CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Dexamethasone (OZURDEX — ALLERGAN CANADA INC.)
Indication: For the treatment of adult patients with diabetic macular edema who are pseudophakic

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that dexamethasone not be reimbursed for the treatment of adult patients with diabetic macular edema (DME) who are pseudophakic.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	Final
Publication Date:	October 2018
Report Length:	8 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

DEXAMETHASONE (OZURDEX — ALLERGAN INC.)

Indication: For the treatment of adult patients with diabetic macular edema who are pseudophakic

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dexamethasone not be reimbursed for the treatment of adult patients with diabetic macular edema (DME) who are pseudophakic.

Reasons for the Recommendation:

1. There was no high-quality direct evidence comparing dexamethasone implant with other active treatments used in Canada for the treatment of adult patients with DME who are pseudophakic (e.g. laser therapy, intravitreal steroid, or anti-VEGF therapies) identified. The two phase III sham-controlled randomized controlled trials (RCTs) identified in the systematic review (MEAD-010 and MEAD-011) were designed to compare dexamethasone implant with sham.
2. Compared with sham, the mean change from baseline in best corrected visual acuity (BCVA) in the pre-specified subgroup of patients with DME who were pseudophakic did not exceed a 10-letter improvement (5.9 letters and 3.6 letters in MEAD-010 and MEAD-011 respectively), and between-treatment differences in the proportion of patients achieving a ≥ 15-letter improvement, favouring dexamethasone were modest; 18.1% (95% confidence interval [CI], 0.8 to 35.4) and 6.0% (95% CI, –5.7 to 17.8) in MEAD-010 and MEAD-011, respectively. Further, the lack of stratification by lens status and failure to control for multiplicity results in uncertainty regarding the magnitude of benefit.
3. Based on a pooled analysis of the MEAD trials, a higher percentage of pseudophakic patients in the dexamethasone group experienced adverse events, such as elevated intraocular pressure , compared with the sham group (29.4% and 9.0% , respectively), which is consistent with the adverse event profile of intravitreal steroid therapies.
4. The manufacturer-submitted indirect comparison (IDC) was limited by clinical and methodologic heterogeneity, and phase II studies comparing dexamethasone implant with ranibizumab or bevacizumab were not stratified by lens status and subgroup analyses for the pseudophakic population were not controlled for multiplicity and lacked statistical power. Thus, no conclusions could be made regarding the comparative efficacy and safety of dexamethasone implant versus relevant comparators for the treatment of adult patients with DME who are pseudophakic.
5. Between 9.1% and 16.0% of patients in the subgroup of pseudophakic patients included in the MEAD-010 and MEAD-011 trials, respectively, had prior experience with anti-VEGF therapy. However, the responses of these patients to anti-VEGF treatment (i.e., whether they had suboptimal responses or simply had been treated previously) is unknown. Therefore, there are insufficient data to assess the safety and efficacy of dexamethasone in patients who would use dexamethasone implants as second-line therapy (e.g., have had an inadequate response to or did not tolerate prior anti-VEGF therapy).

Discussion Points:

- The committee noted that the MEAD trials were designed to assess the efficacy and safety of dexamethasone implant in adults with DME; however, the Health Canada-approved indication was for the subgroup of pseudophakic patients. The sample size of this subgroup for the treatment arms of interest to this review (i.e., dexamethasone 700 mcg and sham) was small in both MEAD-010 (n = 94) and MEAD-011 (n = 93).
- The committee recognized that some patients have difficulty accessing the optimal frequency of injections with anti-VEGF therapy (e.g., due to transportation challenges or the need to take time off work or school), and that this was a key concern for patients. Although less frequent administration of dexamethasone may be advantageous for patients who have difficulty meeting the requirement for more frequent injections with an anti-VEGF, the committee noted that the uncertain efficacy and safety of dexamethasone implant compared to other available therapies was a significant concern.
- The committee noted that an increase in intraocular pressure related to treatment with dexamethasone implant could be managed with topical medications, though this would come at an additional expense and inconvenience.

Background:

Dexamethasone is a synthetic glucocorticoid receptor agonist and has a Health Canada-approved indication for the treatment of macular edema following central retinal vein occlusion, the treatment of non-infectious uveitis affecting the posterior segment of the eye, and the treatment of adult patients with DME who are pseudophakic. Dexamethasone is available as a biodegradable polymer matrix implant containing 700 mcg of dexamethasone for intravitreal injection. The dose recommended by Health Canada is 700 mcg per eye.

