Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Overview of CDR Clinical and Pharmacoeconomic Reports

CDR

August 2008

Ranibizumab

Lucentis® – Novartis Pharmaceuticals Canada Inc.

Indication – Age-related Macular Degeneration (AMD)

Supporting Informed Decisions

À l'appui des décisions éclairées

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LIST OF ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
BSC	best supportive care
CI	confidence interval
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IVT	intravitreal
MC	minimally classic
NNT	number needed to treat
OC	occult
PC	predominantly classic
PDT	photodynamic therapy
QALY	quality-adjusted life year
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
VA	visual acuity
VEGF	vascular endothelial growth factor
VFQ-25	visual function questionnaire - 25 items
VY	vision years (years spent with VA>20/200; i.e. above the threshold for legal blindness)
WDAE	withdrawal due to adverse events

REVIEW in Brief

Ranibizumab (Lucentis®) was submitted by the manufacturer to the Common Drug Review (CDR) for consideration for formulary listing by participating public drug plans. This Review in Brief includes the Canadian Expert Drug Advisory Committee's (CEDAC) recommendation, and information used by CEDAC in making its recommendation including: a summary of the best available clinical and pharmacoeconomic evidence identified and reviewed by the CDR, as well as information submitted by the manufacturer.

CEDAC Recommendation

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that ranibizumab be listed for the treatment of neovascular age-related macular degeneration (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

- Compared to verteporfin photodynamic therapy (PDT) 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 PDT by lesion type. This evaluation estimated cost per quality-adjusted life year (QALY) ranging from $4,200 compared to verteporfin PDT 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 PDT or best supportive care after discontinuation of therapy and for the 10 year time horizon of the model. Re-analyses 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.

Drug

- Ranibizumab is approved for the treatment of neovascular (wet) AMD.
- Ranibizumab is a humanized recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor-A (VEGF-A). It prevents the binding of VEGF-A to its receptors, inhibiting endothelial cell proliferation, neovascularization and vascular leakage.
- Ranibizumab is initiated with a loading phase of one intravitreal (IVT) injection every month for three months, followed by a monitored maintenance phase where ranibizumab may be administered depending on clinical and diagnostic criteria. The recommended dose is 0.5 mg.

Condition

AMD is a degenerative disease of the macula, the part of the retina responsible for detailed vision, leading to loss of vision.

Clinical Review

- A systematic review of double-blind randomized controlled trials (RCTs) of ranibizumab in adults with neovascular AMD was completed.
- 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.

Results

[Number needed to treat (NNT) calculated by CDR.]

Ranibizumab versus Verteporfin PDT in Predominantly Classic AMD (one trial)

After one year of treatment, there were statistically significant differences in favour of ranibizumab 0.5 mg monthly doses compared to verteporfin PDT in the proportion of patients with:

- a visual acuity of 20/200 or worse (NNT = 3)
- a loss of less than 15 letters of visual acuity from baseline (NNT = 4)
- gain of at least 15 letters of visual acuity (NNT = 4)
- an improvement in quality of life using VFQ-25 composite score

Two year results are consistent with one-year results but are complicated by a protocol amendment at 12 months that allowed cross-over from the verteporfin PDT arm to ranibizumab and discontinuation of sham verteporfin PDT in any arm, leading to unblinding.

Ranibizumab versus Sham in Minimally Classic or Occult AMD (two trials)

After one year of treatment with monthly ranibizumab injections (one trial) 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)
- a loss of less than 15 letters of visual acuity from baseline (NNT = 4)
- a gain of at least 15 letters of visual acuity (NNT = 4)
- an improvement in quality of life scores

The two-year results are consistent with the one year results.

After one year of treatment with monthly ranibizumab injections for three months, followed by ranibizumab injections once every three months (one trial), 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)
- a loss of less than 15 letters of visual acuity from baseline (NNT = 3)

There were no statistical differences between groups in:

- gain of at least 15 letters of visual acuity
- quality of life scores

Two year data were not available.

Adverse Events

Serious adverse events occurred in less than 0.1% of patients who received ranibizumab injections and include:

- endophthalmitis
- retinal detachment, retinal tear
- traumatic cataract

A potential risk of thromboembolic events with ranibizumab exists.

Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

Highlights

- Ranibizumab costs $1,575 per injection.
- The manufacturer submitted a cost utility analysis comparing ranibizumab with best supportive care and/or verteporfin PDT by lesion type.
- The economic evaluation assumed that patients would only receive ranibizumab treatment for one to two years (depending on type of AMD) but would continue to benefit beyond that. The optimal duration of treatment is uncertain but it is likely that some patients will require indefinite therapy.
- This evaluation estimated cost per quality-adjusted life year (QALY) ranging from $4,200 compared to verteporfin PDT in predominantly classic AMD to $38,150 compared to best supportive care in occult AMD.
- CDR re-analyses using baseline estimates that CEDAC felt were more feasible suggested less attractive estimates of cost-effectiveness.

