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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Dexamethasone (Ozurdex)

(Allergan Inc.)

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

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
BCVA	best-corrected visual acuity
CDR	CADTH Common Drug Review
DME	diabetic macular edema
DR	diabetic retinopathy
EQ-5D	EuroQol 5 Dimensions Health Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
INESSS	Institut national d'excellence en santé et en services sociaux
ICUR	incremental cost-utility ratio
IOP	intraocular pressure
MCID	minimal clinically important difference
MTC	mixed-treatment comparison
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
QALY	quality-adjusted life-year
RR	relative risk
SMC	Scottish Medicines Consortium
VEGF	vascular-endothelial growth factor
VFQ-UI	Visual Functioning Questionnaire – Utility Index
WTP	willingness to pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Dexamethasone 700 mcg intravitreal implant (Ozurdex)
Study Question	To conduct a cost-utility analysis (from a public-payer perspective) of dexamethasone implant compared with a "watch and wait" treatment strategy (i.e., observation or no treatment) in adult pseudophakic patients with visual impairment due to DME.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with DME who are pseudophakic.
Treatment	Dexamethasone 700 mcg intravitreal implant
Outcome	QALYs
Comparator	Base case: Monitoring-only ("watch and wait") Scenario analysis: Ranibizumab
Perspective	Canadian public health care payer
Time Horizon	15 years
Results for Base Case	• $32,074 per QALY gained vs. "watch and wait." • In 53% of simulations, the ICUR for dexamethasone implant was below $50,000 per QALY, and in 56% of simulations the ICUR was below $100,000 per QALY.
Key Limitations	• Clinical data for the indicated population was limited and associated with uncertainty, which has an impact on the confidence that can be placed on the results of the economic analysis. • The manufacturer did not consider all relevant comparators for the target population (e.g., laser therapy, intravitreal steroids, and anti-VEGF therapies). Although ranibizumab was considered in a scenario analysis, other anti-VEGFs (e.g., bevacizumab) were not included. • The comparative clinical effectiveness of dexamethasone implant with relevant comparators is uncertain, given that the MEAD trial primary outcome for the indicated did not exceed a 10-letter improvement (differences of 5.9 and 3.6 letters in MEAD-010 and MEAD-011 respectively) and were considered modest by the clinical expert consulted for this review, and these results were for a subgroup that was not stratified at randomization or adjusted for multiplicity. • The MTC used to derive comparative effectiveness of dexamethasone implant compared with "watch and wait" (and vs. ranibizumab in a scenario analysis) in the model was associated with substantial uncertainty, and the inclusion of these data in the base-case analysis was not appropriate given the head to head comparative data for dexamethasone implant and "watch and wait" from the MEAD trials, and the manufacturer's argument for excluding anti-VEGF and laser therapy as relevant comparators in the base case. • The modelling approach used by the manufacturer to incorporate treatment effects based on changes between health states of 10 letters may overestimate the effect of dexamethasone implant compared with "watch and wait." • Cost and resource use inputs in the economic evaluation were not reflective of Canadian public payer and overestimated the costs associated with the worst vision health state. • The model lacked appropriate supporting methodological documentation, was inflexible (model structure), and used unconventional methods to assess treatment effect which complicate the understanding of the approach taken by the manufacturer and limited the ability of CDR to conduct relevant reanalyses.

CDR Estimates	Given the limited generalizability of the clinical information, there is substantial uncertainty associated with the estimated cost-effectiveness of the dexamethasone implant for the target population for which the manufacturer is seeking reimbursement. Additional concerns were noted regarding the exclusion of relevant comparators in the base-case analysis, uncertain comparative treatment effect, and the unconventional methodology and lack of flexibility in the submitted economic model. CDR estimated the ICUR for dexamethasone implant vs. "watch and wait" to be $168,439 per QALY based on an alternate measure of treatment effect and revised cost information, though this estimate is associated with notable uncertainty due to the aforementioned limitations. Based on the CDR estimate, a price reduction of 76% would be required to achieve an ICUR less than $50,000 per QALY. The comparative effectiveness of dexamethasone compared with other relevant treatments currently used in clinical practice (e.g., laser therapy, intravitreal steroid, and anti-VEGF therapies) is not known. No conclusions could be made regarding the comparative efficacy and safety of dexamethasone versus other drugs (including anti-VEGFs) for the treatment of adult patients with DME who are pseudophakic.

DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; ICUR = incremental cost-utility ratio; MTC = mixed-treatment comparison; QALY = quality-adjusted life-year; VEGF = vascular-endothelial growth factor.

Drug	Dexamethasone (Ozurdex)
Indication	For the treatment of adult patients with diabetic macular edema who are pseudophakic
Reimbursement Request	As per Health Canada indication
Dosage Form	700 mcg intravitreal implant
NOC Date	April 16, 2015
Manufacturer	Allergan Inc.

Executive Summary

Background

Dexamethasone intravitreal implant (Ozurdex) is a glucocorticoid receptor agonist that targets angiogenic vascular-endothelial growth factor (VEGF) and pro-inflammatory pathways of diabetic macular edema (DME).[1] It received a Health Canada notice of compliance on April 16, 2015 for the treatment of DME in adult patients who are pseudophakic.[2] Dexamethasone implant is available as a 700 mcg intravitreal injection to be administered per eye — re-administered when there is presence of macular edema.[1] The price is $1,400 per single-use 700 mcg intravitreal implant.[3] The manufacturer requested reimbursement for the Health Canada–indicated population.[3]

CADTH previously recommended that dexamethasone implant not be reimbursed for the treatment of macular edema following central retinal vein occlusion due to uncertainty in the duration of treatment effect which resulted in uncertainty in the cost-effectiveness of dexamethasone implant compared with sham treatment.[4]

The manufacturer submitted a cost-utility analysis of dexamethasone implant compared with a "watch and wait" (no active treatment) approach for the Health Canada indication of adults with DME who are pseudophakic from the public-payer perspective over a 15-year time horizon.[3] The manufacturer incorporated health states based on visual acuity as measured by Early Treatment of Diabetic Retinopathy Study (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 three months, and were assumed to receive dexamethasone implant at month zero, month six and then every three months, for a maximum of three years.[3] Data from the MEAD trials[5] (which compared dexamethasone implant with a sham procedure, a proxy for "watch and wait") were used for dexamethasone implant, while relative risks (RRs) for improving, remaining stable, or worsening were applied for "watch and wait" (using dexamethasone implant as the reference product) from a mixed-treatment comparison (MTC) that compared dexamethasone implant to "watch and wait" (as well as laser and anti-VEGF therapies).[6] Although a scenario analysis was undertaken comparing dexamethasone implant with ranibizumab, an anti-VEGF, the manufacturer indicated that this is not a relevant comparator for the base-case analysis. The manufacturer presented two scenario analyses that included ranibizumab as a comparator based on data from the MTC and a retrospective chart review, as well as a supplemental cost comparison analysis for patients who have inadequate response to prior anti-VEGF therapy, accompanied by a summary of

post-hoc analysis, meta-analysis, and a retrospective study to support superiority of dexamethasone implant compared with anti-VEGF therapy. The manufacturer also identified two subgroups of interest; adults with DME who are pseudophakic and unsuitable for anti-VEGF therapy, and adults with DME who have an inadequate response to prior anti-VEGF therapy.[3]

The manufacturer reported that dexamethasone implant was associated with more costs and quality-adjusted life-years (QALYs) than "watch and wait," resulting in an incremental cost-utility ratio (ICUR) of $32,074 per QALY in the base case. The ICUR was less than $50,000 per QALY in 53% of probabilistic iterations. The manufacturer also undertook several scenario analyses; including two analyses that compared dexamethasone with ranibizumab therapy (in addition with "watch and wait"). In these analyses, dexamethasone implant produced fewer incremental QALYs (0.10 to 0.12 QALYs) than ranibizumab (0.20 to 0.25 QALYs) but was also less costly, resulting in an ICUR of $177,000 to $290,000 per QALY for ranibizumab compared with dexamethasone implant. The manufacturer also presented a cost comparison that indicated dexamethasone implant was cost-saving compared with ranibizumab.[3]

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the manufacturer's economic evaluations (cost-utility analysis and supplemental cost comparison), which has an impact on the validity of the submitted analysis and CDR's ability to undertake reanalyses.

Firstly, clinical data for the populations for which the manufacturer is seeking reimbursement are limited. The MEAD trials included only a small proportion of patients with DME who were pseudophakic. For the subgroups identified by the manufacturer, a smaller proportion had previously received anti-VEGF treatment, while it was difficult to assess whether the patients in the MEAD studies were 'unsuitable' for anti-VEGF therapy as defined by the manufacturer (e.g., disease-related complication, frequently hospitalized). The CADTH clinical review noted the study design and population may not be representative of the DME population in Canada and may limit the generalizability of the trial results. The submitted pharmacoeconomic analysis base case was based on pooled-MEAD trials data, as well as an MTC that considered a broader DME population. Data from the DME cohort of a retrospective chart review of ranibizumab that considered a broader retinopathy population was provided in a scenario analysis. Therefore, cost-effectiveness of dexamethasone implant based on the submitted model is highly uncertain; as is the assumption of cost savings compared with ranibizumab presented in the supplemental analysis based on non-comparative studies in populations that do not align with the Health Canada indication.

Secondly, the submitted pharmacoeconomic evaluation did not consider all relevant comparators for the Health Canada-approved indication (i.e., adults with DME who are pseudophakic), or for relevant subgroups identified by the manufacturer (i.e., adults with DME who are pseudophakic and either are unsuitable or inadequately respond to anti-VEGF therapy). Feedback from the clinical expert consulted for this review indicated that anti-VEGF, steroid, and laser therapies are relevant comparators for DME patients who are pseudophakic, and that a subset of patients within the reimbursement request population would receive an intravitreal steroid or laser therapy in current Canadian practice. With the exception of ranibizumab, the cost-effectiveness of dexamethasone implant compared with these treatments was not considered by the manufacturer.

