CDEC FINAL RECOMMENDATION

RANIBIZUMAB
(Lucentis – Novartis Pharmaceuticals Canada Inc.)
New Indication: Macular Edema Secondary to Retinal Vein Occlusion

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that ranibizumab be listed for patients meeting both of the following criteria:

- clinically significant macular edema secondary to non-ischemic branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), not previously treated with a vascular endothelial growth factor (VEG-F) inhibitor
- drug plan coverage limited to 24 months duration, and typically not to exceed 10 or 12 vials for patients with BRVO or CRVO respectively.

Reasons for the Recommendation:

1. In two double-masked randomized controlled trials (RCTs) of patients with macular edema secondary to non-ischemic BRVO or CRVO (the BRAVO and CRUISE studies respectively), compared with sham, ranibizumab resulted in statistically significantly greater improvement in best corrected visual acuity at six months.
2. The cost-effectiveness estimates for ranibizumab were sensitive to changes in assumptions regarding the durability of the treatment effect, and the frequency and duration of ranibizumab use. When CDR considered higher numbers of injections, treatment duration beyond two years, and the attenuation of ranibizumab effect following two years of treatment, the incremental cost per quality-adjusted life-year (QALY) estimates exceeded $100,000.

Of Note:

- The Committee considered the average number of injections administered in the reviewed trials when developing their recommendation.
- Ranibizumab is available as a 10 mg/mL solution for injection in vials containing 0.23 mL each, with the recommended dosing being 0.5 mg (0.05 mL) per treatment. The Committee noted that the drug plans may explore opportunities and mechanisms with prescribers to reduce the potentially large amount of wastage with these vials.
- The Committee noted that ranibizumab treatment requires administration by a qualified ophthalmologist experienced in intravitreal injections.

Background:
This submission for ranibizumab is for the new Health Canada indication of treatment of visual impairment due to macular edema secondary to retinal vein occlusion. Ranibizumab is a VEG-F inhibitor. It is available as a 10 mg/mL solution, and the Health Canada-recommended dose is 0.5 mg injected intravitreally once a month and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on the treatment. The product monograph states that, thereafter, patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular edema secondary to retinal vein occlusion and continued until stable visual acuity is reached again for three consecutive monthly assessments.

Submission History:
Ranibizumab was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for the treatment of neovascular (wet) age-related macular degeneration and received a recommendation to "list with criteria/condition" (see Notice of CEDAC Final Recommendation, March 27, 2008). Ranibizumab was also previously reviewed by CDEC for the treatment of visual impairment due to diabetic macular edema and received a recommendation to "list with criteria/condition" (see Notice of CDEC Final Recommendation, March 19, 2012).

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-masked RCTs of ranibizumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included three, six-month double-masked RCTs of patients with visual impairment due to macular edema secondary to retinal vein occlusion. BRAVO (N = 397) evaluated ranibizumab for the treatment of macular edema secondary to BRVO, while CRUISE (N = 392) and ROCC (N = 32) evaluated ranibizumab for macular edema secondary to CRVO.

The BRAVO and CRUISE studies randomized patients to one of three treatment groups: ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham (needleless) intravitreal injection, once a month for six months. Neither trial was designed for comparisons between the ranibizumab groups. Patients in all three treatment groups in BRAVO could receive concomitant rescue laser photocoagulation, starting at month three, if they met the pre-specified eligibility criteria. The ROCC study randomized patients to ranibizumab 0.5 mg or sham intravitreal injection once a month for three months; for the remaining three months, the administration of randomized treatments was at the discretion of the physician. In all three trials, premature study withdrawal (before the six month visit) was less than 10%; there were no notable differences in the frequency of premature study withdrawal between ranibizumab 0.5 mg and the sham groups.

The masked controlled treatment phases of BRAVO and CRUISE were followed by a six-month observation phase during which all patients could receive as-needed ranibizumab. Patients who completed 12 months in the BRAVO and CRUISE trials were eligible to enter an open-label, single-arm extension study (HORIZON).

Study limitations include the lack of trials directly comparing ranibizumab with other VEG-F inhibitors or dexamethasone implant (for CRVO). The BRAVO study does not represent an ideal comparison of ranibizumab with laser photocoagulation in patients who are candidates for laser since not all patients in the sham group received laser therapy. Since not all sham-treated patients in the sham group of BRAVO required laser therapy, the BRAVO study cohort appears to represent a broader population of BRVO patients than are currently candidates for laser therapy in clinical practice, potentially limiting the generalizability of study results. In addition, the more frequent use of laser in the sham group confounds the comparison of sham and ranibizumab groups. Finally, due to the small number of patients with ischemic retinal vein occlusion at baseline, in both the BRAVO (5%) and CRUISE (1.5%) studies, the generalizability of results to patients with ischemic disease at the time of treatment initiation is uncertain.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: legal blindness, visual acuity, visual function, total and serious adverse events, and withdrawal due to adverse events. The primary outcome in all three of the included trials was the mean change from baseline in best corrected visual acuity.

Legal blindness was defined as a visual acuity (Snellen equivalent) of ≤ 20/200. Best corrected visual acuity was assessed using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart. The ETDRS chart includes a series of five letters on each line of the chart, 14 lines (70 letters). The minimal clinically important difference is five to 10 letters. A loss or gain of three lines (15 letters) is considered a moderate degree of change. Visual function was assessed using the National Eye Institute Visual Function Questionnaire-25 (VFQ-25); the suggested minimal clinically important differences for the VFQ-25 overall score are four points for the eye that has worse sight, and seven to eight points for the eye with better sight.