What is the CDR?

The CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

OVERVIEW

Context

This document is an overview of two Common Drug Review (CDR) reports: the CDR Clinical Review Report (a systematic review of the clinical evidence) and the CDR Pharmacoeconomic Review Report (a critique of the pharmacoeconomic evaluation submitted by the manufacturer). These reports were prepared by the CDR to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that the CDR has identified and compiled, including that submitted by the manufacturer.

This overview report is based on the ranibizumab CDR Clinical Review Report, 66 pages in length with 81 references, and the ranibizumab CDR Pharmacoeconomic Review Report, 24 pages with 13 references. The manufacturer had the opportunity to provide feedback on each of the full reports and on this Overview Report. The CDR has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information as defined in the CDR Confidentiality Guidelines, may have been used in the preparation of these documents and thus may have been considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

Introduction

Ranibizumab, an anti-vascular endothelial growth factor (VEGF) agent, is a humanized recombinant monoclonal antibody fragment targeted against human VEGF-A. It prevents the binding of VEGF-A to its receptors, inhibiting endothelial cell proliferation, neovascularization and vascular leakage. It is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Ranibizumab is initiated with a loading phase of one intravitreal (IVT) injection every month for three months, followed by a maintenance phase where patients are monitored for loss of visual acuity (VA), or clinical or diagnostic evidence of disease activity. If these occur, ranibizumab should be administered. The interval between doses should be a minimum of one month. The recommended dose is 0.5 mg, and it is available in single-use vials of 3.0 mg of ranibizumab per 0.3 mL of injection solution.

AMD is a degenerative disease of the macula, the part of the retina that is responsible for detailed vision. There are two main types of AMD: dry or atrophic, and wet or exudative.[1] Available options for the treatment of wet AMD include photodynamic therapy (PDT) using verteporfin (Visudyne®) – a light-sensitive dye that is administered intravenously and then is activated by a low energy laser; pegaptanib (Macugen®) – an VEGF aptamer; and laser surgery. Anecortave acetate (Retaane) – a new steroid analog for IVT injection is not yet approved for use in Canada. Bevacizumab (Avastin®) – an anti-VEGF agent approved in Canada for the treatment of metastatic colorectal cancer, is also used off-label for the treatment of AMD. Therapies combining two or more of the above are under investigation.

Clinical Review

Objective

To evaluate the effect of ranibizumab on patient outcomes compared with standard therapies and sham treatment in patients with neovascular (wet) AMD.

Methods

For information about the methodology employed in the full CDR Clinical Review of ranibizumab, refer to Appendix I.

