implant can be administered in a community setting, hospital (outpatient clinic), or specialty clinic. An ophthalmologist familiar with the diagnosis and treatment of patients with DME is required to diagnose, treat, and monitor patients that receive dexamethasone implant.

Clinician Group Input

CADTH received 4 clinician group submissions for this review: ECRS (12 clinicians), the Retina Society of Alberta (8 clinicians), CRS (4 clinicians), and Retina Specialists From Western Canada (7 clinicians). ECRS is a group of independent retina specialists practising in various locations throughout Eastern Canada. The Retina Society of Alberta is a retina medical and surgical retina subspecialty practice of 8 physicians based in Edmonton who provide retina-related care to the northern half of Alberta. CRS represents the ophthalmologists in Canada whose primary area of patient care is surgical and/or medical vitreoretinal disease. Retina Specialists From Western Canada is a group of retina specialists practising in Western Canada (Manitoba, Saskatchewan, Alberta, British Columbia). The clinician group input was largely in agreement with the input received from the clinical expert consulted by CADTH.

The clinician groups and the clinical expert consulted generally agreed on the main goals of treatment, unmet needs of patients, and prescribing conditions. In addition to the treatment goals already mentioned, the clinician groups noted longer duration of action as an important treatment goal. The clinician groups indicated that patients who do not respond to anti-VEGF therapy can be identified after receiving 5 to 6 doses or at least 3 months of therapy. According to the ECRS, Retina Specialists From Western Canada, and CRS, patients may be switched to another anti-VEGF therapy after inadequate response with initial anti-VEGF therapy. Following anti-VEGF therapy failure (or if duration of response is shorter than 4 weeks, according to the Retina Society of Alberta), dexamethasone implant and triamcinolone are among the treatment options. In addition, the clinician groups mentioned that dexamethasone was considered particularly well suited for pseudophakic patients and those with vitrectomized eyes, due to predictable and lower risk of elevated IOP and a longer duration of action (most often about 4 months) compared with triamcinolone.

Clinician groups specified that patients with centre-involving DME who are resistant to first-line anti-VEGF therapy after at least 3 monthly injections would be considered to be best suited for the dexamethasone treatment. Patients with DME who would be least suited for dexamethasone treatment would include those with a tractional component (epiretinal membrane or vitreomacular traction), severe glaucoma, a known steroid response with IOP elevation, signs of chronic DME, aphakic eyes, or a compromised posterior capsule.

Clinician groups indicated that a clinically meaningful response to dexamethasone treatment would include resolution of DME (a 30% to 50% reduction in excess central fovea thickness) measured by OCT, VA improvement (20/50 Snellen equivalent or better), decreased frequency of treatment, and/or regression of diabetic severity score. The ECRS submission also mentioned that patients should be assessed monthly when treatment is initiated, and then every 3 months to monitor therapy outcomes and response as well as individual durability of the dexamethasone implant. The clinician groups indicated that chronic DME, potential side effects (elevated IOP, infection or inflammatory response, migration of the implant to the anterior chamber), and lack of clinical improvement (retina thickness and fluid that does not improve) would be considered as discontinuation factors.

The clinician groups and the clinical expert agreed that the duration of action for the dexamethasone injections is approximately 3 to 4 months.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for dexamethasone implant:

- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Protocol-Selected Studies

For this resubmission, the sponsor provided 11 published studies to support the current reimbursement request for the use of dexamethasone implant in pseudophakic patients who have had an inadequate response to anti-VEGF therapy. One of these 11 studies was an RCT that was included in the CADTH systematic review. No additional studies, other than the pivotal MEAD trials reviewed as part of the original Ozurdex submission, were identified in the literature.

The MEAD-10 and MEAD-11 trials were the pivotal studies for dexamethasone implant for the indication for the treatment of DME. As noted in the 2018 CADTH recommendation for dexamethasone implant for DME, between 9.1% and 16.0% of patients in the subgroup of pseudophakic patients included in the MEAD-10 and MEAD-11 trials had prior experience with anti-VEGF therapy, and the responses of these patients to anti-VEGF treatment were unknown. Given the uncertainty regarding response to prior anti-VEGF therapy and the fact that the MEAD trials were not designed or analyzed in a way to determine the efficacy or dexamethasone implant in pseudophakic patients with DME who have had an inadequate response to anti-VEGF treatment, the data from these trials could not be used to inform the present resubmission for dexamethasone implant.