The clinical meaningfulness of the treatment effect between dexamethasone implant and "watch and wait" is associated with uncertainty. CADTH clinical reviewers concluded that the magnitude of improvement in visual acuity of dexamethasone compared with sham is uncertain due to lack of stratified randomization and adjustment for multiplicity in the analysis for the pseudophakic subgroup in MEAD trials, while the between-group differences in visual acuity did not exceed a 10-letter improvement in either MEAD-010 or MEAD-011 (differences of 5.9 and 3.6 letters respectively) and were considered modest by the clinical expert consulted for this review.

Furthermore, treatment effect in the model was derived from a MTC that was of questionable relevance given the manufacturer's assertions that treatments included in the MTC (e.g., laser and anti-VEGF therapy) were not appropriate comparators, and were not considered in the base-case analysis (though one active treatment, ranibizumab, was considered in scenario analyses). The application of data from the MTC appear to overestimate the treatment effect of dexamethasone implant based on the individual patient data-derived treatment effect that was included in the submitted economic model. The CADTH clinical reviewers stated that due to the limitations associated with the MTC, "*no definitive conclusions could be made regarding the comparative efficacy and safety of dexamethasone versus other drugs (including anti-VEGFs) for the treatment of patients with DME who are pseudophakic*." The manufacturer also considered a comparison of dexamethasone implant and "watch and wait" (based on the MTC) against ranibizumab based on a naive comparison, as data for ranibizumab were based on a retrospective chart review that was not incorporated into the MTC. No evidence pertaining to the comparability of the populations for the real-world evidence to undertake the naive comparison was presented. CADTH considered the results of this analysis highly questionable.

Additionally, the community care and residential care costs used in the model may not be reflective of costs incurred in the Canadian public health care system and overestimate the costs for the worst vision health state.

Finally, the submitted model lacked flexibility (e.g., the model structure did not allow CDR to alter questionable inputs, such as considering alternate sources of utility values, inappropriate coding for the probabilistic analysis), appropriate supporting methodological documentation, and used an unconventional methodology to model clinical benefit (e.g., the RRs were calculated for "watch and wait" and applied to dexamethasone implant as the reference treatment).

CDR assessed the limitations identified where possible, and undertook scenario analyses to assess the impact of the parameters and the associated uncertainty on the cost-effectiveness of dexamethasone implant compared with "watch and wait." CDR considered a reanalysis in which treatment efficacy was modelled using RRs based on the MEAD trial data provided by the manufacturer, and community care costs and resource use reflective of the Canadian setting, while excluding residential care resource use, to best represent the CDR estimate. This resulted in an ICUR of $168,439 per QALY (incremental cost of $7,827, gain of 0.05 QALYs). However, CDR notes the uncertainty associated with this estimate given the issues with generalizability of the clinical data, the exclusion of relevant comparators, and other limitations that could not be adequately addressed. Such uncertainty contributes to a wide range of possible outcomes, from the manufacturer's submitted ICUR of $32,074 per QALY, to a CDR exploratory analysis which produced an ICUR of $652,815 per QALY. Based on CDR's estimate, a price reduction of 76% would be required for dexamethasone implant to achieve an ICUR less than $50,000 per QALY.

Conclusions

There is substantial uncertainty associated with the estimated cost-effectiveness of dexamethasone implant for the target population due to the uncertainty as to whether the clinical data are representative of the DME population in Canada, the quality of the comparative clinical effectiveness of dexamethasone implant with relevant comparators, and the methodology and lack of flexibility in the submitted economic model.

Based on an alternate measure of treatment effect and revised cost information, CDR estimated that the ICUR for dexamethasone implant compared with “watch and wait” may be $168,439 per QALY. However, CDR noted that the ICUR varied substantially depending on the magnitude of the incremental treatment effect attributable to dexamethasone implant. Based on CDR’s estimate, a price reduction of 76% would be required for dexamethasone implant to achieve an ICUR less than $50,000 per QALY. In this context, additional treatments (such as anti-VEGF therapies) would be relevant comparators, however CADTH clinical reviewers stated that no conclusions could be made regarding the comparative efficacy and safety of dexamethasone versus other drugs (including anti-VEGFs) for patients with DME who are pseudophakic, thus, no conclusions regarding the comparative costs or cost-effectiveness can be made for dexamethasone versus other drugs.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a Markov cohort-state transition model that compared dexamethasone 700 mcg implant with no treatment ("watch and wait") in adults with diabetic macular edema (DME) who are pseudophakic. A probabilistic analysis of 5,000 simulations during a 15-year time horizon with three-month cycles was considered.[3] This analysis was conducted from the perspective of a Canadian publicly funded health care payer. Dexamethasone implant was assumed to be administered every three months starting six months after the first dose (three times in the first year, four times each subsequent year). Costs and benefits were discounted at a rate of 1.5%. A half-cycle correction was incorporated.[3]

Patients entered the model with their better-seeing and worse-seeing eyes distributed across six best-corrected visual acuity (BCVA) health states that are based on the ETDRS scoring system (Figure 1).[3] Patients could have unilateral (treatment in one eye) or bilateral DME (treatment of both eyes), and only DME-affected eyes are eligible for treatment up to a maximum of three years. Patients could develop DME in their other eye (i.e., bilateral DME through fellow eye involvement) at the end of the first or second year in the model. Fellow eye involvement in subsequent years was not modelled to reduce model complexity. Each eye was modelled separately and allowed to transition to next best or next worse visual acuity states, and experience treatment-related adverse events (AEs), treatment discontinuations, and death.[3]

Patient characteristics were informed by the pseudophakic subpopulation data from the pooled-MEAD trials and represented a [redacted]% male population of [redacted] years of age on average. [redacted]% of patients had unilateral DME at baseline ([redacted]% had bilateral DME).[3] Mortality rates specific to DME and diabetes were incorporated with values from Canadian life tables. Treatment efficacy was modelled as a combination of health state transitions based on the individual patient data from the dexamethasone implant arm of the MEAD trials, and relative risks (RRs) of visual acuity changes derived from an unpublished mixed-treatment comparison (MTC) conducted by the manufacturer.[3,6] Raised intraocular pressure (IOP), retinal detachment, endophthalmitis, and vitreous hemorrhage were modelled as AEs; patients who experienced AEs were assumed to incur additional costs, but not AE-related disutilities. The rates of AEs were informed by MEAD trials data.[5] Utilities in the model were driven only by BCVA of better-seeing and worse-seeing eyes. To derive utilities for each visual acuity health state, mean BCVA scores of each state are multiplied by coefficients derived from a regression analysis of visual function specific utilities (Visual Functioning Questionnaire – Utility Index; VFQ-UI) and BCVA in MEAD trials. VFQ-UI values were elicited using National Eye Institute Visual Functioning Questionnaire 25 (NEI-VFQ-25) quality of life data collected in the pivotal trials.[3]

Direct medical and non-medical costs were included in the model. Drug acquisition, administration, and monitoring costs for the comparator treatments were included, as were additional treatments required for AEs (e.g., raised IOP), procedure costs associated with treatment of AEs, and community and residential care service costs for the most severe vision health state. Medical resource uses were sourced from clinician estimates. Drug costs were sourced from the manufacturer, or from the Ontario drug formulary, procedure costs

were sourced from the Ontario Schedule of benefits for physician services, and community care and residential care unit costs were informed by Quebec private-sector cost estimates,[3] and their utilization was informed by UK and US data.[7]

The manufacturer submitted a supplemental cost comparison for the subpopulation of adult, pseudophakic DME patients who have had inadequate response to anti-VEGF therapy,[3] which presented three studies to infer superiority of dexamethasone implant compared with anti-VEGF therapy.[8-10] The manufacturer also identified two subgroups of interest; adults with DME who are pseudophakic and unsuitable for anti-VEGF therapy, or who have an inadequate response to prior anti-VEGF therapy.

Manufacturer's Base Case

In their base-case analysis, the manufacturer reported a probabilistic ICUR of $32,074 per QALY gained for dexamethasone 700 mcg implant compared with "watch and wait" (Table 2). At a willingness-to-pay (WTP) threshold of $50,000 per QALY, the probability of dexamethasone implant being cost-effective compared with "watch and wait" was 53%, while the probability of being cost-effective was 56% at a WTP of $100,000 per QALY.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost vs. 'Watch and Wait' ($)	Total QALYs	Incremental QALYs vs. 'Watch and Wait'	Incremental Cost per QALY ($) vs. 'Watch and Wait'
'Watch and wait'	10,459	-	5.62	-	-
Dexamethasone implant	13,711	3,252	5.72	0.10	32,073

Source: derived from Manufacturer's Pharmacoeconomic Submission.[3]

QALY = quality-adjusted life-year.

Summary of Manufacturer's Additional Analyses

One-way sensitivity analyses conducted by the manufacturer identified that the largest drivers of the cost-effectiveness outcomes were treatment effect RRs, discount rates, proportion of severe vision loss patients receiving residential care, and mortality.

Scenario analyses were undertaken using deterministic analyses, which reported that shorter time horizons at 10 years and 5 years increased ICUR to $48,863 per QALY and $140,070 per QALY, respectively. ICUR also increased with discount rate; health and cost discount rates of 0% and 5% resulted in ICUR of $23,552 per QALY and $47,547 per QALY, respectively. A scenario analysis using RRs derived from MEAD trials instead of the MTC used in the base case resulted in higher ICUR of $100,061 per QALY. Using visual acuity utility coefficients calculated from MEAD trial baseline EQ-5D values instead of VFQ-UI resulted in higher ICUR of $67,245 per QALY. A scenario analysis from the societal perspective reported that dexamethasone implant was more effective and less costly than (dominated) "watch and wait."