Selection Criteria

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

Table 1: Selection Criteria

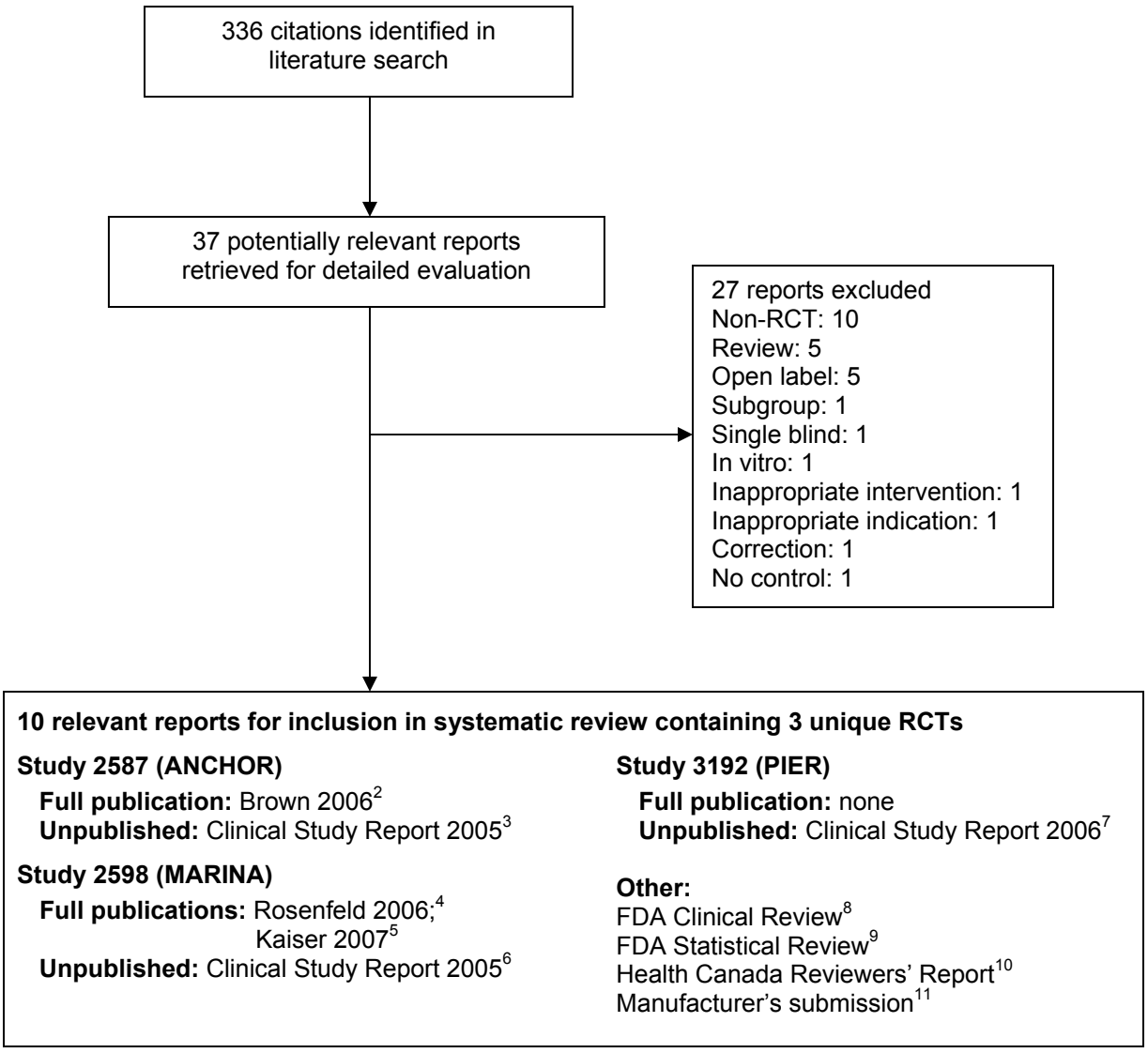
Clinical Trial Design	Patient Population	Interventions	Appropriate Comparators*	Outcomes
DB RCT	Adults with neovascular (wet) AMD	Ranibizumab used as monotherapy or in combination Potential subgroups: monotherapy combination therapy	Verteporfin PDT Pegaptanib Bevacizumab Photocoagulation Steroids Sham	**Primary** • Blindness (legal) • Change in VA • Quality of Life • SAEs (ocular or non-ocular) **Secondary** • Eye Infection • Injection-related AE • Visual function (assessed by validated measures) • Choroidal neovascularization • Non-serious AEs

AE=adverse event; DB=double blind; PDT=photodynamic therapy; RCT=randomized controlled trial; SAE=serious adverse event; VA=visual acuity.
*Standard therapies available in Canada (may include drug or non-drug interventions)

Results

Findings from the Literature

Figure 1: QUOROM Flowchart Detailing Flow of Studies



RCTS=randomized controlled trials

Summary of Evidence

Included Studies and Trial Characteristics

Three double-blind, randomized controlled trials (RCTs) were included in this review. ANCHOR is a 24-month study that compared ranibizumab 0.3 mg or 0.5 mg with verteporfin PDT.[3,4,12] The other two studies (MARINA[5-8] and PIER[13]) compared these two doses of ranibizumab with sham, and were also 24 months in length, although only 12-month data was available from PIER. MARINA and ANCHOR had published reports, while PIER was unpublished. In PIER, subjects received ranibizumab every month for the first three months, then every three months thereafter. In the other studies, ranibizumab was administered every month throughout the trial. MARINA had the largest population (N=716) followed by ANCHOR (N=423) and PIER (N=184). In the ANCHOR study nearly all patients were classified as having predominantly classic (PC) AMD (96% to 99%). Subjects in the MARINA study all had either minimally classic (MC) or occult (OC) AMD, and the subjects in PIER had representation from all types with a minority being PC (13% to 22%). At present, the influence of lesion type on prognosis or response to therapy is unclear.
All studies had subjects randomized in a 1:1:1 fashion. All studies were manufacturer-funded.

Summary of Results

See Table 2 for a summary of trial outcomes.

Ranibizumab versus Verteporfin PDT after 12 months (ANCHOR)[3,4,12]
Note: for statistical comparisons of ranibizumab versus verteporfin PDT, all p-values are p<0.0001 unless stated otherwise.

