CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

RANIBIZUMAB
(Lucentis™ – Novartis Pharmaceuticals Canada Inc.)

Description:
Ranibizumab, a humanized recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor-A (VEGF-A), is approved for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Dosage Forms:
3 mg/0.3 mL vial for intravitreal injection. The recommended dose is 0.5 mg (0.05 mL) administered by intravitreal injection once a month. Treatment may be reduced to one injection every three months after the first three injections if monthly dosing is not feasible.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that ranibizumab be listed for the treatment of neovascular AMD when drug plan coverage is limited to a maximum of 15 vials per patient used to treat the better seeing affected eye. Ranibizumab should not be funded in combination with verteporfin.

Reasons for the Recommendation:
1. Compared to verteporfin photodynamic therapy in patients with predominantly classic AMD and best supportive care in patients with minimally classic and occult AMD, ranibizumab has been shown to be more effective in stabilizing and improving visual acuity.

2. Ranibizumab costs $1,575 per injection. The optimal duration of treatment is uncertain but it is likely that some patients will require indefinite therapy. The manufacturer submitted a cost utility analysis comparing ranibizumab with best supportive care and/or verteporfin photodynamic therapy by lesion type. This evaluation estimated cost per quality-adjusted life year (QALY) ranging from $4,200 compared to verteporfin photodynamic therapy in predominantly classic AMD to $38,150 compared to best supportive care in occult AMD. The economic evaluation assumed that patients with predominantly classic AMD would only receive ranibizumab treatment for one year and patients with minimally classic and occult AMD would only receive treatment for two years, but that all patients treated with ranibizumab would continue to have better visual acuity than those treated with verteporfin photodynamic therapy or best supportive care after discontinuation of therapy and for the 10 year time horizon of the model. Reanalyses using baseline estimates that the committee felt were more feasible suggested less attractive estimates of cost-effectiveness. Although the model did not allow assessment of the impact of longer-term use of ranibizumab, it is likely that

the cost per QALY of ranibizumab will increase substantially if patients require repeat treatment beyond that in the economic evaluation. The manufacturer did not conduct a sensitivity analysis using longer treatment durations.

3. This economic evaluation was also based on a Product Listing Agreement proposed by the manufacturer whereby if a patient requires more than nine vials in the first year of treatment, or six vials in subsequent years, the manufacturer would cover the cost of the additional treatment. The condition in the Product Listing Agreement that drug plans would continue to cover the cost of up to six treatments per year after the first two years of therapy is inconsistent with the economic evaluation submitted by the manufacturer. It was the Committee's opinion that the product listing agreement should be consistent with the economic model submitted by the manufacturer; therefore the Committee recommends that drug plan costs be limited to a maximum of 15 vials per patient.

Summary of Committee Considerations:

The Committee considered a systematic review of double-blind randomized controlled trials (RCTs) in adults with neovascular AMD. Three RCTs in a total of 1,323 patients met the inclusion criteria for the systematic review. All three trials were of two years duration, though only one year data are currently available from one of these trials.

One trial compared ranibizumab 0.3 and 0.5 mg monthly doses with verteporfin photodynamic therapy in patients with predominantly classic AMD. After one year of treatment, there were statistically significant differences in favour of ranibizumab 0.5 mg monthly doses compared to verteporfin in the proportion of patients with a visual acuity of 20/200 or worse (number needed to treat [NNT] = 3), loss of less than 15 letters from visual acuity (NNT = 4) and gain of at least 15 letters of visual acuity (NNT = 4). There was also a statistically significant greater improvement in quality of life scores with ranibizumab compared to verteporfin. The two year results are consistent with the one year results, however the analysis is complicated by the fact that about one-third of verteporfin photodynamic subjects crossed over to ranibizumab during the second year, and that approximately one-third of ranibizumab subjects stopped taking sham verteporfin during the second year.

Two trials compared ranibizumab 0.3 and 0.5 mg doses with a sham procedure in patients with minimally classic or occult AMD. In a trial of monthly ranibizumab injections, after one year of treatment there were statistically significant differences in favour of ranibizumab 0.5 mg versus sham in the proportion of patients with a visual acuity of 20/200 or worse (NNT = 4), loss of less than 15 letters from visual acuity (NNT = 4) and gain of at least 15 letters of visual acuity (NNT = 4). There was also a statistically significant greater improvement in quality of life scores with ranibizumab compared to sham. The two year results are consistent with the one year results. In the trial of ranibizumab every month for the first three months, followed by injections every three months thereafter, ranibizumab 0.5 mg was associated with statistically significant improvements in the proportion of patients with a visual acuity of 20/200 or worse (NNT = 4) and loss of less than 15 letters from visual acuity (NNT = 3), but there were no statistical differences between groups in gain of at least 15 letters of visual acuity or change in quality of life. Two year data from this trial are not yet available.

Serious adverse events related to the intravitreal administration of ranibizumab and occurring in <0.1% of injections include endophthalmitis, retinal detachment, retinal tear and traumatic cataract. Due to the mechanism of action of ranibizumab, there is a potential risk of arterial thromboembolic events following intravitreal use of ranibizumab.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. The Committee was aware that patients with classic and non-classic forms of AMD are being treated in Canada by ophthalmologists with intravitreal bevacizumab. The Committee acknowledged that this use is outside the approved indication and that there is limited information on the effectiveness and safety of bevacizumab. Given the significantly lower cost of bevacizumab and the similarities in the mechanisms of action of bevacizumab and ranibizumab, the Committee had concerns regarding the incremental cost-effectiveness of ranibizumab. The Committee's final recommendation to list ranibizumab as above considered a Request for Reconsideration submitted by the manufacturer and clarification from drug plans that bevacizumab was not a comparator that could be funded for the treatment of AMD.

3. Based on utilization of ranibizumab and new evidence on treatment options for neovascular AMD, drug plans may seek further advice from the Committee on the role of ranibizumab. Specifically, the Committee recommends a further review of ranibizumab when the results of head to head trials comparing it with bevacizumab are available.

4. The manufacturer supplies ranibizumab single use vials containing 3.0 mg in 0.3 mL. As the recommended dose is 0.5 mg (0.05 mL), the manufacturer and drug plans should explore opportunities to reduce the large amount wastage with these vials.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.