Submission History:

Dexamethasone was previously reviewed for the treatment of macular edema following central retinal vein occlusion and received a "do not list" recommendation from CDEC (see *Notice of CDEC Final Recommendation, April 25, 2012*).

The reasons for that recommendation were as follows:

1. Based on pooled data from two masked RCTs, the percentage of patients with macular edema due to central retinal vein occlusion who achieved a gain of at least 15 letters on the visual acuity chart was statistically significantly greater for dexamethasone intravitreal implant compared with sham treatment at days 30 and 60, but not at days 90 and 180.
2. Given the uncertainty around the duration of treatment effect, CDEC felt there was considerable uncertainty around the cost-effectiveness of dexamethasone intravitreal implant compared with sham.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of dexamethasone, one IDC submitted by the manufacturer, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience treating patients with DME as well as information submitted by patient groups about outcomes and issues important to patients with DME.

Patient Input Information:

Three patient groups — the Canadian Council of the Blind, the Canadian National Institute for the Blind, and the Foundation Fighting Blindness — responded to CDR's call for patient input. Patient perspectives were obtained from online surveys. The following is a summary of key input from the perspective of patient groups:

- DME has a significant impact on patients' daily lives, particularly on their ability to participate in work and school activities. The patient groups indicated that the psychological burden of the disease increases in parallel with the disease's seriousness.
- Patients' family members and friends also share in the disease burden. They often accompany patients to the hospital and other health centres, wait with them at these facilities, and provide care after the injection.
- Approximately 27% of survey respondents indicated they missed appointments in the past due to weather conditions (especially for those living in rural areas), length of travel time, anxiety about the injection, inability to get time off work or school, cost of transportation, or illness. Among the patients who were not compliant, the reasons for missing appointments were unaffordable drug prices (50%) and long wait times to see a specialist (50%).
- Overall, the cost, injection frequency, and accessibility of treatments were most important to patients. When evaluating any potential new treatments, a patient's overall experience and quality of life (both during and after treatment) are imperative.

Clinical Trials

CDR's systematic review included two phase III, multi-centre, multi-national, sham-controlled pivotal RCTs in patients with DME designed to assess the benefits and harms of dexamethasone based on BCVA using the ETDRS method. MEAD-010 (N = 494) and MEAD-011 (N = 554) randomized patients with DME in a 1:1:1 ratio of dexamethasone 700 mcg, dexamethasone 350 mcg, or sham. Retreatment could occur no sooner than six months and patients could receive up to seven treatments over the three-year duration of the studies. Both trials enrolled adults with type 1 or type 2 diabetes mellitus with fovea-involved DME, BCVA scores between 34

letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye as measured by the ETDRS method, and retinal thickness ≥ 300 µm as measured by optical coherence tomography (OCT) in the 1 mm central macular subfield of the study eye.

The Health Canada-approved indication is limited to adult patients with DME who are pseudophakic. Therefore, CDR focused on the pre-specified subgroup of patients enrolled in the MEAD trials that had a pseudophakic lens status (MEAD-010, n = 141; MEAD-011, n = 134 across the dexamethasone 700 mcg, 350 mcg, and sham treatment groups) that were derived from the intent-to-treat population and the safety population of the overall DME population. Furthermore, the Health Canada–approved intervention of interest for CDR was the dexamethasone 700 mcg intravitreal injection treatment arm; therefore, the dexamethasone 350 mcg intravitreal injection treatment arm will not be discussed.

Key limitations associated with the interpretation of the data from the MEAD trials include randomization not being stratified based on pseudophakic lens status, a lack of adjustment for multiple statistical testing, and imbalances in attrition and patient characteristics between treatment groups.