The manufacturer presented two scenario analyses comparing dexamethasone with ranibizumab as well as "watch and wait." One scenario analysis based on the manufacturer's MTC reported that dexamethasone implant and ranibizumab treatments result in gains in QALYs compared with "watch and wait" (0.12 and 0.25, respectively), as well as incremental costs ($3,340 and $23,272, respectively). The ICUR for dexamethasone implant was $28,147 per QALY compared with "watch and wait," while ranibizumab had an

ICUR of $177,604 per QALY compared with dexamethasone implant. The other scenario analysis was based on naive comparison of data from the MTC (for dexamethasone and "watch and wait") and a retrospective chart review of ranibizumab, which incorporated broader population than pseudophakic DME patients.[11] In this analysis, dexamethasone implant and ranibizumab treatments resulted in 0.10 and 0.18 QALYs gains compared with "watch and wait," respectively, as well as incremental costs ($3,210 and $23,599, respectively). The ICUR for dexamethasone implant was $31,466 per QALY compared with "watch and wait," while ranibizumab had an ICUR of $290,370 per QALY compared with dexamethasone implant.

The manufacturer also undertook a supplemental analysis in the form of a cost comparison for the subpopulation of adult, pseudophakic DME patients who have had inadequate response to anti-VEGF therapy, reporting lower annual cost of dexamethasone implant and potential savings of $11,375 to $16,100 per year compared with anti-VEGF therapy.[3]

Limitations of Manufacturer's Submission

The following limitations were identified with the manufacturer's pharmacoeconomic submission:

- **Lack of consideration of appropriate comparators:** The manufacturer stated that laser and intravitreal steroids, such as triamcinolone acetate, are not appropriate comparators due to concerns regarding safety, efficacy, and formulation.[3] Feedback from the clinical expert consulted for this review indicated that these therapies are currently used in Canada for at least a subset of patients that fulfill the Health Canada indication, and therefore should have been considered within the manufacturer's pharmacoeconomic submission. Additionally, anti-VEGFs should have been included as relevant comparators in the base-case analysis, particularly the preferred initial therapy for DME, bevacizumab.[12] The cost-effectiveness of dexamethasone implant compared with laser therapy and triamcinolone is not addressed by this submission and remains uncertain.
- **The effectiveness of dexamethasone implant compared with "watch and wait" for the pseudophakic DME population is associated with uncertainty:** Although patients in the MEAD trials were reported to achieve improvements from baseline visual acuity for the pseudophakic population (i.e., 5.9 letters adjusted least-square mean difference in MEAD-010, 3.6 letters in MEAD-011), the clinical expert consulted for this review considered the improvement modest. CADTH clinical reviewers concluded that the magnitude of improvement in visual acuity is uncertain, given that the subgroup results were not adjusted using stratified randomization for lens status and were not adjusted for multiplicity. CADTH pharmacoeconomic reviewers noted these data were also used to inform the MTC.
- **Uncertain RRs derived from unpublished MTC associated with clinical heterogeneity:** The comparative effectiveness of dexamethasone implant with "watch and wait" in the base case, and with "watch and wait" and ranibizumab in a scenario analysis was based on RRs derived from a MTC which had notable heterogeneity [redacted], and included comparators that were ultimately not considered by the manufacturer in their base-case analysis (ranibizumab and laser therapy), which may influence the results of the MTC (see CDR Clinical Review for full critique of the MTC). Given that data used in the MTC [redacted], the use of direct comparative evidence already incorporated in the model from MEAD trials would have been more appropriate for the manufacturer's base-case analysis. Final results from the 3-year trial are also more reflective of the three-year

treatment duration assumed in the model than the MTC RRs that were derived from 12-month trial results. The manufacturer provided an alternative set of RRs derived from MEAD trials for use in a scenario analysis. However, there were no methodological details regarding the derivation of these RRs provided, which resulted in notable uncertainty in this analysis. Given the comparator in the model is "watch and wait" and the MEAD trials compared dexamethasone implant to sham procedure which was used as a proxy for "watch and wait," data from the MEAD trials alone should have been used to populate the model results for the manufacturer's base case.

The manufacturer's MTC also considered an anti-VEGF therapy, ranibizumab,[6] and produced RRs that were incorporated into a scenario analysis that included ranibizumab as an additional comparator.[3] Due to the substantial uncertainty associated with this MTC as previously noted, the comparative effectiveness of dexamethasone implant compared with ranibizumab is uncertain. Although the MTC was associated with substantial uncertainty, [redacted].

In an alternative scenario analysis, the manufacturer sourced the comparative effectiveness of ranibizumab from both the manufacturer's MTC and a retrospective chart review[11]. These data were assessed through a naive comparison that did not adjust for any potential treatment effect confounders. As the study also involved a broader population that adults with DME who are pseudophakic and only the 12-months results were incorporated into the model, it is uncertain whether these results would be representative of the Health Canada–indicated population during a longer time horizon and unlikely that these patient populations should have been compared.

- **Model potentially overestimates comparative benefit of dexamethasone implant:** The submitted model used health states based on ETDRS 10 letter increments to capture visual acuity change (< 36, 36 to 45, 46 to 55, 56 to 65, 66 to 75, > 75). It is thus uncertain whether utility values assigned to health states based on 10 ETDRS letter increments overestimates the extent the health utilities are influenced by visual acuity in the model, particularly when the changes between cycles may have been less than 10 letters (i.e., change from 53 letters to 57 letters which would involve movement to a different health state with improved utility values, but not necessarily any clinically meaningful change in vision).
- **Unconventional methodology used to assess comparative effectiveness:** The model used dexamethasone implant as the reference treatment using data from the MEAD trials to populate the transition probabilities, then used a RR derived from an MTC for "watch and wait" relative to dexamethasone implant. Furthermore, the model uses utility values derived from VFQ-UI, a disease specific utility based on visual function quality of life measure NEI-VFQ-25.[13] Although this utility index has been found to be valid, reliable and reproducible in uveitis population,[14] the use of utility values specific to visual function specific rather than a more general and comprehensive health function may not be reflective of overall patient preferences. Furthermore, the use of coefficients to model change did not allow CDR to appropriately test the inputs based on published literature reporting utility values for the relevant visual acuity health states.
- **Uncertain generalizability of the modelled population to Canada:** The CDR Clinical Review indicates that the patient characteristics of the MEAD trial arms are unbalanced in the pseudophakic subgroup. In addition to concerns regarding selection bias, the CDR Clinical Review also noted that the observed Canadian DME population are younger

than the patients in the MEAD trial population. The use of MEAD trials data thus may not be generalizable to the Canadian population for the requested indication, contributing to further uncertainty in the submitted model.

- **Cost and resource utilization not representative of Canadian public-payer setting:** The costs and resource utilization for community care and residential care associated with severe vision loss in the model were sourced from private-sector and international estimates respectively. Public health care costs[15] and Canada specific resource utilization would have been preferred given the decision problem. In Ontario, a 24-hour nursing care is required for admission to a provincial long-term care facility[16] and at least 90% of care home residents have cognitive impairment and multiple chronic conditions.[17] Severe vision loss alone is unlikely to incur such an extensive level of nursing care and unlikely to warrant attribution to residential care in such jurisdictions. Due to the high cost of residential care included in the submitted model and the reasons necessitating this type of care, the decision to include this cost could bias results in favour of dexamethasone implant due to less severe vision loss.
- **Potential post-treatment efficacy waning not considered:** Post-treatment visual acuity change probabilities in the model were sourced from an observational study of diabetic retinopathy patients with four-year follow-up, recruited from 1979 and 1980,[18] and adjusted for alignment to more recent diabetes management practices.[19] In addition to concerns regarding the generalizability of this data to the Canadian population, these visual acuity change probabilities are applied to eyes with discontinued treatment throughout the entire 15-year model time horizon. It may be possible that efficacy gained during treatment is eventually lost post-treatment. The MEAD trial results indicate that treatment efficacy peaks early during the first year.[5] Assuming no post-treatment efficacy waning may favour of dexamethasone implant, as the visual acuity gained by the treatment group would be maintained indefinitely relative to the untreated group in the post-treatment period.
- **Data are limited in the subgroups of interest for the manufacturer:** The MEAD trials included only a small proportion of patients who were pseudophakic and had previously received anti-VEGF therapy ([redacted]%, n =[redacted]), and there was no pre-requisite that patients had to fail anti-VEGF therapy before being included in the trials. Additionally, it is difficult to ascertain whether the patients included in the studies were 'unsuitable' for anti-VEGF treatment, given the vague nature of the definition.
- Various sources of information (post-hoc trial analysis, meta-analysis, and retrospective study publications) were used by the manufacturer to support the cost comparison that assesses dexamethasone implant or ranibizumab in patients who had an inadequate response to anti-VEGF therapy. However, this information was not comparative in nature and thus the claim of non-inferiority of dexamethasone implant and ranibizumab cannot be established, and the submitted cost comparison is inappropriate. Furthermore, the majority of these data were not derived from the pseudophakic DME population, thus the effect of dexamethasone implant in the relevant treatment population is still unknown.
- **The submitted model lacked flexibility and appropriate supporting methodological documentation:** The model was structured in a way that did not allow CDR to reasonably alter inputs based on available information, such as the methodology used to model utility inputs and duration of dexamethasone therapy (including for fellow eye involvement).

Additional limitations or areas of concern were noted in the Data Sources and Key Assumptions tables (Table 13 and Table 14).

