CDEC FINAL RECOMMENDATION

RANIBIZUMAB
(Lucentis – Novartis Pharmaceuticals Canada Inc.)
New Indication: Visual Impairment due to Diabetic Macular Edema

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

- clinically significant diabetic macular edema for whom laser photocoagulation is also indicated, and
- a hemoglobin A1c of less than 11%, and
- drug plan coverage limited to nine vials per patient.

Reasons for the Recommendation:

1. In two randomized controlled trials (RCTs), ranibizumab, with or without concomitant laser photocoagulation, resulted in statistically significantly greater improvement in best corrected visual acuity at 12 months, compared with laser photocoagulation alone.

2. An economic evaluation submitted by the manufacturer reported an incremental cost-utility ratio (ICUR) for ranibizumab plus laser photocoagulation, compared with laser photocoagulation alone, of $33,317 (assuming seven vials used in year one, two vials used in year two). The analysis was sensitive to the frequency and duration of treatment with ranibizumab, with the ICUR increasing to more than $80,000 when the cost of seven vials used in year one and seven vials used in year two was considered in a more conservative scenario by the Common Drug Review (CDR).

Of Note:

1. Ranibizumab is available as a 10 mg/mL solution for injection in vials containing 0.23 mL each, with the recommended dose 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.
2. 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 diabetic macular edema. Ranibizumab is a vascular endothelial growth factor inhibitor. It is available as a 10 mg/mL solution and the dose recommended by Health Canada 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. Thereafter, patients are required to be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to diabetic macular edema 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).

Summary of CDEC Considerations:
The Committee considered the following information prepared by the 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 four double-masked RCTs of ranibizumab intravitreal injection; comparators included sham injection (needle-less), laser photocoagulation, and triamcinolone intravitreal injection. Trials are further described below.

Three trials, of 12 months' duration each, enrolled patients aged 18 years or older with type 1 or type 2 diabetes, who had decreased vision due to diabetic macular edema.

- Study D2201 (151 study eyes and patients) randomized patients to one of three treatment groups: ranibizumab (0.3 mg or 0.5 mg) or sham injection. The dose of ranibizumab could be doubled from 0.3 mg to 0.6 mg and from 0.5 mg to 1.0 mg.
- Study D2301 (345 study eyes and patients) randomized patients to one of three treatment groups: ranibizumab 0.5 mg plus sham laser photocoagulation, ranibizumab 0.5 mg plus laser photocoagulation, or sham injection plus laser photocoagulation.
- Study DRCR.net (854 study eyes; 691 patients) randomized eyes to one of four treatment groups: ranibizumab 0.5 mg plus prompt laser photocoagulation, ranibizumab 0.5 mg plus deferred laser photocoagulation, sham injection plus prompt laser photocoagulation, or triamcinolone 4 mg plus prompt laser photocoagulation.

In the above three trials, ranibizumab was administered by intravitreal injection monthly, or every four weeks unless treatment was successful or intolerable; the specific criteria for success were slightly different across the studies. Laser photocoagulation was initiated at entry into the study; re-treatment was based on predefined criteria or treatment guidelines.

One additional trial of 14 weeks' duration enrolled a special subpopulation: adult patients with severe nonproliferative or proliferative diabetic retinopathy and decreased vision due to diabetic macular edema for which the investigator performed panretinal photocoagulation.

- Study PDR-DME (345 study eyes; 319 patients) randomized patients to one of three treatment groups: ranibizumab 0.5 mg plus laser photocoagulation, sham injection plus laser photocoagulation, or triamcinolone 4 mg plus laser photocoagulation. Patients received intravitreal injections at baseline and week four; laser photocoagulation was performed three to 10 days after intravitreal injection.

The patient characteristics of the included trials were similar to those of the general population of patients with diabetic macular edema with respect to gender, age, diabetes type, hemoglobin A1c, and type of diabetic macular edema. However, there was a lack of data in patients with a hemoglobin A1c of 11% or greater in any of the studies.

Outcomes

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

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 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. Quality of life was assessed using the European Quality of Life – 5 Dimension (EQ-5D) questionnaire and the National Eye Institute Visual Function Questionnaire-25 (VFQ-25).