Results

The Committee focused its discussion on the comparison of ranibizumab 0.5 mg with sham in the BRAVO and CRUISE studies.

Efficacy or Effectiveness

BRAVO Study:

- The percentage of patients meeting the criteria for legal blindness at six months was statistically significantly lower for patients treated with ranibizumab compared with sham: 0.8% versus 9.1% respectively.
- Compared with sham, ranibizumab-treated patients had statistically significantly improved best corrected visual acuity at six months; mean difference (MD), 10.6 letters. The percentage of patients achieving an improvement of ≥ 15 letters was statistically significantly higher for ranibizumab compared with sham: 61.1% versus 28.8% respectively.
- Compared with sham, ranibizumab-treated patients had statistically significantly greater improvement in visual function, as measured by the composite score on the VFQ-25 at six months; MD, 4.8.

CRUISE Study:

- The percentage of patients meeting the criteria for legal blindness at six months was statistically significantly lower for patients treated with ranibizumab compared with sham: 11.5% versus 27.7%.
- Compared with sham, ranibizumab-treated patients had statistically significantly improved best corrected visual acuity at six months; MD, 13.8 letters. The percentage of patients achieving an improvement of ≥ 15 letters was statistically significantly higher for ranibizumab compared with sham: 47.7% versus 16.9% respectively.
- Compared with sham, ranibizumab-treated patients had statistically significantly greater improvement in the composite score on the VFQ-25 at six months; MD, 3.5.

Harms (Safety and Tolerability)

- One death occurred in the three reviewed trials; a patient who was randomized to ranibizumab 0.5 mg died due to a cerebral hemorrhage.
- Ocular adverse events were common in the treated eye in BRAVO and CRUISE. The most frequently reported ocular adverse events in the ranibizumab groups were conjunctival hemorrhage and retinal exudates, both of which occurred in approximately 10% to 15% more patients treated with ranibizumab than those treated with sham. Elevated intraocular pressure occurred in 5% to 8% of the ranibizumab-treated patients; approximately two to three times more than in sham-treated patients.
- The incidence of ocular or non-ocular serious adverse events was similar between ranibizumab and sham injection.
- The percentage of patients who withdrew due to adverse events (ocular or non-ocular) was similar between the treatment groups.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis comparing ranibizumab with laser photocoagulation in patients with BRVO and observation in patients with CRVO, over a patient lifetime horizon (~ 33 years). The economic model is comprised of nine health states (eight best corrected visual acuity states and death), where transition probabilities between best corrected visual acuity states were obtained from a number of studies: BRAVO, CRUISE, HORIZON, SCORE, and the Beaver Dam Eye Study. Quality of life was estimated from the utility data collected from the unpublished Canadian utility study on patients with retinal vein occlusion, using the health utilities index (HUI) 3. The manufacturer assumed that patients would receive only two years of treatment: patients with BRVO would receive eight injections of ranibizumab or 1.5 laser photocoagulation session in year one, followed by 1.9 injections of ranibizumab or one laser photocoagulation session in year two; patients with CRVO would receive nine injections of ranibizumab in year one, followed by three injections in year two. The manufacturer also assumed that the improvement in best corrected visual acuity for ranibizumab, versus the comparator, at the end of the two-year treatment period would be maintained over the remaining lifetime of the patients. The manufacturer reported that in patients with BRVO ranibizumab compared with laser photocoagulation was associated with a cost per QALY of $36,725; in patients with CRVO, the reported cost per QALY was $28,046 for ranibizumab compared with observation.

CDR noted uncertainty with a number of assumptions, which could affect the incremental cost-utility ratio (ICUR). There is no clinical evidence to support the assumption of sustained best corrected visual acuity with ranibizumab. Where the effects of ranibizumab attenuate following

the treatment period (from year three onward), CDR noted that the cost per QALY estimates could exceed $100,000. Treatment frequency was based on the BRAVO and CRUISE studies. If the actual frequency of treatment with ranibizumab is greater than observed in the trials or treatment duration is longer than two years, the ICUR will be greater. Quality of life was not directly measured in the clinical trial and the secondary data used in the model may overestimate the benefits.

Ranibizumab is priced at $1,575 per 2.3 mg vial. The manufacturer estimates that the cost of laser photocoagulation is $182.75 per session, based on the Ontario Schedule of Benefits.

Patient Input Information:
The following is a summary of information provided by two patient groups that responded to the CDR Call for Patient Input:

- Patients stated that the loss of the ability to read and drive results in decreased quality of life and a loss of independence. Caregivers report emotional and financial burden, due to the need to take time off of work to act as a sighted guide and to assist patients with activities of daily living.
- Patient groups indicated that working age adults with vision loss are underemployed and that improvements in vision could allow individuals to continue or resume working.
- Depression, serious falls, and hip fractures were noted to be important consequences of vision loss.

Other Discussion Points:

- The Committee discussed that laser photocoagulation is an element of standard care for BRVO, but not CRVO, and that the BRAVO study was not designed to compare ranibizumab with laser photocoagulation in patients with BRVO who are candidates for laser photocoagulation. The Committee noted that an ongoing manufacturer-sponsored RCT (the RABAMES study) may assist in determining the benefit of ranibizumab compared with laser photocoagulation in such patients.

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.

September 19, 2012 Meeting

Regrets:
Three CDEC members 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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