

Ranibizumab

Product:

RANIBIZUMAB (Lucentis®) 3mg/0.3mL injection vial

Class of drugs:

Anti-vascular endothelial growth factor

Indication:

Treatment of neovascular (wet) age-related macular degeneration (AMD)

Manufacturer:

Novartis Pharmaceuticals Canada Inc.

CED Recommendation

The CED recommended that ranibizumab (Lucentis) not be listed on the Ontario Drug Benefit Formulary. The CED acknowledged that ranibizumab (Lucentis) is effective in the treatment of neovascular age-related macular degeneration but noted the high cost of funding.

Executive Officer Decision

Based on the CED's recommendation and a subsequent listing agreement that addresses both price and utilization, the Executive Officer decided to list ranibizumab (Lucentis) on the Ontario Drug Benefit Formulary.

Status

Funding available through the Ontario Public Drug Programs.

Highlights of Recommendation:

- ◆ Ranibizumab (Lucentis) is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).
- ◆ Verteporfin (Visudyne) is an alternative treatment funded by the Ministry of Health and Long-Term Care for the treatment of wet AMD.
- ◆ In clinical practice, many ophthalmologists are also using bevacizumab (Avastin) to treat wet AMD because it costs significantly less than ranibizumab (Lucentis). Health Canada has not approved bevacizumab (Avastin) for this purpose, and there is currently no randomized controlled trial evidence to support the use of bevacizumab (Avastin) for this indication.
- ◆ There are several studies to support improved efficacy of ranibizumab (Lucentis) over placebo and verteporfin in the treatment of wet AMD. Study results indicate that a greater percentage of patients treated with ranibizumab (Lucentis) maintained or improved their vision compared with patients who were treated with placebo or verteporfin.
- ◆ There is currently no data available comparing the efficacy of ranibizumab (Lucentis) relative to bevacizumab (Avastin). An international clinical study is now underway to compare the two treatments. Data from this study will likely be available in one to two years.
- ◆ The most common side effects reported with ranibizumab (Lucentis) were related to the injection procedure or to the anesthesia required for the treatment. Most side effects were transient and mild in severity.
- ◆ Ranibizumab (Lucentis) costs \$1,575 per injection and continuous treatment, ranging from months to years, is generally required. Given the substantial number of patients who are affected with AMD, the Committee indicated that the cost impact would be very significant. Moreover, the cost of treatment would be highly variable depending on the number of doses required per patient.

- ◆ Overall, the Committee acknowledged that ranibizumab (Lucentis) showed clinical benefits for patients with wet AMD. However, the Committee noted that listing this therapy would be excessively costly to the public drug program in Ontario.

Background:

Age-related macular degeneration (AMD) is a disease in which the central part of the retina, called the macula, deteriorates over time. The macula is the part of the eye responsible for detailed vision.

The neovascular or wet form of AMD occurs when abnormal blood vessels develop under the retina. These new blood vessels tend to be very fragile and often leak blood and fluid. This, in turn, damages the retina. Only 10 percent of AMD patients have the wet form of the disease, but they account for more than 90 percent of patients with severe loss of vision due to AMD.

Ranibizumab (Lucentis) is administered by injection into the eye. It works by preventing the development of blood vessels under the retina.

Detailed Discussion:

- ◆ In its evaluation of ranibizumab (Lucentis), the Committee considered three randomized controlled trials, the ANCHOR, MARINA, and PIER studies.
- ◆ The ANCHOR and MARINA trials demonstrated that monthly intravitreal injections of ranibizumab (Lucentis) administered over a period of 12 and 24 months respectively, led to clinically significant visual outcomes compared to verteporfin photodynamic therapy (PDT) and sham treatment. The PIER trial validated the efficacy of a modified, reduced dosing schedule.