Results

The Committee focused its discussion of efficacy on the two 12-month trials that employed the Health Canada–approved dose of ranibizumab: studies D2301 and DRCR.net. The Committee discussed harms reported in all four included trials.

Efficacy or Effectiveness

- In study D2301, compared with laser photocoagulation alone, eyes treated with ranibizumab or ranibizumab plus laser photocoagulation had statistically significantly improved best corrected visual acuity at 12 months: mean difference of 5.4 and 4.9 letters, respectively. Similarly, in study DRCR.net, compared with prompt laser photocoagulation, eyes treated with ranibizumab plus either prompt or deferred laser photocoagulation had statistically significantly improved best corrected visual acuity at 12 months: mean difference of 5.8 and 6.0 letters, respectively.
- In studies D2301 and DRCR.net, compared with laser photocoagulation alone, eyes treated with ranibizumab, with or without laser photocoagulation, had statistically significant reductions in central retinal thickness.
- Across all included studies, there were greater proportions of eyes with an improvement of ≥ 10 letters and ≥ 15 letters, and lower proportions of eyes with a worsening of ≥ 10 letters and ≥ 15 letters in the ranibizumab groups compared with the control groups. These differences were reported as statistically significantly different for studies D2301 and DRCR.net.

- Only one study (D2301) examined visual function and quality of life. Compared with laser photocoagulation alone, patients treated with ranibizumab or ranibizumab plus laser photocoagulation reported statistically significantly greater improvement in visual function, as measured by the VFQ-25. However, there were no between-treatment differences in quality of life as measured by the EQ-5D.

Harms (Safety and Tolerability)

- Compared with patients who received laser photocoagulation alone, ranibizumab-treated patients were more likely to experience ocular adverse events, such as conjunctival hemorrhage and elevated intraocular pressure.
- The risks of ocular or non-ocular serious adverse events were similar between ranibizumab, sham injection, and laser photocoagulation.
- The percentage of patients who withdrew due to adverse events (ocular or non-ocular) was comparable between the treatment groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis in adults with diabetic macular edema, comparing ranibizumab monotherapy and ranibizumab plus laser photocoagulation with laser photocoagulation alone over a patient lifetime horizon (~30 years). Clinical inputs were obtained from study D2301 (year one), the DRCR.net follow-up study (year two), and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) that describes the natural history of disease (beyond year two). Quality of life was estimated from the utility data collected from study D2301, using EQ-5D score by visual acuity group (not by treatment allocation). CDR identified uncertainty with a number of assumptions that affected the ICUR: inclusion of non–vision-related costs; frequency of ranibizumab use (seven vials in year one; two to three vials in year two); duration of treatment with ranibizumab (two years); and durability of the treatment effect with ranibizumab.

In its reference case, the manufacturer reported that ranibizumab versus laser photocoagulation is associated with a cost per quality-adjusted life-year (QALY) of $27,379; ranibizumab plus laser photocoagulation versus laser photocoagulation alone is associated with a cost per QALY of $33,317. Where only direct vision-related costs were considered and the dosing frequency was seven vials in year one and seven vials in two (14 vials in total), CDR calculated a cost per QALY estimate of $69,098 for ranibizumab versus laser alone, and $83,884 for ranibizumab plus laser photocoagulation versus laser photocoagulation alone.

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

Patient Input Information:

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

- Patients with vision loss are anxious to retain or restore their vision.
- Patients stated that vision loss results in significantly decreased quality of life, much of which is related to the relationship between significant vision loss and unemployment. Patient groups also pointed out that even marginal improvement in vision could improve quality of life and facilitate a return to employment for some.

- Patient groups indicated that individuals with vision loss have a reduced ability to self-care in relation to management of their diabetes.
- Depression, serious falls, and hip fractures were noted to be important consequences of vision loss.

Other Discussion Points:
- The Committee discussed the need for more RCT data related to functional improvements that are of direct relevance to patients (e.g., ability to read, drive, and self-care related to diabetes management).
- The Committee noted that treatment strategies for diabetic macular edema should encompass lifestyle modifications, exercise, and smoking cessation, in addition to control of blood sugar, blood pressure, blood lipids, and body mass index.

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

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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