CADTH Common Drug Review Reanalyses

CDR identified considerable uncertainty with several parameters in the submitted model, leading CDR to undertake several scenario analyses to highlight this uncertainty. CDR undertook the reanalyses presented in Table 3, revising the manufacturer's values for alternate estimates identified by CDR or provided by the manufacturer. These revisions resulted in notable changes to the cost-effectiveness of dexamethasone implant compared with "watch and wait" (Table 4).

Table 3: Parameters and Values of Interest Tested by CDR (Compared with "Watch and Wait")

Parameter	Manufacturer's base case	Source	CDR scenario analysis	Source
Community care (costs, proportion of severe patients to whom cost is applied)	$7,804, 6%	Private sector and UK	$3,680, 50%	Ontario, assumption
Residential care (costs, proportion of severe patients to whom cost is applied)	$18,890, 30%	Private sector and UK	$62,377, 0%	Ontario, assumption
RR of improving / remaining stable / worsening	0.56 / 1.06 / 2.11	Manufacturer's MTC (DEX as reference)	0.40 / 1.43 / 0.85[a]	MEAD data (provided by manufacturer, DEX as reference)
Utility coefficients (BSE, WSE)	0.0023, 0.0013	Derived from MEAD trial (VFQ-UI over trial length)	0.0016, 0.0003	Derived from MEAD trial (EQ-5D at baseline)
Proportion of patients receiving treatment at each time point up to end of 4 years	70% at 6 months, then for each 3 months after; 7%, 55%, 10%, 50%, 10%, 36%, 16%, 30%, 25%, 23%, 23%, 26%, 26%	Pseudophakic population use from MEAD trial at each relevant time point	50% at each time period	Assumption based on treatment effect seen over time from MEAD

BSE = best-seeing eye; DEX = dexamethasone implant; EQ-5D = EuroQol 5-dimensions questionnaire; MTC= mixed-treatment comparison; RR = relative risk; VFQ-UI = Visual Function Questionnaire – Utility Index; WSE = worse-seeing eye.

[a] CDR tested these values in the probabilistic analyses using a 20% standard error and normal distribution.

Table 4: CDR Scenario Analysis Results on the Manufacturer's Base Case (versus 'Watch and Wait')

Comparator	Total Costs ($)	Incremental Costs ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY gained)
Revised Resource Use and Costs for Community Care Costs, Residential Care Excluded					
"Watch and wait"	5,146	—	5.61	—	—
Dexamethasone implant	11,908	6,743	5.72	0.10	66,155
Revised RR of Improving/Remaining Stable/worsening: MEAD Trials, Manufacturer-Provided Values					
"Watch and wait"	6,869	—	5.66	—	—
Dexamethasone implant	13,721	6,852	5.71	0.05	142,000
Revised Utility Coefficients for BSE Based on EQ-5D Values					
"Watch and wait"	10,450	—	5.43	—	—
Dexamethasone implant	13,712	3,262	5.51	0.10	38,873
Revised Utility Coefficients for BSE and WSE Based on EQ-5D Values					
"Watch and wait"	10,583	—	5.19	—	—
Dexamethasone implant	13,703	3,121	5.24	0.05	61,302
Revised Proportion of Patients Receiving Dexamethasone Implant at Each Modelled Time Point (50%)					
"Watch and wait"	10,428	—	5.61	—	—
Dexamethasone implant	16,802	6,374	5.71	0.10	63,381

BSE = best-seeing eye; EQ-5D = EuroQol 5-dimensions questionnaire; ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year; RR = relative risk; WSE = worse-seeing eye.

CDR considered the revised cost inputs and assumptions, and the manufacturer's RRs from MEAD data (though CDR noted the uncertainty with the given the manufacturer's RRs from the MEAD trials given the lack of methodology provided regarding their calculation) to provide an estimate for the CDR reanalysis that would be more appropriate than the submitted analysis. This resulted in an ICUR of $168,439 per QALY for dexamethasone compared with "watch and wait" (Table 5); however, this estimate is associated with uncertainty given the limitations highlighted earlier. CDR also undertook an exploratory analysis (Appendix 5) using RRs calculated from IPD-derived health state transitions in the submitted model to test the uncertainty associated with treatment effect.

Table 5: CDR Estimate (Compared with "Watch and Wait")

Comparator	Total Costs ($)	Incremental Costs ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY Gained)
Manufacturer Base Case					
'Watch and wait'	10,459	—	5.62	—	—
Dexamethasone implant	13,711	3,252	5.72	0.10	32,073
CDR Estimate					
'Watch and wait'	4,064	—	5.67	—	—
Dexamethasone implant	11,891	7,827	5.71	0.05	168,439

ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year.

A price reduction of 76% is required to achieve an ICUR below $50,000 per QALY (Table 6).

Table 6: CDR Reanalysis Price Reduction Scenarios

ICURs of Dexamethasone vs. "Watch and Wait"		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Submitted	$32,073 per QALY	$168,439 per QALY
10% reduction	$25,377 per QALY	$142,525 per QALY
20% reduction	$18,811 per QALY	$132,652 per QALY
30% reduction	$10,918 per QALY	$124,599 per QALY
40% reduction	$3,617 per QALY	$101,522 per QALY
50% reduction	Dominant	$96,905 per QALY
60% reduction	Dominant	$75,355 per QALY
70% reduction	Dominant	$61,569 per QALY
76% reduction	Dominant	$48,957 per QALY
80% reduction	Dominant	$45,942 per QALY
90% reduction	Dominant	$28,465 per QALY

ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year.

Issues for Consideration

- **Impact of diabetes treatment:** Feedback from the clinical expert consulted by CDR indicated that if a patient is adequately controlled for their diabetes, this may impact the need for treatment specific to DME. However, information on the impact of this is not well reported.
- **Pipeline treatments.** Additional DME treatments, such as intravitreal steroid fluocinolone acetonide, may be soon approved in Canada, which could impact the cost-effectiveness of dexamethasone implant.

Patient Input

Input was received from three patient groups: the Canadian Council of the Blind (CCB), the Canadian National Institute for the Blind (CNIB), and the Foundation Fighting Blindness (FFB). Sixty-four persons living with DME provided input and noted that DME is a disabling condition that exerts a significant impact on many aspects of their life including their ability to participate in work and maintain employment, their psychosocial functioning, and their ability to undertake activities of daily living. Additionally, frequent use of health care services, particularly among persons receiving injections to treat their DME, was reported to have a significant impact on patients' productivity, as well as on the lives of their family members or caregivers. Loss of productivity, caregiver burden, and other indirect costs such as home modifications were incorporated in a scenario analysis for the societal perspective. Respondents reported that as DME is also frequently associated with other comorbid conditions, there was a need to consult a range of health care providers to manage their condition and associated complications. This was not captured in the submitted model.

Patients noted that laser treatment and anti-VEGF therapies comprise the mainstay of DME treatment; yet, access to and compliance with recommended therapies may be problematic for some patients. Namely, improved access to injection therapy was associated with older age, residence in an urban setting, and higher income. While the majority of patients receiving injection therapy were compliant with the recommended treatment regimen, one in ten patients who were recommended monthly injections were noncompliant, and about one-

third of respondents indicated having previously missed medical appointments (due to length of travel time, injection-related anxiety, cost of transportation, illness, or inability to take time off work). Access to treatment was not considered in the submitted model. While the majority of respondents did not report any experience with dexamethasone implant, a decreased frequency of injection was considered a key factor which may lead to improved compliance and overall improvement in patients' quality of life.

Conclusions

There is substantial uncertainty associated with the estimated cost-effectiveness of dexamethasone implant for the target population due to the uncertainty as to whether the clinical data are representative of the DME population in Canada, the quality of the comparative clinical effectiveness of dexamethasone implant with relevant comparators, and the methodology and lack of flexibility in the submitted economic model.

Based on an alternate measure of treatment effect and revised cost information, CDR estimated that the ICUR for dexamethasone implant compared with "watch and wait" may be $168,439 per QALY. However, CDR noted that the ICUR varied substantially depending on the magnitude of the incremental treatment effect attributable to dexamethasone implant. Based on CDR's estimate, a price reduction of 76% would be required for dexamethasone implant to achieve an ICUR less than $50,000 per QALY. In this context, additional treatments (such as anti-VEGF therapies) would be relevant comparators, however CADTH clinical reviewers stated that no conclusions could be made regarding the comparative efficacy and safety of dexamethasone versus other drugs (including anti-VEGFs) for patients with DME who are pseudophakic, thus, no conclusions regarding the comparative costs or cost-effectiveness can be made for dexamethasone versus other drugs.