No clinical trials of dexamethasone implant versus other active treatments for pseudophakic patients with DME met the criteria for inclusion in the CDR systematic review. Three phase II trials which evaluated the effects of dexamethasone implant compared to anti-VEGF therapies (ranibizumab, bevacizumab) were identified, however these trials enrolled the general DME population, of which approximately 24% to 50% were pseudophakic. Some pseudophakic subgroup results were reported, however the lack of stratification at randomization based on this factor, as well as the absence of reporting on baseline characteristics for the pseudophakic population make it difficult to assess the comparative efficacy and harms between dexamethasone and anti-VEGF agents (i.e., bevacizumab and ranibizumab). These trials were also likely underpowered to detect differences between treatments in the psuedophakic subgroup and there was no control for multiple statistical testing.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed:

- average BCVA mean change from baseline using the area-under-the-curve (AUC) approach, change from baseline in BCVA at different times during the study, and ≥ 15-letter improvement from baseline by end of study, all of which were assessed using the ETDRS 14-line/70-letter visual acuity chart
- health-related quality of life as assessed by the National Eye Institute Visual Functioning Questionnaire–25 (NEI VFQ-25)
- central retinal thickness (CRT) as measured by OCT
- adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms (specifically, endophthalmitis, eye inflammation, eye infections, retinal detachment, increased intraocular pressure, arterial thrombotic event, dislocated implants, glaucoma, damage to optic nerve, defects in visual acuity and visual field, necrotizing retinitis, conjunctival hemorrhage, and vitreous hemorrhage).

Originally, the primary efficacy outcome in the MEAD trials was the proportion of patients with ≥ 15-letter improvement by the end of the study. The protocol was subsequently amended and the primary end point was changed to the average BCVA mean change (using the AUC approach) from baseline during the study.

Efficacy

The efficacy results presented are for the Health Canada-approved dose of dexamethasone (700 mcg intravitreal injection) for the subgroup of patients who are pseudophakic.

The adjusted least-square mean differences in average BCVA mean change from baseline between dexamethasone 700 mcg and sham treatment as measured by the ETDRS and using the AUC approach in the intention-to-treat population were 5.9 letters ([95% CI, [redacted]], $P < 0.001$) and 3.6 letters ([95% CI, [redacted]], $P = 0.018$) in MEAD-010 and MEAD-011, respectively. The minimal clinically important difference ranges were between 10 and 15 letters. Sensitivity analyses using a per-protocol population in both MEAD-010 and MEAD-011 were consistent with the primary analysis.

The difference in the proportion of patients achieving a ≥ 15-letter improvement by study end versus sham was 18.1% ([95% CI, 0.8 to 35.4], *P* = 0.043) and 6.0% ([95% CI, –5.7 to 17.8], *P* = 0.461) in MEAD-010 and MEAD-011, respectively. Based on pooled analysis of the two trials the difference in the proportion of patients achieving a ≥15 letter improvement at last visit was 12.4% (95% CI, 1.6 to 23.2) in favour of dexamethasone.

The adjusted least-square mean differences in average CRT as measured by OCT using the AUC approach were –117.9 µm ([95% CI, [redacted]], *P* < 0.001) and –61.5 µm ([95% CI, [redacted]], *P* = 0.007) in MEAD-010 and MEAD-011, respectively. The changes from baseline in CRT as measured by OCT were also evaluated at the last study visit and in a sensitivity analysis using the per-protocol population and were consistent with the AUC method.

The MEAD trials evaluated vision-related outcomes using the NEI VFQ-25. No statistically significant differences were observed between treatment groups with adjusted average least-square mean differences for the overall composite score of 2.4 ([95% CI, –2.0 to 6.8], *P* = 0.288) and –1.5 ([95% CI, –6.2 to 3.3], *P* = 0.542) in MEAD-010 and MEAD-011, respectively.

Harms (Safety and Tolerability)

Frequencies of AEs, SAEs, WDAEs, and notable harms were provided for the individual MEAD trials. However the most common AEs, SAEs, WDAEs, and notable harms were only reported based on a pooled analysis of adult patients with DME who were pseudophakic from the two MEAD trials.

A greater proportion of patients in the dexamethasone group experienced AEs compared with the sham group (74.1% and 61.0%, respectively). The AEs that occurred more frequently in the dexamethasone treatment groups compared with the sham groups were elevated intraocular pressure (29.4% and 9.0%, respectively) and secondary cataracts (5.9% and 2.0%, respectively), which is consistent with the AE profile of intravitreal steroid therapies. The frequency of blepharitis in the dexamethasone groups was lower than those observed in the sham groups ([redacted], respectively).