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- ◆ In ANCHOR, patients with predominantly classic choroidal neovascularization (CNV) lesions were enrolled and followed for 12 months. At 12 months, 95% of patients treated with 0.5mg of ranibizumab (Lucentis) maintained vision compared to 64% of patients receiving PDT.
- ◆ In MARINA, patients with minimally classic and occult CNV lesions were enrolled and followed for 24 months. At 24 months, 90% of patients treated with 0.5mg of ranibizumab (Lucentis) maintained vision compared to 53% of those receiving sham injections.
- ◆ In both the ANCHOR and MARINA studies, 34 - 40% of patients treated with 0.5mg of ranibizumab (Lucentis) experienced a clinically significant and sustained improvement in vision, defined as a gain of 15 or more letters of acuity at 12 months regardless of lesion subtype.
- ◆ The PIER trial included patients with all subtypes of CNV and randomized patients to receive injections of ranibizumab (Lucentis) 0.3 mg, 0.5 mg or sham injections monthly for 3 consecutive months followed by a dose every 3 months. Patients were followed for 12 months. Following monthly dosing of ranibizumab (Lucentis), there was an initial increase in visual acuity up to month 3. Between months 3 and 12, coincident with the reduced frequency of injection to once every 3 months, visual acuity declined and returned to baseline levels. At 12 months, however, 90% of patients treated with 0.5mg of ranibizumab (Lucentis) maintained vision compared to only 49% of sham-treated patients.
- ◆ The most common ocular adverse events reported with higher frequency in the ranibizumab (Lucentis) treatment arms of the studies were related to the injection procedure and subconjunctival anesthesia. Adverse events included conjunctival hemorrhage, eye pain, vitreous floaters and increased intraocular pressure. Most of these side effects were mild and transient in severity.
- ◆ A small percentage of patients treated with ranibizumab (Lucentis) in the trials experienced endophthalmitis, retinal detachment, retinal tears and traumatic cataracts.
- ◆ During the first year of treatment in the ANCHOR and MARINA trials, there was a small trend towards increased frequency of arterial thromboembolic events (vascular deaths, non-fatal myocardial infarctions and non-fatal strokes) in patients treated with ranibizumab (Lucentis). The increased risk of thromboembolic events was not sustained in the second year of the MARINA study.
- ◆ Data on comparative efficacy between ranibizumab (Lucentis) and bevacizumab (Avastin) is not available. The current evidence to support bevacizumab (Avastin) in the treatment of wet AMD is mainly non-controlled, retrospective case studies with short follow-up periods. Efficacy of bevacizumab (Avastin) in the treatment of wet AMD has not been conclusively demonstrated in any large-scale, randomized placebo-controlled trials. The U.S. National Eye Institute and the National Institute of Health have funded a new multicenter clinical trial to compare the efficacy of bevacizumab (Avastin) to ranibizumab (Lucentis). One-year data are forecasted for release in 2009.
- ◆ The Committee was concerned about the potential off-label use of ranibizumab (Lucentis) for other eye conditions for which there is no evidence of efficacy (e.g. CNV lesions caused by other diseases).
- ◆ Off-label combination therapy with PDT for the treatment of AMD was also a concern. All of the clinical trials assessed the efficacy of ranibizumab (Lucentis) as monotherapy. The role of combination therapy was not specifically addressed. The DENALI trial, evaluating combination therapy for the treatment of AMD, is currently underway. Combination therapy should not be considered until trial results are available.
- ◆ Ranibizumab (Lucentis) costs \$1,575 per injection and continuous treatment, ranging from months to years, is generally required. The Committee evaluated the manufacturer's pharmacoeconomic analysis and noted that the economic model was biased in favour of ranibizumab (Lucentis) and did not allow assessment of the impact of longer-term use of ranibizumab (Lucentis).
- ◆ The manufacturer's budget impact analysis underestimated the cost of therapy to the Ministry. Given the substantial number of patients who are affected with AMD and the number of treatments required for each patient, the Committee noted that the cost impact of ranibizumab (Lucentis) to public drug funding in Ontario would be very significant.
- ◆ Overall, the Committee acknowledged that ranibizumab (Lucentis) showed clinical benefits for patients with wet AMD. However, the Committee noted that listing this therapy would be excessively costly to the public drug program in Ontario.

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that ranibizumab (Lucentis) 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 (Lucentis) should not be funded in combination with verteporfin.



Ministry of
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Ontario Public Drug Programs

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