CDEC FINAL RECOMMENDATION

DEXAMETHASONE INTRAVITREAL IMPLANT
(Ozurdex – Allergan Inc.)
Indication: Macular Edema Following Central Retinal Vein Occlusion

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that dexamethasone intravitreal implant not be listed.

Reasons for the Recommendation:
1. Based on pooled data from two masked randomized controlled trials (RCTs), the percentage of patients with macular edema due to central retinal vein occlusion that 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, the Committee felt that there was considerable uncertainty around the cost effectiveness of dexamethasone intravitreal implant compared with sham.

Background:
Dexamethasone intravitreal implant has a Health Canada indication for the treatment of macular edema following central retinal vein occlusion. The product is available as a biodegradable polymer matrix implant containing 700 mcg of dexamethasone for intravitreal injection. The dose recommended by Health Canada is one 700 mcg implant. Further, the Health Canada–approved product monograph includes a warning that no more than two consecutive injections should be used, and an interval of approximately six months should be allowed between the two injections.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of dexamethasone intravitreal implant and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials

The systematic review included two six-month, masked RCTs of patients with macular edema following central or branch retinal vein occlusion. Studies 008 and 009 were of identical design and patients were randomized to one of three treatment groups: dexamethasone intravitreal implant (either 350 mcg or 700 mcg) or sham (needle-less applicator). Randomization was stratified based on type of retinal vein occlusion (central or branched); a total of 1,267 patients were randomized across both trials.

Given the Health Canada–approved indication and dosage for dexamethasone intravitreal implant, the focus of the CDR review was the subgroup of patients with central retinal vein occlusion treated with dexamethasone intravitreal implant 700 mcg or sham, pooled from studies 008 and 009 (n = 283). Eight percent of the dexamethasone 700 mcg group, and 6% of the sham group, did not complete the six-month study.

The CDR identified no double-blind RCTs comparing dexamethasone intravitreal implant with other active treatments for the treatment of macular edema following central retinal vein occlusion.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: changes in visual acuity, quality of life, serious adverse events, adverse events, and withdrawals due to adverse events. The primary outcome for both trials was initially the proportion of patients achieving a ≥ 15-letter improvement in best corrected visual acuity on day 180. However, following a review of the data from study 009, which failed to meet its primary outcome, the primary outcome was amended to the time to achieve a ≥ 15-letter improvement from day zero to day 180.

Best corrected visual acuity was assessed using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart. ETDRS charts include a series of five letters on each line of the chart: 14 lines (70 letters). The minimally clinically important difference is five to 10 letters. A loss or gain of three lines (15 letters) is considered to be a moderate degree of change. Legal blindness was defined as a best corrected visual acuity of 20/200 or worse on the Snellen eye chart. Quality of life was assessed using the National Eye Institute Visual Function Questionnaire 25.

Results

Efficacy or Effectiveness

The efficacy results described below are for the pooled subgroup of patients with central retinal vein occlusion treated with dexamethasone intravitreal implant 700 mcg or sham.

- The time to achieve a 15-letter improvement was statistically significantly shorter for dexamethasone 700 mcg compared with sham. However, the proportion of patients achieving a ≥ 15-letter improvement at day 180 was not statistically significantly different between dexamethasone 700 mcg and sham: 18% versus 12%, respectively. Analyses of other pre-specified time points revealed that the proportion of patients achieving a ≥ 15-

letter improvement was statistically significantly higher for dexamethasone 700 mcg than for sham-treated patients at days 30 and 60, but not thereafter (days 90 and 180).
- The proportion of patients experiencing a loss of ≥ 15 letters, or meeting the criteria for legal blindness at day 180, was not statistically significantly different between dexamethasone 700 mcg and sham: 14% versus 20%, and 23% versus 29%, respectively.
- No statistically significant between-treatment changes in quality of life were reported.

Harms (Safety and Tolerability)
Harms data described below are for both central and branch retinal vein occlusion patients for six months after receiving the study treatment.

- The incidence of serious adverse events was not statistically different between dexamethasone 700 mcg and sham (5% versus 6%, respectively). Increased intraocular pressure classified as a serious adverse event occurred in two dexamethasone 700 mcg patients, and ocular hypertension occurred in one dexamethasone 700 mcg patients.
- The incidence of total adverse events and ocular adverse events was statistically significantly higher in dexamethasone 700 mcg–treated patients than in sham: 72% versus 57%, and 63% versus 43%, respectively. The most common ocular adverse events, occurring more frequently with dexamethasone 700 mcg than with sham, were increased intraocular pressure (25% versus 1%), eye pain (7% versus 4%), and ocular hypertension (4% versus 1%). Conjunctival hemorrhage and retinal exudates were also observed. Eye infections were infrequent events, and there was no difference in the incidence of eye infections between dexamethasone 700 mcg and sham.
- There was no difference in the incidence of withdrawals due to adverse events between dexamethasone 700 mcg and sham (2% of patients in each group).

Cost and Cost-Effectiveness
The manufacturer submitted a cost-utility analysis comparing dexamethasone intravitreal implant with sham in patients with macular edema and vision loss following a central retinal vein occlusion, over a lifetime time horizon. The Markov model considered seven health states: six states that modeled progressively best corrected visual acuity, and a death state. Patients transitioned among health states based on probabilities derived from pooled results from trials 008 and 009. Treatment with dexamethasone intravitreal implant was assumed to occur at six-month intervals over the first three years of the model. Visual acuity was assumed to stabilize after three years and best corrected visual acuity was assumed to remain constant over the remainder of the analysis horizon. The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) estimate of $21,568 for dexamethasone intravitreal implant compared with sham.

CDR identified a number of issues with the manufacturer's submission. The manufacturer did not conduct a cost-utility analysis versus active comparators. Data from short-term trials indicating that benefits of dexamethasone intravitreal implant compared with sham are achieved at 30 and 60 days but not at 90 and 180 days, for patients with macular edema due to central retinal vein occlusion, do not support the assumption that improvement in visual acuity and health related quality of life will be maintained over the remaining life time of patients. Given the aforementioned limitations, there was considerable uncertainty in cost per QALY estimates, even when the Health Canada-approved maximum of two injections approximately six months apart was assumed.

The cost per 700 µg dexamethasone intravitreal implant is $1,295 which is recommended to be administered every six months (expected annual cost of $2,590).

Patient Input Information:
No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:
- The Committee further noted a higher incidence of cataract formation in patients receiving dexamethasone intravitreal implant injections in an open-label extension of the reviewed trials.
- The Committee noted that the use of a needle-less sham control makes it difficult to ascertain the risks associated with the dexamethasone intravitreal implant versus those of an intravitreal injection.
- The Committee noted the Health Canada–approved product monograph warns that no more than two consecutive injections of the implant should be used, and an interval of approximately six months should be allowed between the two injections.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

February 15, 2012 Meeting

Regrets:
None.

Conflicts of Interest:
None.

April 18, 2012 Meeting

Regrets:
One CDEC member did not attend.

Conflicts of Interest:
None.

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information

submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.
The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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