Canadian Expert Drug Advisory Committee
Summary of Discussion

Ranibizumab (Lucentis™— Novartis Pharmaceuticals Canada Inc.)
Indication — Age-related Macular Degeneration

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating
Dr Braden Manns (Chair), Dr Anne Holbrook (Vice-Chair), Dr Ken Bassett, Dr Bruce Carleton, Dr Michael Evans, Dr Malcolm Man-Son-Hing, Dr Laurie Mallery, Ms Nancy McColl, Mr Brad Neubauer, Dr Lindsay Nicolle, Dr Bob Peterson, Dr Dale Quest, Dr Kelly Zarnke.

Regrets
None.

Conflict of interest
CEDAC members reported no conflicts of interest related to this submission.

Description of Drug
Ranibizumab is a humanized recombinant monoclonal antibody fragment that targets vascular endothelial growth factor A (VEGF-A). Ranibizumab prevents binding of all active forms of VEGF-A to its receptors, reducing endothelial cell proliferation. Ranibizumab has been shown to prevent neovascularisation, and vascular leakage that occurs in the neovascular form of age-related macular degeneration (AMD). Ranibizumab is approved for the treatment of neovascular (wet) AMD.

Discussion of Clinical and Pharmacoeconomic Reviews
CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR and a CDR review of a pharmacoeconomic evaluation supplied by the manufacturer. An overview of these reviews and the complete CEDAC Final Recommendation and Reasons for Recommendation (technical and plain language) are available in the CDR Drug Database on the CADTH web site (www.cadth.ca).

The following is a summary of presentations by CEDAC members and discussions regarding this drug at the CEDAC meetings held on November 21, 2007, January 23, 2008 and March 19, 2008.

Therapeutic Rationale and Need
AMD is the leading cause of visual loss in people over 50 years of age in North America. Current therapy is limited as persistence and recurrence of neovascularization remains a problem. AMD treatment focuses on the use of intravenous verteporfin followed by photodynamic therapy, which is approved for use in predominantly classic types of wet AMD. This treatment decreases loss of vision by destroying abnormal choroidal new blood vessels, while anti-VEGF-A therapy prevents the emergence of new blood vessels. Retreatment with verteporfin/photodynamic therapy occurs at 3 month intervals. Pegaptanib, another anti-VEGF-A therapy, is indicated for all types of wet AMD, but efficacy beyond one year is unknown and the cost is high.

Clinical trials
Three high quality double-blind randomized controlled trials of 12-24 months were evaluated. The ANCHOR (n=423) study compared intravitreal ranibizumab 0.3 and 0.5 mg to verteporfin/photodynamic therapy in patients with predominantly classic lesions. This 24 month trial was a double dummy design with sham verteporfin/photodynamic therapy and sham ranibizumab injections. The MARINA study (n=716) and the PIER study (n=184) compared the same ranibizumab doses to sham ranibizumab injections over 24 and 12 months, respectively, in patients with mostly minimally classic or occult lesions. In the ANCHOR and MARINA studies, ranibizumab was administered monthly. In the PIER study, ranibizumab was given monthly for 3 months and then once every 3 months.

The difficulty of blinding the treatment groups was discussed. Sham verteporfin/photodynamic therapy was administered as saline injection followed by the same laser dose as in the true verteporfin/ photodynamic therapy group in ANCHOR. Sham ranibizumab injections were administered by pressing a syringe to the eye, with no actual injection, in all three studies. In the second year of the ANCHOR study, about 30% of patients crossed over from the control arm (verteporfin/photodynamic therapy) to ranibizumab, and about 30% of the ranibizumab patients stopped taking sham verteporfin/photodynamic therapy. This followed a protocol amendment of the extension trial.

Comparators or Other Available Treatment Options
Ranibizumab was compared to verteporfin/photodynamic therapy and sham ranibizumab therapy. Ranibizumab has not been compared to either pegaptanib or bevacizumab.

Outcomes
Visual acuity [blindness (20/200 or worse), change from baseline in letters, loss of fewer than 15 letters, gain of at least 15 letters] was measured using the Early Treatment Diabetic Retinopathy Study eye chart, which is considered a better measure of visual acuity than the more commonly used Snellen chart. Quality of life was measured using the National Eye Institute Visual Function Questionnaire 25. Near vision which is difficult to accurately measure was not tested; however, it does correlate with distance vision.