Appendix 1: Cost Comparison

The comparators presented in Table 7 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 7: CDR Cost Comparison Table of Treatments for Adults with DME Who Are Pseudophakic

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost per Eye ($)
Dexamethasone implant	**700 mcg (single use)**	**intravitreal implant**	**1,400.0000[a]**	**700 mcg intravitreally as needed**	**1,400 to 5,600 (1 to 4 injections)[b]**
VEGF inhibitors for the treatment of retinal conditions					
Aflibercept (Eylea)	2 mg/50 mcL (40 mg/mL) (single-use vial)	solution for intravitreal injection	1,418.0000	2 mg intravitreally once every four weeks for first 5 consecutive doses, then 1 injection every 8 weeks	**First year:** 12,762 (9 injections) **Subsequent years:** 8,508 to 9,926 (6 to 7 injections)
Ranibizumab (Lucentis)	10 mg/mL (2.3 mg/0.23 mL single-use vial or 1.65 mg/0.165 mL pre-filled syringe)	solution for intravitreal injection	1,575.0000	0.5 mg monthly until max visual acuity achieved (i.e., stable for 3 consecutive months), resume if recurrence of vision loss	**Maximum:** 18,900 (12 injections) **Observed in trial:** 11,025 in the first year (7 injections)[f] **Subsequent years:** 4,725 to 6,300 (3 to 4 injections)[g]
Other VEGF inhibitors — not indicated for DME					
Bevacizumab (Avastin)	100 mg/4 mL 400 mg/16 mL	solution for injection	519.1700[h] 2,076.7104[h]	1.25 mg every four to six weeks[i]	4,673 to 6,749 (9 to 13 injections)[d]
Other Corticosteroid Therapies — not indicated for DME					
Triamcinolone acetonide (Kenalog-40, generic)	40 mg/1 mL 200 mg/5 mL	injectable suspension	8.9600 31.6500	4 mg once every 3-4 months[c]	27 to 36 (3 to 4 injections)[d]
Triamcinolone acetonide (Triesence)	40 mg/1 mL (single-use vial)	suspension for intravitreal injection	41.6800[e]	1 to 4 mg intravitreally (25 mcL to 100 mcL of 40 mg/mL) every 3-4 months	125 to 167 (3 to 4 injections)
Other treatments					
Laser photocoagulation	NA	NA	182.7500[j]	As needed when retreatment criteria met, no more than every 12 weeks[k]	183 to 914 (1 to 5 treatments)

DME = diabetic macular edema; NA = not applicable; VEGF = vascular-endothelial growth factor.
All prices are from the Ontario Drug Benefit Formulary (accessed August 2018) unless otherwise indicated and do not include costs of product dispensing, dose preparation, or administration. Annual period assumes 52 weeks, or 13 x 4 weeks per year (365 days for all comparators). The calculated annual doses are based on product monograph where available and reported as a range of discrete number of doses if the calculated average dose is not a whole number. When multiple formulations were available, the least expensive type was used to calculate costs.

[a] Manufacturer submitted price.[3]

[b] Dosing based on MEAD trials. Patients received one to seven doses during the course of three years, mean 4.1 doses. Retreatment was available every three months.[5 c] Dosing based on the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study[20]

[d] For off-label products that may require compounding, maximum costs were calculated assuming single-use formulation and product wastage.

[e] Wholesale acquisition price based on IQVIA DeltaPA database (accessed November 2017)[21]

[f] Based on rounded average dosing in the RESTORE study: seven doses in year 1, of which the first three monthly injections were administered to all patients.[22]

[g] Based on rounded average dosing in the RESTORE extension study: patients with prior ranibizumab treatment received mean 6.8 doses over months 12 to 35.[23 h] Wholesale acquisition price based on IQVIA DeltaPA database is $129.7925 per mL in 4 mL or $129.7944 per mL16 mL vial.[21]

[i] Dosing based on American Academy of Ophthalmology.[24]

[j] Ontario Schedule of Benefits for Physician Services Under the Health Insurance Act (effective April 1, 2016), code E154[25]

[k] Dosing based on VIVID DME trial.[26]

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes & Quality of Life, How Attractive Is Dexamethasone 700 mcg Intravitreal Implant Relative to "Watch and Wait?"

Dexamethasone 700 mcg intravitreal implant Vs. 'Watch and wait'	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio	$168,439 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Note: Based on CDR reanalysis.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	References could not be verified for some inputs, including clinician surveys and individual patient-level data. Methodology for deriving the inputs used in a scenario analysis and the probabilistic analysis were unclear.		
Was the material included (content) sufficient?			X
Comments	The manufacturer provided a weak rationalization for excluding relevant comparators in their submission. The submitted economic model programmed utility values as a function of visual acuity only – this inflexible model structure prevented reanalyses using other health state utility values as these could not be converted as a function of visual acuity.		
Was the submission well organized and was information easy to locate?			X
Comments	Both the economic model and report are inconsistent and suffer from multiple errors. Though multiple attempts were made to obtain additional information from the manufacturer; uncertainties still remain.		

Table 10: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

The cost-effectiveness of dexamethasone intravitreal implant for the treatment of DME has been assessed by National Institute for Health and Care Excellence (NICE)[27] and the Scottish Medicines Consortium (SMC)[28] in the UK, Quebec's Institut national d'excellence en santé et en services sociaux (INESSS),[29] and (twice) by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.[30,31] The NICE, SMC, PBAC, and INESSS reviews are summarized in Table 11 and Table 12.

Intravitreal dexamethasone was also assessed by the Haute Authorité de Santé (HAS) in France for the treatment of DME, who recommended intravitreal dexamethasone for the indicated population, with reimbursement rate set at 30%.[32]

Table 11: HTA Findings: NICE and SMC

	NICE (July 2015)[27]	SMC (April 2015)[28]
Treatment	Dexamethasone 700 mcg intravitreal implant (DEX)	
Price	Redacted.	£870 to £1,740 in 1st year (1.00 GBP = 1.85 C$; April 2015)
Similarities with CDR submission	• CUA that compared DEX with watch and wait. • 15-year Markov model included six health states (defined by a 10-letter range in BCVA). • Patients treated in their BSE and WSE were modelled separately, and bilateral treatment was included. • Clinical data inputs for the DEX arm were sourced from the MEAD trials. • Patients were treated for three years (maximum), after which natural history rates were applied. • Utility estimates appear to be from the same sources.	
Differences with CDR submission	• Different base case (all DME) population. • Base case: RAN as comparator. • Supplemental analyses: vs. bevacizumab, laser, "watch and wait" in pseudophakic DME; vs. fluocinolone acetonide in phakic DME. • Data from full DME pop proxy for population unsuitable/not responding to non-corticosteroids.	• Different base case (all DME) population. • RAN comparator for pseudophakic population. • Scenario analysis: DEX vs. fluocinolone in pseudophakic. • Efficacy of "watch and wait," RAN, laser, fluocinolone estimated from MTC.
Manufacturer's results	• DEX dominated "watch and wait" for DME patients. • In pseudophakic, ICER for RAN vs. DEX = £89,531/QALY.	• DEX less costly, less effective vs. RAN in pseudophakic. • DEX dominated "watch and wait" in patients unsuitable/not responding to non-corticosteroid therapy (cost: –£1,046; QALY: 0.6026).
Issues noted by the review group	• Baseline BSE and WSE distributions across BCVA states independent, WSE may be in better BCVA state than BSE at baseline and throughout model. • Stable relative treatment effect from treatment onset to 3 years uncertain (MEAD suggests this is not correct). • Normalization of transition probabilities likely introduced bias — direction / magnitude bias unclear. • Can only move 1 BCVA state/cycle - not reflect trial. • Fluocinolone acetonide, laser not included.	• Limitations with MTC (patient populations, study design); caution assuming comparable efficacy for DEX and RAN. • Unclear if "watch and wait" appropriate comparator. • Non-significant differences in efficacy for DEX and "watch and wait" (from MTC) — may be inappropriate. • Results in total DME of MEAD assumed for patients unsuitable/insufficiently responsive to non-corticosteroid therapy — appropriateness not clear.

	NICE (July 2015)[27]	SMC (April 2015)[28]
Results of reanalyses by the review group	• Corrections do not change dominance of DEX vs. "watch and wait" for all DME. • Pseudophakic: RANI dominant at 50% discount. • Corrections to model: £50,849 to £52,494/QALY at list price of RAN.	None reported.
Recommendation	DEX recommended if: treated eye has pseudophakic lens; **and**, DME doesn't respond to non-corticosteroid treatment or such treatment is unavailable.	DEX accepted for adults with visual impairment due to DME who are pseudophakic, or don't respond to/unsuitable for non-corticosteroid therapy.

BCVA = best-corrected visual acuity; BSE = best-seeing eye; CUA = cost-utility analysis; DEX = dexamethasone implant; DME = diabetic macula edema; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; MTC = mixed-treatment comparison; NICE = National Institute for Health and Care; QALY = quality-adjusted life-year; RAN = ranibizumab; SMC = Scottish Medicines Consortium; WSE = worst-seeing eye.

Table 12: HTA Findings: PBAC and INESSS

	PBAC (March 2015 and March 2016)[30,31]	INESSS (February 2016)[29]
Treatment	Dexamethasone 700 mcg implant (posterior segment drug delivery system)	Dexamethasone 700 mcg intravitreal implant
Price	Redacted	$1,295 per implant
Similarities with CDR submission	• Resubmission assessed cost-effectiveness in pseudophakic DME patients for similar population (patients otherwise treated with anti-VEGF where no alternative exists and patients who fail to respond to anti-VEGF). • Comparative effectiveness using MEAD and indirect comparisons. • Costs of managing elevated IOP (with DEX) included.	• CUA of DEX vs. "watch and wait" in pseudophakic DME, unsuitable for anti-VEGF. • 6 state Markov model, with treatment discontinuation, unilateral and bilateral DME, 15-year time horizon. • Efficacy of DEX from MEAD; efficacy "watch and wait" from unpublished NMA. • Utility estimates appear to be the same.
Differences with CDR submission	• First submission: CMA vs. RAN. • Resubmission: CMA vs. RAN, aflibercept; supplemental CEA (cost per BCVA letter gained).	• CMA initially submitted; INESSS requested CUA • Societal perspective • Patients contraindicated to anti-VEGF or who failed anti-VEGF not considered.
Manufacturer's results	Redacted (although PBAC report noted CMA indicated DEX resulted in cost savings vs. VEGF inhibitors).	Redacted.
Issues noted by the review group	• CMA approach not justified — non-inferiority not supported by clinical evidence. • Exchangeability of patient populations in indirect comparisons subject to uncertainty. • Estimates of relative frequency of retreatments of DEX vs. anti-VEGF unreliable — problems with sample size, exchangeability, applicability of data sources. • PBS noted it would be appropriate to reduce price of DEX vs. least costly PBS-listed anti-VEGF.	• Original CMA did not consider anti-VEGF, and was not justified based unsupported clinical claims. • Results of unpublished NMA were uncertain. • Proportion of patients with >10-letter vision loss in MEAD not statistically significant, deemed inappropriate for inclusion in analysis. • 10-year TH sufficient to capture differences in clinical benefits (per RAN submission).
Results of reanalyses by review group	None reported.	• $176,382/QALY, using a 10-year TH • $126,523/QALY, if price DEX reduced by 25% • $77,665/QALY, if price DEX reduced by 50%.
Recommendation	• **March 2015:** PBAC rejected DEX; evidence did not conclusively establish clinical non-inferiority of DEX vs. RAN and bevacizumab. Eligible patient population and place in therapy of DEX not well defined.	• List DEX with clinical criteria and conditions for the treatment of visual impairment due to DME in pseudophakic patients for whom anti-VEGF therapy is unsuitable.