Similar frequencies of SAEs were reported in the dexamethasone groups compared with the sham groups. No data regarding the most common reasons for ocular SAEs were provided for the subgroup of patients who are pseudophakic. The overall WDAEs were similar between treatment groups; however, no data regarding the withdrawals due to ocular AEs were provided for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

A total of three deaths occurred in the MEAD trials in the pseudophakic subgroup. However, investigators did not consider any of the deaths to be related to study treatment.

The occurrence of the remaining notable harms (specifically, eye inflammation, retinal detachment, arterial thrombotic event, dislocated implants, glaucoma, damage to the optic nerve, conjunctival hemorrhage, and vitreous hemorrhage) was similar in both treatment groups across the MEAD trials. Endophthalmitis, eye infection, defects in visual acuity and visual field, and necrotizing retinitis were not reported in the MEAD trials.

Indirect Treatment Comparison

The manufacturer submitted an unpublished IDC to assess the comparative efficacy and safety of dexamethasone implant for use in the treatment of DME. [redacted]

[redacted]

Cost and Cost-Effectiveness

Dexamethasone intravitreal implant is available as a 700 mcg single use implant for intravitreal injection, at a submitted price of $1,400 per implant. At the recommended dose of one implant per treatment as required, the annual cost per patient may range from $1,400 (one dose per year) to $5,600 (four doses per year).

The manufacturer submitted a cost-utility analysis comparing dexamethasone implant with a no-treatment 'watch and wait' strategy for the treatment of DME in adults who are pseudophakic. The analysis was conducted from the public payer perspective over a 15 year time horizon. The manufacturer incorporated health states based on best corrected visual acuity measured by ETDRS scores (35 letters or less, then for every 10 letters gained, up to 76 letters or more). Patients could transition between health states every 3 months, and were assumed to receive dexamethasone implant at month 0, month 6, and then at every 3 months for a maximum of three years. The manufacturer also undertook scenario analyses comparing dexamethasone implant with ranibizumab (an anti-VEGF), but did not regard ranibizumab as a relevant comparator. Clinical inputs were primarily sourced from the three-year MEAD trials which compared dexamethasone implant with a sham procedure (a proxy for 'watch and wait'), and an IDC that incorporated one-year MEAD trials results along with other treatments including laser and anti-VEGFs.

The manufacturer highlighted a subgroup of patients: adults with DME who are pseudophakic and unsuitable for anti-VEGF therapy. They deemed this population to be clinically the same as the population assessed in the base case. The manufacturer presented a cost comparison analysis for the population of adults with DME who are pseudophakic and have had inadequate response to prior anti-VEGF therapy, based on a summary of post-hoc analysis, meta-analysis, and retrospective study data, to support a claim of superiority of dexamethasone implant compared to anti-VEGF therapy.

In their base case, the manufacturer reported that dexamethasone implant was associated with an incremental cost-utility ratio (ICUR) of $32,074 per quality-adjusted life-year (QALY) compared with the "watch and wait" strategy. The ICUR was less than $50,000 per QALY in 53% of probabilistic iterations. In the cost comparison, dexamethasone implant was cost-saving compared to anti-VEGF treatment.

CDR identified the following key limitations:

- Clinical data for the Health Canada-approved indication and key subgroup populations were limited and associated with uncertainty.
- The manufacturer did not consider all relevant comparators (e.g., laser therapy, intravitreal steroids).
- The comparative clinical effectiveness of dexamethasone implant with relevant comparators is uncertain. The primary outcome for the indicated population from MEAD trials lacked stratified randomization or adjustment for multiplicity and the submitted IDC (comparing dexamethasone implant with laser therapy and anti-VEGF treatments) was associated with substantial uncertainty given the clinical and methodological heterogeneity of the included trials.

CADTH considered an alternate measure of treatment effects using relative risks based on MEAD trial data provided by the manufacturer and revised cost information in re-analyses, resulting in an ICUR of $168,439 per QALY for dexamethasone implant compared with "watch and wait". There remains notable uncertainty associated with the cost-effectiveness of dexamethasone implant as the magnitude of incremental clinical benefit is unclear and there were limitations which could not be addressed by CADTH.

February 21, 2018 Meeting

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None.

October 17, 2018 Meeting

CDEC Members:

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None.