Description of Studies

The study authored by Shah et al. (2016) was a prospective, randomized, patient-masked, phase III trial conducted at a single site in the US. The study was supported by an investigator-initiated trial grant provided by Allergan, Inc. Patients with DME and inadequate response to prior anti-VEGF therapy who met the eligibility criteria were randomized to 1 of 2 treatment groups: bevacizumab or dexamethasone implant. Patients whose right and left eye both met the eligibility criteria had 1 eye randomized to 1 treatment, with the other

eye assigned the other treatment. The study lasted for 7 months, and patients received monthly follow-up.

Eligible patients were adults aged 18 years and older with type 1 or type 2 diabetes mellitus with best corrected VA (BCVA) scores between 24 and 78 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/32 to 20/320 Snellen equivalent). Patients were required to have persistent DME, which was defined as a CST of greater than 340 mm measured by spectral domain OCT, despite at least 3 anti-VEGF injections within the previous 5 months. The mean changes from baseline to month 7 in VA and CST were assessed as the primary outcomes. Other outcomes included safety outcomes and proportion of 10- and 15-letter gainers from baseline to month 7.

Between January 29, 2014, and October 15, 2014, 50 eyes from 45 patients (mean age: 61 years; standard deviation [SD]: 10 years) were enrolled in the study, of which 23 eyes were assigned to the bevacizumab group and 27 eyes to the dexamethasone implant group. Most eyes were in patients with type 2 diabetes (20 eyes [87%] in the bevacizumab group and 27 eyes [100%] in the dexamethasone implant group). Nine eyes (39%) were pseudophakic in the bevacizumab group, versus 14 eyes (52%) in the dexamethasone implant group, and the rest of the eyes were phakic. The mean BCVA was 59 ETDRS letters (SD = 13) in the bevacizumab group and 59 ETDRS letters (SD = 12) in the dexamethasone group.

The bevacizumab group received 1.25 mg (in 0.05 mL) intravitreal injection of bevacizumab at baseline and every month thereafter, if re-treatment criteria were met. The dexamethasone implant group received 0.7 mg dexamethasone implant at baseline, month 3, and month 6. In the event that the eye did not meet the re-treatment criteria at month 3, the dexamethasone implant was administered at month 4. In cases where a patient's eye did not meet re-treatment criteria at month 6, a sham injection was administered. Re-treatment was administered only if VA was less than 83 letters or if CST was 300 µm or more.

The mean number of previous intravitreal anti-VEGF injections in the bevacizumab group was 15 (SD = 11) and 18 (SD = 12) in the dexamethasone implant group. Eleven eyes in the bevacizumab group and 29 eyes in the dexamethasone implant group had previously received intravitreal triamcinolone injections. The mean number of prior intravitreal triamcinolone injections in the bevacizumab group was 8 (SD = 6) and 9 (SD = 6) in the dexamethasone implant group. Three eyes in each group had previously received dexamethasone implant.

Efficacy Results

Visual Acuity

Mean BCVA at month 7 was 64 ETDRS letters (SD = 11) in eyes receiving the dexamethasone implant and 65 ETDRS letters (SD = 16) in eyes receiving bevacizumab. The mean change in BCVA from baseline to month 7 in eyes receiving the dexamethasone implant was 5.8 ETDRS letters (SD = 7.6) and 5.6 ETDRS letters (SD = 6.1) in eyes receiving bevacizumab, with a P value of 0.785 for the between-group comparison. The mean number of eyes considered as 10-letter gainers from baseline to month 7 was 9 (33%) in the dexamethasone implant group and 6 (26%) in the bevacizumab group. The mean number of eyes considered as 15-letter gainers from baseline to month 7 was 4 (15%) in the dexamethasone implant group and 3 (13%) in the bevacizumab group. In both treatment groups, no eyes were considered 10-letter or 15-letter losers. The mean time to 10-letter gain was 3.5 months (SD = 1.9) in the dexamethasone implant group versus 3.6 months (SD = 1.9) in the bevacizumab group.

Central Subfield Thickness

CST measurements were missing at 1 visit for 1 eye and 3 visits for another eye in the bevacizumab group, as well as at 1 visit each for 2 eyes in the dexamethasone implant group.

The mean CST at month 7 in eyes receiving dexamethasone implants was 336 µm (SD = 89) compared to 471 µm (SD = 157) in eyes receiving bevacizumab. The mean change in CST decreased by 122 µm (SD = 120) in the dexamethasone implant group, compared to a decrease of 13 µm (SD = 105) in eyes receiving bevacizumab (P = 0.001).