	PBAC (March 2015 and March 2016)[30,31]	INESSS (February 2016)[29]
	• **March 2016:** PBAC recommended DEX be listed on basis of inferior effectiveness and safety compared with RAN, aflibercept, thus on appropriately-adjusted estimates of cost-effectiveness, as well as on an unmet clinical need for this therapy.	

DEX = dexamethasone implant; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis; DME = diabetic macula edema; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; INESSS = Institut national d'excellence en santé et en services sociaux; NMA = network meta-analysis; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; QALY = quality-adjusted life-year; RAN = ranibizumab; TH = time horizon; VEGF = vascular-endothelial growth factor.

Appendix 5: Reviewer Worksheets

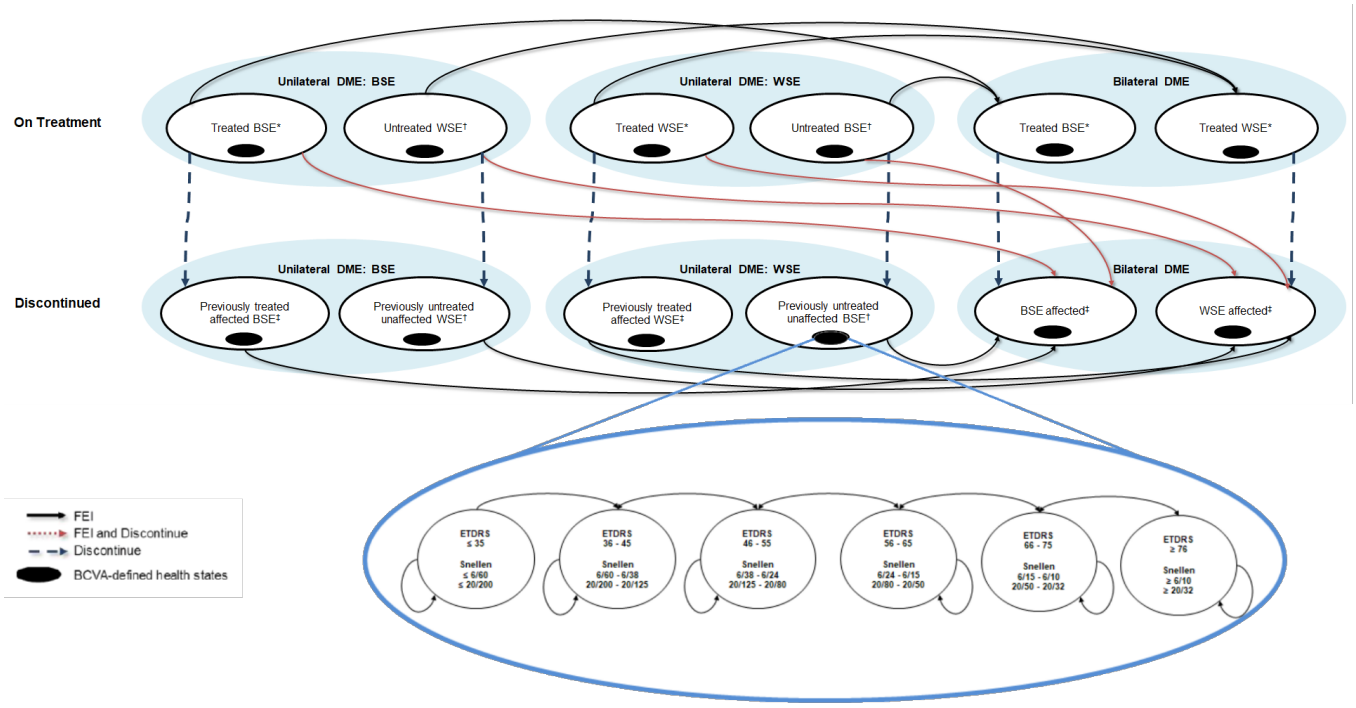
Manufacturer's Model Structure

The manufacturer stated that the submitted model was an adapted version of similar models reviewed and accepted by the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Institut national d'excellence en santé et en services sociaux (INESSS) and have resulted in positive funding decisions.[33] The submitted Markov cohort-state transition model consisted of 145 health states: 72 on-treatment states, 72 off-treatment states, and an absorbing death state (Figure 1).

Age, sex, treatment choice, treatment status, and DME presence influence the transition probabilities between each health state. Age and sex influence mortality risk; treatment choice influences risks of adverse event, discontinuation, and BCVA progression; and treatment status and DME presence influences BCVA progression. Transition probabilities associated with ≥10 ETDRS letters BCVA improvement, ≥ 10 ETDRS letters BCVA worsening, and <10 ETDRS letters BCVA improvement or worsening for the dexamethasone treatment cohort were generated from pooled-MEAD trial individual patient-level data. The model additionally incorporated relative risks (RRs) of sham treatment compared with dexamethasone implant, sourced from a network meta-analysis of DME treatment trials, to the BCVA change transition probabilities to model transition in the "watch and wait" cohort.

Health state utilities in the model were based on a regression analysis estimating the association of BSE BCVA and WSE BCVA with utilities converted from NEI-VFQ-25 quality of life metric using VFQ-UI. BCVA and NEI-VFQ-25 measurements were sourced from MEAD trials, and each increment of BSE BCVA or WSE BCVA was associated with a change in utility.

Figure 1: Manufacturer's Model Structure



BCVA = best-corrected visual acuity; BSE = better-seeing eye; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; FEI = fellow eye involvement; WSE = worse-seeing eye.

Source: Adapted from manufacturer's pharmacoeconomic submission.[3] Each black ellipse represents a series of BCVA health states differentiated by 10 ETDRS letter intervals. 6 metre and 20 feet Snellen-equivalent ranges are reported within each BCVA health state for comparison. Health states denoted with asterisk (*) follow transition probabilities associated with assigned treatment; health states denoted with dagger (†) maintain stable visual acuity; health states denoted with double dagger (‡) follow transition probabilities associated with DME natural history. Patients can progress to death from any health state.

Table 13: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Pooled-MEAD trials DEX 700 mcg pseudophakic group individual patient-level data (Safety population)	Uncertain whether the MEAD population is reflective of the Health Canada indication, given the exclusion criteria, low rate of prior use of anti-VEGF, and imbalances between treatment groups in the pseudophakic subgroup. Furthermore, modelled population may not be generalizable to Canada. Observed Canadian data (confirmed by clinical expert consulted for review) suggests the indicated population in Canada are younger.[34]
Efficacy • ETDRS BCVA Health State Transitions • RRs of: ○ ≥ 10 ETDRS letters BCVA improvement ○ ≥ 10 ETDRS letters BCVA worsening ○ < 10 ETDRS letters BCVA improvement or worsening	Individual patient data from the pooled-MEAD trials were used to populate number of dexamethasone-treated patients transitioning between BCVA health states. The RRs of a sham treatment compared with DEX 700 mcg PRN in the pseudophakic population were derived from a MTC of DME treatment trials.[6] The relevant network nodes were informed by 12-month BCVA results from MEAD-10 and MEAD-11 trials.[3,5]	CDR Clinical Review appraised the submitted MTC and identified several limitations that call into question the validity of the results; including RRs used in the economic model. The MTC only captures 12-month results and is less reflective of efficacy in earlier and later treatment periods. The use of the MTC RRs is unnecessary since the submitted economic base-case analysis does not consider any other comparator. As such, IPD from the MEAD trials is a more appropriate data source for informing treatment effect (taking into account generalizability limitations). Furthermore, the IPD-based health state transitions in the submitted model was modified so that BCVA transitions were restricted to one health state improvement or worsening at most to accommodate the MTC RRs. Given the issues with the MTC above, using IPD-based health state transitions for both the DEX and "watch and wait" groups may capture less artificially restricted visual acuity progression throughout the modelled treatment period.
	The efficacy of ranibizumab for scenario analysis 9 was derived from the same MTC described above.	There is an uncertainty associated with the comparison of ranibizumab and DEX 700 mcg PRN efficacies using the MTC as the network of trials that connect ranibizumab to DEX 700 mg PRN include a trial with a heterogeneous patient population that also include those who are not pseudophakic, who are not part of the Health Canada–indicated population.
	The efficacy of ranibizumab for scenario analysis 10 was partly derived from a naive comparison against a retrospective chart review. The RR of improvement vs. DEX 700 mcg PRN was sourced from the retrospective	Further uncertainty regarding the efficacy of ranibizumab compared with DEX 700 mcg PRN stemmed from the use of a naive comparison that did not adjust for many potential confounders that exist in the