Efficacy or Effectiveness
At 12 months, ranibizumab improved visual acuity, visual function and quality of life compared to verteporfin/photodynamic therapy in the ANCHOR study and compared to sham injections in the MARINA study. Most measures improved in the PIER study except gain of 15 letters and quality of life, perhaps due to the increased dosing interval. The 24-month data for the MARINA study was consistent with 12-month results. The 24-month ANCHOR data was also consistent from 12 to 24 months but the high crossover to ranibizumab, and the high dropout from the sham verteporfin/photodynamic therapy group makes the 24-month data difficult to evaluate. The 24-month data from the PIER study is not yet available.

Harms (Safety and Tolerability)
Serious visual adverse effects included endophthalmitis, vitreous hemorrhage, retinal detachment and cataract. Systemic VEGF inhibition is associated with significant cardiovascular risk; in the MARINA study, the 0.5 mg dose resulted in a numerically higher risk of cerebrovascular events. The SAILOR study, an open label trial of over 2000 patients with AMD, was reviewed only for safety data because it did not have a non-ranibizumab control arm. The incidence of stroke was 1.2% and 0.3% in the ranibizumab 0.5 mg and 0.3 mg groups, respectively. The manufacturer has sent a letter advising health professionals of the risk of stroke with ranibizumab, and of the increased risk of stroke in patients with a history of previous stroke.

Cost and Pharmacoeconomic Evaluation

Ranibizumab costs $1575 per vial. The manufacturer has proposed to cover the cost if more than 9 injections are used in the first year, and more than 6 per year in subsequent years. For nine treatments in the first year, the cost is $14,175 per eye. Verteporfin/photodynamic therapy costs $7000 per year. The economic evaluation is based on one to two years of treatment, depending on the type of lesion, with treatment effect persisting for three to six months upon discontinuation, after which it is assumed that the AMD then progress at the same rate as that in patients receiving best supportive care over a period of up to 10 years. If retreatment is required after the one to two year period, the cost would be considerably higher than estimated.

Other Discussion Points

- The Committee recognized that ophthalmologists in Canada are currently using intravitreal bevacizumab for treatment of AMD, despite the lack of an approved indication. Bevacizumab is approved in Canada for the treatment of colon cancer but is used in AMD in doses 300 to 500 times lower than in colon cancer. Drug plans clarified that they could not fund bevacizumab for AMD without an approved indication and/or with stronger evidence to support its effectiveness and safety. The Committee was aware of one small single-dose published RCT that shows a similar effect of bevacizumab compared to verteporfin/photodynamic therapy in AMD; however, there are no trials comparing it to ranibizumab. Head to head trials comparing ranibizumab and bevacizumab are underway and when the results are available the Committee recommended a further review of ranibizumab.
- Bevacizumab costs $1400 per vial and can be divided into about 40 doses thereby resulting in lower costs per dose than ranibizumab.
- Listing decisions for ranibizumab in Ontario and Quebec and the coverage decisions in other countries were discussed.
- Concern was expressed about the cost of ranibizumab and the impact on provincial budgets.
- The Committee noted that ranibizumab was not cost-effective unless the Product Listing Agreement offered by the manufacturer was implemented by the drug plans. Some federal, territorial and provincial drug plans have difficulty in implementing product listing agreements; however, the manufacturer stated that it would work with the drug plans to ensure that all could implement the cap of a maximum of 9 injections per patient in the first year and 6 injections per patient in subsequent years. If patients required additional treatment with ranibizumab, the manufacturer would cover the costs. The Committee discussed the inconsistency of the treatment duration of the Product Listing Agreement compared with the economic model submitted by the manufacturer; the disease progression when treatment is stopped; and the impact on the incremental cost utility ratio if the second eye requires treatment as the reported cost-effectiveness was based on treating the better seeing eye only.
- Ranibizumab is available in single use vials containing 3 mg but the approved dose is 0.5 mg thereby resulting in wastage with every dose. The Committee advised that drug plans explore options for minimizing wastage.
- It was noted that it is unknown whether beneficial effects of the drug will continue beyond the two year period for which it has been studied. The economic evaluation submitted by the manufacturer assumed that, in comparison with best supportive care, ranibizumab was associated with less disease progression on treatment, some but less disease progression in the 3-6 months after stopping treatment, and the same rate of disease progression thereafter.

CEDAC Recommendation

The Canadian Expert Drug Advisory Committee (CEDAC) recommended 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.

CEDAC Reasons for the Recommendation

- 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.
- 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.
- 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.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation for participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

The information in this summary should not be used as a substitute for clinical judgment in the care of a particular patient, nor is it intended to replace professional advice. CADTH is not liable for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.