Harms Results

Adverse events (AEs) were not systematically reported aside from specific harms, ocular SAEs, and systemic SAEs. No withdrawals from study treatment due to AEs and no deaths were reported. Two eyes (7%) in the dexamethasone implant group and 3 eyes (13%) in the bevacizumab group had serious ocular adverse events. One eye (4%) in the dexamethasone group and 4 eyes (17%) in the bevacizumab group were in patients who had serious systemic adverse events.

An IOP of greater than 21 mm Hg was reported for at least 1 visit in 14 eyes (52%) for the dexamethasone implant group and none in the bevacizumab group. A greater proportion of eyes receiving dexamethasone implant presented with elevated IOP requiring glaucoma agents to control (n = 13; 50%) compared to eyes in the bevacizumab group (n = 1; 5%). No eyes required laser or incisional surgery for glaucoma in either group. Cataract progression was reported in 7 eyes (26%) in the dexamethasone implant group and 4 eyes (17%) in the bevacizumab group. There were no reports of endophthalmitis in either study group.

Critical Appraisal

Despite randomization, there appeared to be differences between groups in some baseline characteristics; for instance, pseudophakia was more common in the dexamethasone group and type 1 diabetes was more common in the bevacizumab group. Given the relatively small sample sizes in each group, these numerical differences may not be clinically important. Nevertheless, the differences undermine the RCT design of the study and suggest that characteristics of patients that may influence outcomes were not evenly distributed between treatment groups. Additionally, other potential confounders (e.g., baseline diabetes control measured by glycated hemoglobin, or hyperlipidemia, which can worsen the retinal exudate) were not reported.

There was no clearly stated hypothesis or adjustment for multiple outcomes, and it is likely that the trial was not powered to detect statistically significant differences between the 2 groups. There were no subgroup analyses in pseudophakic eyes. Patient history of cataract at baseline and cataract surgery during the study may have impacted the VA and CST findings because the study enrolled phakic eyes; however, this information was not clearly reported and the potential impact is unknown.

There is a potential for selection bias in favour of dexamethasone implant, given the possibility that patients were poor responders to anti-VEGF therapy based on their treatment history (mean number of prior anti-VEGF injections was 15 in the bevacizumab group and 18 in the dexamethasone implant group). According to the clinical expert consulted by CADTH, inflammation may have played a greater role in the etiology of DME in the study population compared with patients who have received fewer anti-VEGF injections. However, the influence

of treatment history in this study (which also included triamcinolone acetonide injections and dexamethasone implants for some patients) on treatment response remains unclear.

Bevacizumab may not have been the most appropriate anti-VEGF comparator in the RCT, given that patients had already received a mean of 15 to 18 anti-VEGF injections before being enrolled in the study. It was unclear whether patients were previously treated with bevacizumab only or switched to other anti-VEGFs. According to the clinical expert consulted by CADTH, patients who show inadequate response after receiving their first anti-VEGF will likely be switched to another anti-VEGF therapy before a corticosteroid such as dexamethasone implant is considered.

The frequency of administration of dexamethasone differed from the recommended dosage in the Health Canada–approved product monograph, but was consistent with the treatment interval of 3 to 4 months identified as appropriate and aligned with how dexamethasone is used in practice, according to clinical expert input.

Indirect Comparisons

No relevant indirect evidence was included in the sponsor's submission to CADTH or identified in the literature search conducted by CADTH.

Other Relevant Evidence

Of the remaining 10 studies in the sponsor's resubmission, 2 were retrospective observational studies (Busch et al. [2018] and Thomas et al. [2016]) with relevant comparisons and were summarized and appraised. The rest of the submitted studies were published observational studies; however, none included a relevant comparison, and all had significant limitations. Therefore, they do not adequately address the evidence gaps identified by CDEC and are not discussed further.

Description of Studies

The Busch et al. (2018) study was a multi-centre, retrospective, case-control study designed to compare the effectiveness of continued use of anti-VEGF therapy versus switching to dexamethasone implant on functional and anatomical outcomes in eyes with DME, with inadequate response following 3 initial anti-VEGF injections. Eligible eyes were treatment-naive at presentation and were initially treated with 3 monthly anti-VEGF injections (aflibercept, ranibizumab, or bevacizumab) at the loading phase, leading to an inadequate response. Inadequate response was defined as "5 or less letter gain in VA (including vision loss), or reduction of less than 20% of CST on SD-OCT 1 month after the third anti-VEGF injection."