Data Input	Description of Data Source	Comment
	chart review, while the RR for stable vision and worsening vision were based on the same assumptions from MTC used in scenario analysis 9.	retrospective chart review. The retrospective chart review was based on patients who use ranibizumab for purposes other than DME, and did not exclude patients who were not pseudophakic, though the data included for the ranibizumab arm were reported to be from a cohort of DME patients.
Natural History	Visual acuity transitions for DME-affected eyes that do not receive dexamethasone treatment or discontinue treatment were modelled based on a published visual acuity health state transition probabilities derived from WESDR natural history data.[19]	Questionable generalizability to the indicated population. WESDR study follows DR patients of unknown lens status and only about half of the patients had macular edema.[18] Study patients were recruited between 1979 and 1980, the VA change after a 4-year follow-up used to model the transition probabilities. Although the transition probabilities were adjusted for vision loss rates for more effective diabetes management practices in more recent decades,[19] the referenced WESDR study does not report whether these changes were statistically significant, and it is uncertain that the 4-year follow-up results would be representative of the longer time horizon used in the submitted analysis.
Discontinuations • Due to lack of efficacy • Due to AE	The transition probabilities of both types of discontinuations for DEX were sourced from pooled-MEAD trials data.	Questionable generalizability of MEAD trial data to the indicated population.
Utilities	Base-case utilities were derived from a regression analysis of pooled-MEAD trials patient-level BSE BCVA, WSE BCVA, and NEI-VFQ-25 data. NEI-VFQ-25 data were transformed to utility values using VFQ-UI. Mean BCVA in each visual acuity health state were sourced from pooled-MEAD trials data. A sensitivity analysis considered utility derived from a regression analysis based on EQ-5D scores rather than NEI-VFQ-25.	Questionable generalizability of MEAD trial data to the indicated population. VFQ-UI, a utility index developed with funding from the manufacturer, is more sensitive to WSE visual acuity than EQ-5D. The utility index would benefit from further validation and reliability testing. The utility index was found to be valid, reliable, and reproducible in a study in the uveitis population.[14] The need for specific visual function utility index is yet unclear as another conventional utility mapping method, HUI3, is reported to be more sensitive to visual acuity than EQ-5D, [35] and the vision-specific utility may not comprehensively reflect general patient health preferences. EQ-5D scores used in the scenario analysis were only measured at trial baseline and may not reflect the different health states incorporated in the model.
Adverse Event Incidence • Raised IOP • Retinal detachment • Endophthalmitis • Vitreous hemorrhage	Annual incidence for year 1, 2, and 3 in the general MEAD trial safety population data.	Questionable generalizability of MEAD trial data to the indicated population. Inappropriate to use general MEAD trials safety population if information from pseudophakic subgroup population is available.

Data Input	Description of Data Source	Comment
Mortality	Additional mortality risk due to DM compared with the general population,[36] and additional mortality risk due to DME compared with DM[37] were applied to all-cause mortality derived from age and sex-adjusted Canadian life tables.[38]	Appropriate sources, though there is a risk of double counting (acknowledged by the submitter).
Costs And Resource Use		
Drug	Manufacturer submitted price.	Appropriate
Administration	Unit costs for treatments including procedures and monitoring visits were based on Ontario physician services schedule of benefits.	Appropriate to use the Ontario physician schedule of benefits, however inappropriate codes and dated costs were used. This did not have a notable impact on the results.
Severe vision loss event	Rehabilitation aid cost was sourced from a Canadian National Institute for the Blind (CNIB) publication[39] and inflated from 2000/2001 Canadian dollars to 2017 Canadian dollars. Non-medical community and residual care were based on Quebec provincial costs reported by Sunlife.[3]	Questionable whether the per-individual cost estimate for low vision aids and devices is still generalizable in 2017. Inappropriate. Quebec is not a CDR-participating province and costs incurred in Quebec may not be reflective of rest of Canada. The reported costs are from the perspective of consumers and do not reflect public health plan expenditures. More appropriate provincial cost sources are available [15,40]
AEs	Unit costs for AE treatments including medications and procedures were based on Ontario formulary and physician services schedule of benefits.	Appropriate
Resource Use	DEX frequency was based on maximum allowable scenario in the MEAD trial protocols. Clinician surveys were used to derive resource utilization for treatment strategies. Resource utilization for severe vision loss direct non-medical cost was based on a published systematic review and economic evaluation of ranibizumab and pegaptanib for the treatment of age-related macular degeneration (AMD).[41]	Given that DEX is administered PRN, costing maximum possible number of treatments for this analysis could overestimate the cost of DEX over three years of treatment. While the submitted model incorporates up to 11 potential DEX treatments, only 7 maximum treatments were observed from MEAD trials.[5] Given questionable generalizability of MEAD trials to the indicated population. The submitted approach is acceptable as a conservative assumption. Appropriate. Questionable. Resource utilization based on international literature[7] may not be reflective of community care and residential care eligibility and admission practices in Canada. Vision loss in better-seeing eye alone is unlikely to trigger a long-term care home admission in Ontario as this event alone would not necessitate 24-hour nursing care.[16].

AE = adverse event; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BSE = better-seeing eye; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DEX = dexamethasone implant; DM = diabetes mellitus; DME = diabetic macula edema; DR = diabetic retinopathy; EQ-5D = EuroQol 5 Dimensions Health Questionnaire; HUI3 = Health Utility Index Mark 3; ICER = incremental cost-effectiveness ratio; IPD = individual patient data; MTC = multiple treatment comparison; NEI-VFQ-25 National Eye Institute Visual Functioning Questionnaire-25; NMA = network meta-analysis; PRN = as needed; QALY = quality-adjusted life-year; RR = relative risk; VA = visual acuity; VEGF = vascular-endothelial growth factor; VFQ-UI = Visual Functioning Questionnaire – Utility Index; WSE = worse-seeing eye.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
Model structure	
The modelled population is representative of the Health Canada indication.	Potentially acceptable
All relevant comparators have been considered.	Inappropriate. The manufacturer reported that off-label TA and laser should not be considered as comparators as they are not used often. As these therapies are used for these indications in the absence of dexamethasone implant, TA and laser should be considered as comparators. Clinical expert consulted by CDR confirmed the clinical use these therapies in the indications of interest. Additionally, although the manufacturer included ranibizumab as a comparator in a scenario analysis, the analysis did not include bevacizumab, a preferred initial anti-VEGF therapy recommended by a CADTH therapeutic review of anti-VEGF therapies.[12]
Health states based on ETDRS BCVA score 10-letter intervals.	Questionable. While the FDA considers the MCID to be a 15-letters difference, [42] clinical expert consulted by CDR confirmed that a 10-letter difference may make meaningful change in patients' QoL. It is uncertain whether assigning change in utility values based on 10 ETDRS letter increments overestimates the extent health utilities are influenced by VA in the model.
Each eye was modelled individually.	As BSE and WSE are not paired, CDR could only assess the distributions of each health state (BSE and WSE) separately. This resulted in some uncertainty associated as to whether WSE may have greater utility than BSE at certain time points.
Model time horizon is 15 years.	Questionable. More than a quarter of the patient cohort is still alive at the end of the 15-year time horizon. Given the possibility of continuing treatment indefinitely, lifetime time horizon should be explored.
Maximum 3 years of treatment assumed for all patients from the initiation of treatment.	Questionable. While consistent with MEAD studies, the clinical expert consulted by CDR reported the possibility for longer term use if there was continued efficacy.
Treatment	
Data sources informing the treatment efficacy in the model is representative of the Health Canada–indicated population.	Questionable. It is unclear how representative the modelled comparative treatment effects represent adults with DME who are pseudophakic. See CADTH clinical review of MEAD trials, MTC, and phase II studies. The use of naive comparison to inform comparative effectiveness of ranibizumab for a scenario analysis is also inappropriate.
Movement between VA health states was restricted to one health state to facilitate MTC-derived RRs. This restriction also persists in health state transitions for natural history.	Questionable. Restricting to a change of one health state may not reflect what is seen in clinical practice. See limitations section in the main body of the report, and the CDR Clinical Review critique of the MTC. The application of the MTC-derived RRs in the model is itself a source of further bias and uncertainty as the normalization of transition probabilities further transforms RRs in difficult to predict manner.
Same RRs associated with treatment were assumed to apply throughout the modelled time horizon regardless of the starting health state.	
Patients with DME were assumed to receive monotherapy, and upon discontinuation receive no further treatment and experience vision change at the natural history rate of patients with DR. This natural history rate is assumed to be held constant over time.	Acceptable as a simplifying assumption. However, the assumption would also lead to maintenance of a constant treatment effect during time between dexamethasone and "watch and wait" group. MEAD trial data submitted by the manufacturer seems to indicate efficacy waning.[33]
Patients had both unilateral and bilateral DME.	Uncertain. While in practice, this is likely to be appropriate, the product monograph for dexamethasone implant states that treatment of both eyes concurrently is not recommended. CDR could not determine the measures in the model to ensure that alignment with the product monograph was met.

Assumption	Comment
Natural history	
Fellow eye involvement was assumed to occur in years 1 or 2 only of the model.	Appropriate as a simplifying assumption. However, the reduced opportunity for fellow eye involvement in the subsequent years in the model would bias the analysis results toward null difference. Cost-effective treatments will appear less so, while less cost-effective treatments will not appear as much.
No additional mortality due to blindness.	Appropriate since excluded to avoid double counting in relation to additional mortality due to DME.
Eyes without DME are assumed to have stable vision.	Appropriate as a simplifying assumption.
BSE and WSE defined at baseline and assumed fixed through the model time horizon.	Appropriate as a simplifying assumption.
Scenario analysis: patients with inadequate response to prior anti-VEGF therapy	
Patients with inadequate response to anti-VEGF treatment continue to achieve inadequate response to other anti-VEGF treatments.	A clinical expert contacted by CDR commented that while those who respond inadequately to ranibizumab may also respond similarly to bevacizumab, aflibercept could be tried after an inadequate response to a prior anti-VEGF.