Eligible eyes either continued with an anti-VEGF therapy or switched to dexamethasone implant (referred to here as the "dexamethasone implant" group) after a maximum of 1 additional anti-VEGF injection. Patients were also required to have VA and CST measurements at baseline, month 3 (after 3 loading anti-VEGF injections), at month 12, and at either month 6 or 9. Follow-up lasted 9 months (from month 3 to month 12). The mean changes in VA and CST from month 3 to month 12 were the primary end points examined. Mean change in the standardized area under the curve (AUC) of VA and CST from month 3 to month 12, and proportion of eyes gaining 10 or more and 5 or more letters, were secondary end points. There were 110 eyes in total from 105 patients, of which 72 eyes (n = 67 patients)

were treated with anti-VEGF therapy only, and 38 eyes (n = 38 patients) were switched to the dexamethasone implant.

Each eye receiving anti-VEGF therapy only was propensity score–matched to the eyes in the dexamethasone implant group. In total, 38 eyes (from 38 patients) were included in the matched anti-VEGF group, which were compared with the dexamethasone implant group. The mean age of patients in the matched anti-VEGF group versus the dexamethasone implant group at baseline was 61.2 years versus 63.1 years, respectively. There were 15 eyes (39.5%) in the matched anti-VEGF group that were pseudophakic, compared to 18 eyes (47.7%) in the dexamethasone implant group. The mean VA at month 3 was 0.52 logMAR (approximately 55 to 61 ETDRS letters) in the matched anti-VEGF group and 0.53 logMAR (approximately 55 to 61 ETDRS letters) in the dexamethasone implant group. The mean CST at month 3 was 444.0 µm (SD = 118.3) in the matched anti-VEGF group and 472.1 µm (SD = 124.1) in the dexamethasone implant group.

The Thomas et al. (2016) study was a retrospective, comparative, case series study designed to assess the effectiveness of therapeutic responses of matched contralateral eyes of patients with "recalcitrant" DME to continued anti-VEGF therapy versus dexamethasone implant. Eligible patients had bilateral DME and had previously undergone consistent monthly bilateral intravitreal injections with an anti-VEGF agent (ranibizumab). Patients were considered to have recalcitrant DME "if regular (monthly) anti-VEGF therapy were maintained for at least 3 months, and there was persistent central macular edema (greater than 300 µm) and/or a minimal response to therapy (less than 25% reduction in CMT) in both eyes." Patients received dexamethasone implant in 1 eye while being maintained on anti-VEGF therapy at regular intervals in the collateral eye. Patients were followed every 4 to 6 weeks, and the study lasted 3 months. VA, CMT, and IOP were evaluated on every visit.[17] The cohort included 11 eyes treated with the dexamethasone implant and 11 paired contralateral eyes that continued treatment with ranibizumab in the 3-month study period.

In the 11 patients enrolled, the mean age was 62 years (range, 51 years to 84 years). All patients had type 2 diabetes with a mean hemoglobin A1C of 6.51% (range, 5.9% to 7.0%) (most recent measurement). Eyes receiving dexamethasone implants had received a median of 8.0 prior anti-VEGF injections at treatment baseline versus a median of 8.5 anti-VEGF injections in contralateral eyes receiving ranibizumab. Eight eyes receiving the dexamethasone implant and 7 eyes receiving ranibizumab were pseudophakic.

Effectiveness Results

Visual Acuity

In the Busch et al. study, eyes that switched to dexamethasone implant had a mean VA of 0.41 logMAR (approximately 61 to 65 ETDRS letters) at month 12 compared to 0.53 logMAR (approximately 55 to 61 ETDRS letters) in the matched anti-VEGF group. The mean change in VA from month 3 (after 3 or 4 initial doses of anti-VEGF) to month 12 was an increase of 6.1 ETDRS letters in eyes in the dexamethasone implant group compared to a decrease of 0.4 letters in the anti-VEGF matched eyes (P = 0.004, multivariate analysis).

The mean change in VA from month 3, to month 12 based on AUC approach was an increase of 15.2 ETDRS letters in eyes in the dexamethasone implant group compared to an increase of 2.4 ETDRS letters in the matched anti-VEGF group (P = 0.008, multivariate analysis).

In the Thomas et al. study, the mean logMAR VA at baseline in eyes receiving dexamethasone implants was 0.415 (approximately 61 to 65 ETDRS letters) versus 0.394 (approximately 65 to 70 ETDRS letters) in eyes continuing with ranibizumab. The mean logMAR VA improved in both groups at month 3 and was 0.261 (approximately 70 to 76 ETDRS letters) in the dexamethasone implant group and 0.269 (approximately 70 to 76 ETDRS letters) in eyes continuing with ranibizumab. The difference between the groups was not statistically significant.

Central Subfield Thickness

In the Busch et al. study, the mean CST at month 12 was 380.3 µm in the dexamethasone implant group compared to 462.5 µm in the matched anti-VEGF group. The mean change in CST from month 3 to month 12 was a decrease of 92.8 µm in eyes receiving dexamethasone implants and an increase of 18.3 µm in the matched group of anti-VEGF eyes.

Central Macular Thickness

In the Thomas et al. study, the mean CMT from baseline to month 3 also improved in both treatment groups, with a larger decrease in the dexamethasone group (net decrease of 105.8 µm) than in the ranibizumab group (net decrease of 47.9 µm). The mean CMT at month 3 in eyes receiving dexamethasone implants was 355.6 µm (SD = 110.2) compared to 373.2 µm (SD = 142.6) in eyes receiving ranibizumab.

Harms Results

The Busch et al. study did not present any safety outcomes. No infectious endophthalmitis, vitreous hemorrhage, retinal detachment, or lens disruption or subluxation, were reported for both treatment groups during the study period of the Thomas et al. study. Two eyes receiving dexamethasone reportedly had an IOP of greater than 30 mm Hg during the study, which did not require IOP-lowering medications and they returned to normal levels at the end of the study.

Critical Appraisal

Several limitations were identified in both studies which impacts the interpretation of the findings and their generalizability to patients with DME who are pseudophakic and have had an inadequate response to prior anti-VEGF therapy.

It was unclear whether each study site in the Busch et al. study used standardized methods and procedures to collect data, which may introduce variability in measurements across centres. It was not reported in either study whether outcome measurements were validated for quality (completeness, correctness) before study initiation; therefore, there is a potential risk of information bias, and the direction of bias is uncertain.

In the Busch et al. study, propensity-matching procedures were used to ensure that the 2 groups investigated were comparable for various baseline prognostic factors and potential confounders. Differences in the matched characteristics were assessed using univariate logistic regression (an approach that is not recommended, because P values comparing the baseline factors between the treatment groups are influenced by sample size). However, the rationale behind the matching factors used was not provided; it was not clear whether the groups were adequately matched, as few details were provided regarding the balance diagnostics to determine the quality of the matching; and the distribution of these factors was not reported. The Thomas et al. (2016) study included contralateral eyes, which may have reduced variability in some confounders and other measurements. Although key potential

confounders important for DME patients were assessed at baseline included in the study, there remains a potential risk of confounding bias for other confounders (such as background care and concomitant medications) that may have impacted the findings. According to the clinical expert consulted by CADTH, key factors such as type of diabetes, diabetes control, and baseline cataract status (especially because the population was a mix of phakic and pseudophakic eyes) should have been considered.

Treatment exposure (number of injections) was reported in the Busch et al. study, but it was unclear whether patients who completed the initial anti-VEGF dosing period continued with the same drug afterward or had been allowed to switch to another anti-VEGF. If patients continued receiving the same anti-VEGF that they had an inadequate response to in the initial phase, then this may bias results in favour of dexamethasone implant. Additional treatments administered to patients (including ocular hypertensives) were reported in the Busch et al. (2018) study. Within the reported data, there appeared to be imbalances in panretinal photocoagulation and cataract surgery during the study period, which is concerning as these treatments are potential confounders in terms of efficacy; it is also unknown whether these imbalances point to underlying differences between the 2 groups. The Thomas et al. study did not present information on concomitant treatments.

HRQoL and other important outcomes identified in the CADTH protocol were not reported in either study. The effectiveness of the dexamethasone implant on HRQoL and other outcomes in patients in both study populations is uncertain.

It is unclear what treatment strategies (i.e., doses and treatment intervals) were used in the studies and whether they varied across centres in the Busch et al. (2018) study. This made it challenging to assess the generalizability of the interventions, particularly in the anti-VEGF groups.