BSE = better-seeing eye; BCVA = best-corrected visual acuity; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DME = diabetic macula edema; MCID = minimal clinically important difference; MTC = multiple treatment comparison; RR = relative risk; QoL = quality of life; TA = triamcinolone acetate; VA = visual acuity; VEGF = vascular-endothelial growth factor; WSE = worse-seeing eye.

Manufacturer's Results

The base-case results are presented in Table 2. The one-way sensitivity analyses conducted by the manufacturer identified the treatment effect RRs, discount rates, proportion of severe vision loss patients receiving residential care, mortality hazard ratio of DME patients compared with patients with diabetes, and baseline age were the largest drivers of the model. The scenario analysis results are reported below (Table 15).

Table 15: Manufacturer's Scenario analyses: Mean Probabilistic Results

Comparator	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY gained)
Scenario 1: Patients with DME who are pseudophakic and who are unsuitable for anti-VEGF therapy.					
"Watch and wait"	10,459	—	5.62	—	—
Dexamethasone 700 mcg	13,711	3,252	5.72	0.10	32,073
Scenario 2: "Watch and wait" treatment effect is modelled using MEAD trial individual patient data.					
"Watch and wait"	5,173	—	5.70	—	—
Dexamethasone 700 mcg	12,185	7,012	5.77	0.07	100,061
Scenario 3: Utilities from EQ-5D					
"Watch and wait"	10,274	—	6.57	—	—
Dexamethasone 700 mcg	13,692	3,419	6.62	0.05	67,245
Scenario 4: Time horizon 10 years					
"Watch and wait"	8,071	—	4.51	—	—
Dexamethasone 700 mcg	12,244	4,173	4.59	0.09	48,863
Scenario 5: Time horizon 5 years					
"Watch and wait"	3,852	—	2.66	—	—
Dexamethasone 700 mcg	10,260	6,409	2.70	0.05	140,070
Scenario 6: Discount rate 0%					
"Watch and wait"	14,397	—	6.13	—	—

Comparator	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY gained)
Dexamethasone 700 mcg	11,657	2,740	6.25	0.12	23,552
Scenario 7: Discount rate 5%					
"Watch and wait"	8,443	—	4.67	—	—
Dexamethasone 700 mcg	12,377	3,934	4.75	0.08	47,547
Scenario 8: Societal perspective					
"Watch and wait"	50,834		5.62	—	—
Dexamethasone 700 mcg	29,304	–21,529	5.72	0.10	Dominant
Scenario 9: Ranibizumab comparison[a]					
"Watch and wait"	10,194	—	5.53	—	—
Dexamethasone 700 mcg	13,534	3,340	5.64	0.12	28,147
Ranibizumab	36,807	23,272	5.78	0.13	177,604
Scenario 10: Ranibizumab comparison based on LUMINOUS retrospective chart review					
"Watch and wait"	10,511	—	5.61	—	—
Dexamethasone 700 mcg	13,721	3,210	5.71	0.10	31,466
Ranibizumab	37,321	23,599	5.79	0.08	290,370

Source: derived from Manufacturer's Pharmacoeconomic Submission[3]

DME = diabetic macular edema; EQ-5D = EuroQol 5 Dimensions Health Questionnaire; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; VEGF = vascular-endothelial growth factor.

[a] The manufacturer reported deterministic results instead of probabilistic results for this analysis; the analysis appears to have been conducted sequentially.

The manufacturer reported a qualitative assessment of dexamethasone vs. anti-VEGF for the DME patient population who are pseudophakic and had inadequate treatment response to prior anti-VEGF therapy in lieu of an economic model-based analysis. The manufacturer claimed dexamethasone 700 mcg intravitreal implant dominated anti-VEGF therapy based on the assertions and rationales provided by the manufacturer in Table 16. The two post-hoc analyses and a meta-analysis submitted by the manufacturer are not comparative evidence and force speculation of how dexamethasone implant will compare to ranibizumab. Furthermore, the data presented are generally not for the Health Canada–indicated population (DME patients who are pseudophakic). The submitted evidence also does not address other relevant comparators such as off-label triamcinolone acetate and laser therapies. Overall, the submitted evidence is insufficient to establish non-inferiority of dexamethasone implant compared with anti-VEGF therapy and a cost comparison is not justified.

Table 16: Submitted Evidence for Inadequate Anti-VEGF Response Group Scenario Analysis

<table>
<tr><th>Source[33]</th><th>Manufacturer-Interpreted Results</th></tr>
<tr><td colspan="2">Those who have inadequate response to an anti-VEGF therapy will continue to experience inadequate response to an anti-VEGF therapy.</td></tr>
<tr><td>Gonzalez et al. 2016 DRCR.net protocol I RCT post-hoc analysis for ranibizumab</td><td>• Vision change in the first 3 months of anti-VEGF treatment is predictive of overall response up to 3 years.
• Of those who repeat anti-VEGF injections, up to 40% of patients either show no vision change or achieve only minimal vision improvement (i.e., < 5 letters).</td></tr>
<tr><td colspan="2">Dexamethasone 700 mcg intravitreal implant is more effective than an anti-VEGF therapy in this patient group.</td></tr>
<tr><td>Khan et al. 2017 meta-analysis</td><td>• Dexamethasone 700 mcg intravitreal implant treatment in patients with DME refractory to anti-VEGF therapy is associated with a mean improvement of 20 ETDRS letters.</td></tr>
<tr><td>Pacella et al. 2016 retrospective study</td><td>• In patients categorized as anti-VEGF therapy resistant according to clinical parameters, OCT, or absence of CMT and BCVA improvement after three anti-VEGF injections, patients who received dexamethasone 0.7mg intravitreal implant injections every 6 months had significant improvement in BCVA from baseline each month (P < 0.001)</td></tr>
<tr><td colspan="2">Dexamethasone 700 mcg intravitreal implant is less costly than an anti-VEGF therapy.</td></tr>
<tr><td>Manufacturer-provided cost comparison</td><td>
<table>
<tr><th>Annual dexamethasone cost ($)</th><th>Annual ranibizumab cost ($)</th><th>Incremental savings ($)</th></tr>
<tr><td rowspan="4">2,800
(2 injections)</td><td>18,900
(12 injections)</td><td>16,100</td></tr>
<tr><td>17,325
(11 injections)</td><td>14,525</td></tr>
<tr><td>15,750
(10 injections)</td><td>12,950</td></tr>
<tr><td>14,175
(9 injections)</td><td>11,375</td></tr>
</table>
</td></tr>
</table>

Source: derived from Manufacturer's Pharmacoeconomic Submission[3]

BCVA = best-corrected visual acuity; CMT = central macular thickness; DME = diabetic macula edema; ETDRS = Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; RCT = randomized controlled trial; VEGF = vascular-endothelial growth factor.

CDR Exploratory Analysis

Given the lack of documentation supporting the methodology used by the manufacturer for the MEAD trials-derived RRs, CDR undertook an exploratory analysis deriving RRs from the MEAD trial IPD-derived transitions data that was included in the model by the manufacturer. CDR derived these alternative RRs from 12 cycles (36-months equivalent) of IPD-based health state transitions included in the submitted model. Rates of improving, stable, and worsening vision were calculated by dividing total counts of each event over total counts of all events (representing exposure) across 12 cycles. These 12-cycle rates were then converted to single cycle probabilities, from which the RRs of watch and wait vs. dexamethasone implant were derived as a ratio of probabilities. The main limitation of this approach is that CDR was unable to adjust for patient characteristics which may have influenced individual odds of experiencing each type of transition event (given the aggregate data provided). The derived RRs and the exploratory results are presented in Table 17 and Table 18, respectively.

Although the RRs calculated in the exploratory analysis were derived from the same data set as the RRs provided by the manufacturer (and used by CDR in the revised base case), CDR noted the large difference between the estimates, enhancing CDR's concerns regarding the uncertainty of the available treatment effect estimates. The results of the

exploratory analysis indicated a difference in QALYs that may not align with the clinical data, which further calls into question the manufacturer's model structure.

Table 17: Parameters and Values of Interest Explored by CDR

Parameter	Manufacturer's base case	Source	CDR exploratory analysis	Source
RR of improving / remaining stable / worsening	0.56 / 1.06 / 2.11	Manufacturer's MTC (DEX as reference)	0.85 / 1.05 / 1.04[a]	MEAD IPD-based health state transitions (calculated by CDR, DEX as reference)

CDR = CADTH Common Drug Review; DEX = dexamethasone implant; IPD = individual patient data; MTC = mixed-treatment comparison; RR = relative risk.

[a] CDR tested these values in the probabilistic analyses using a 20% standard error and normal distribution.

Table 18: CDR Exploratory Analysis Results on the Manufacturer's Base Case

Comparator	Total Costs ($)	Incremental Costs ($)	Total QALYs	Incremental QALYs	ICUR ($ per QALY gained)
Manufacturer Base Case					
"Watch and wait"	10,459	—	5.62	—	—
Dexamethasone implant	13,711	3,252	5.72	0.10	32,073
CDR Estimate					
"Watch and wait"	4,064	—	5.67	—	—
Dexamethasone implant	11,891	7,827	5.71	0.05	168,439
Revised RR of improving/remaining stable/worsening: MEAD trials, CDR values calculated from IPD-based transitions					
"Watch and wait"	5,875	—	5.70	—	—
Dexamethasone implant	13,718	7,843	5.71	0.01	652,815

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility analysis; IPD = individual patient data; QALY = quality-adjusted life-year; RR = relative risk.

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