Both studies enrolled a mix of phakic and pseudophakic patients, whereas the HC indication only includes pseudophakic patients. The sample sizes were limited and there were no analyses by lens status; thus, the generalizability of the findings to patients with DME who are pseudophakic is uncertain. The studies did not report some important patient characteristics (e.g., type of diabetes, baseline hemoglobin A1C, medications to control glucose levels) and therefore it could not be fully determined how well the study population was generalizable to practice.

The duration of the Thomas et al. study was considered relatively short by the clinical expert consulted, and may not have been appropriate to evaluate the long-term effectiveness and safety of dexamethasone implant on patient eyes with DME.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with DME who are pseudophakic and have had an inadequate response to prior anti- VEGF therapy
Treatment	Dexamethasone intravitreal implants
Submitted price	Dexamethasone intravitreal implant, 0.7 mg, single-use injection: $1,446.03
Treatment cost	$2,892 to $5,784 per year (2 to 4 injections)
Comparators	• Anti-VEGFs (basket comprised of aflibercept and ranibizumab) • Triamcinolone acetonide
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	15 years
Key data sources	• Efficacy data for dexamethasone implants were obtained from the MEAD studies (2 phase III, randomized, placebo-controlled trials). • Dexamethasone implants were assumed by the sponsor to be equally effective compared to all comparators.
Key limitations	• The assumption of equivalent efficacy between dexamethasone implants and comparators is associated with a high degree of uncertainty and is not adequately supported by the submitted evidence. No head-to-head RCTs have been performed comparing dexamethasone implants to ranibizumab, aflibercept, or triamcinolone, and the sponsor determined that an indirect treatment comparison was not feasible. The studies submitted by the sponsor to support equivalent effectiveness among treatments were subject to methodological limitations and poor generalizability to the reimbursement population. • Bevacizumab and brolucizumab were not included in the sponsor's analysis, which was deemed inappropriate based on clinical expert feedback obtained by CADTH. • Anti-VEGF therapy was modelled as a weighted basket instead of as individual interventions, which does not account for the individual efficacy and safety profile of each anti-VEGF agent. • The frequency of administration of dexamethasone implants is uncertain. The sponsor's submission is based on a 6-month injection frequency, which is in line with the Health Canada–approved monograph. Clinical expert input indicated that more frequent administrations may be required in clinical practice and that patients may receive up to 4 dexamethasone implants per year.
CADTH reanalysis results	• Given the key limitations with the available clinical evidence, the comparative clinical effects of dexamethasone implants compared to anti-VEGFs and triamcinolone in the reimbursement population are uncertain. The CADTH reanalysis assumed that there would be no difference in treatment effects (i.e., no difference in total QALYs), and a cost comparison between dexamethasone implant and its comparators was conducted to highlight the differences in drug costs. This assumption of equal efficacy is conservative, given that there is insufficient evidence to conclude that dexamethasone implant is not less effective than comparators in this population. • The annual cost for dexamethasone implants is $2,892, which is more costly than bevacizumab and

Component	Description
	triamcinolone (annual costs ranging from $2 to $138) but less costly than aflibercept and ranibizumab (annual costs ranging from $9,926 to $19,399). • There is insufficient evidence to justify a price premium for dexamethasone implant compared to currently available treatment options. A price reduction of greater than 99% would be required for the submitted price of dexamethasone implant to be equivalent to the lowest price comparator (triamcinolone).

DME = diabetic macular edema; LY = life-year; QALY = quality-adjusted life-year; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the proportion of market share allocated to triamcinolone was overestimated, and the administration frequency of dexamethasone implants is uncertain.

CADTH reanalysis included changes to the market shares of triamcinolone and anti-VEGFs and the annual number of dexamethasone implants. In the CADTH base case, which assumed 2 dexamethasone implants per patient per year, the estimated cost savings of funding dexamethasone implants was $959,445 in year 1, $1,660,656 in year 2, and $2,378,903 in year 3, for a 3-year total cost savings of $4,999,004. Should a more frequent injection frequency be adopted in clinical practice, the 3-year cost savings would be lower; at 4 injections per year, reimbursement of dexamethasone implants may be associated with cost savings of $1,905,534 over 3 years.

CADTH was unable to account for the use of bevacizumab owing to the structure of the sponsor's model and a lack of market share data. Should dexamethasone implant displace bevacizumab usage, the predicted savings may not be realized, and the reimbursement of dexamethasone implant may lead to increased costs to the drug plans.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: October 27, 2022

Regrets: None

Conflicts of interest: None