- There were statistically fewer ranibizumab subjects who had a VA of 20/200 or worse in each ranibizumab arm versus verteporfin PDT [ranibizumab 0.5 mg (baseline): 16% (25%) versus verteporfin PDT: 57% (28%)]. Number needed to treat (NNT) of 3 for ranibizumab to prevent VA of 20/200 or worse.
- The mean (SD) change from baseline in letters VA was statistically greater for ranibizumab versus verteporfin PDT [ranibizumab 0.5 mg: 11.0 (15.8) versus verteporfin PDT -8.5 (17.8)].
- There were statistically more ranibizumab subjects versus verteporfin PDT who lost fewer than 15 letters VA from baseline [ranibizumab 0.5 mg: 98% versus verteporfin PDT: 66%].
- There were statistically more ranibizumab subjects who gained at least 15 letters VA from baseline versus verteporfin PDT (ranibizumab 0.5 mg: 37% versus verteporfin PDT: 11%). NNT of 4 for ranibizumab to have one subject gain ≥15 letters.
- There were statistical improvements in mean (SD) change from baseline in visual function (letters contrast sensitivity) with ranibizumab versus verteporfin PDT [ranibizumab 0.5 mg: 4.1 (6.0) versus verteporfin PDT: -3.1 (7.6)].
- There was a statistically greater mean [standard deviation (SD)] improvement in quality of life scores (VFQ-25 composite – a visual function questionnaire) for ranibizumab arms versus verteporfin PDT [ranibizumab 0.5 mg: 8.1 (16.4), versus verteporfin PDT: 2.2 (15.0); p=0.002].
- There were no statistical differences between ranibizumab arms and verteporfin PDT in the proportion of subjects with ocular or non-ocular SAEs. There were three ranibizumab 0.3 mg subjects (cardiac arrest, respiratory arrest, and viral syndrome) and two ranibizumab 0.5 mg subjects (cardiac failure, worsening chronic heart failure) who died; compared with two verteporfin PDT (cardiac arrest, chronic obstructive pulmonary disease) subjects.

- There were no statistical differences in the proportion of subjects with an ocular (study eye) or non-ocular AE between ranibizumab and verteporfin PDT arms.

Ranibizumab versus sham after 12 months (MARINA, PIER)[5-8,13]
Note: for statistical comparisons of ranibizumab versus sham, all p-values are p<0.0001 unless stated otherwise.

- There were statistically fewer ranibizumab subjects who had a VA of 20/200 or worse in each ranibizumab arm versus sham in MARINA [ranibizumab 0.5 mg (baseline): 12% (16%), versus sham: 43% (11%)] and in PIER [ranibizumab 0.5 mg (baseline): 25% (16%) versus sham: 52% (16%), p=0.001].
- The mean (SD) change from baseline in letters VA was statistically greater in each ranibizumab arm versus sham in MARINA [ranibizumab 0.5 mg: 6.3 (14.1) versus sham: -11.0 (17.9)] and in PIER [ranibizumab 0.5 mg: -0.2 (13.1) versus sham: -16.3 (22.3)].
- There were statistically more ranibizumab subjects who lost fewer than 15 letters VA from baseline in MARINA (ranibizumab 0.5 mg: 91% versus sham: 60%) and in PIER (ranibizumab 0.5 mg: 90% versus sham: 49%).
- There were statistically more ranibizumab subjects who gained at least 15 letters VA from baseline in MARINA (ranibizumab 0.5 mg: 31% versus sham: 6%), but not in PIER (ranibizumab 0.5 mg: 13% versus sham: 10%).
- There were statistical improvements in mean (SD) change from baseline in visual function (contrast sensitivity) in ranibizumab arms versus sham in MARINA [ranibizumab 0.5 mg: 2.1 (4.8) versus sham: -3.1 (6.9)] and in PIER [ranibizumab 0.5 mg: -0.1 (5.5) versus sham: -5.9 (7.8)].
- There was a statistically greater mean (SD) improvement in quality of life scores (VFQ-25 composite) in MARINA [ranibizumab 0.5 mg: 5.6 (13.6) versus sham: -2.8 (13.5)] but not in PIER [ranibizumab 0.5 mg: -1.3 (15.3) versus sham: -1.3 (12.6)].
- There were no statistical differences between ranibizumab arms and sham in the proportion of subjects with ocular or non-ocular SAEs in either MARINA or PIER. There was one ranibizumab 0.3 mg subject (heart attack) and two ranibizumab 0.5 mg subjects (small bowel infarct, chronic asthma/chronic obstructive pulmonary disease) who died in MARINA, and no deaths in sham. There were no deaths in PIER.
- There were more ranibizumab 0.3 mg subjects with a non-ocular AE compared with sham in MARINA and PIER, and this difference was statistically significant in MARINA (89% versus 81%; p=0.02 by CDR analysis). Otherwise there were no other statistically significant differences between ranibizumab and sham.

24-month data

- The 24-month efficacy and safety results for the MARINA study are consistent with the 12-month results. The statistically significant treatment effect was maintained for all outcomes, and the magnitude of response did not increase or decrease significantly from 12 to 24 months. The 24-month data from the ANCHOR study is difficult to interpret given that about one-third of verteporfin PDT subjects crossed over to ranibizumab during the second year, and about one-third of ranibizumab subjects stopped taking sham verteporfin during the second year. No 24-month data was available for the PIER study.

Table 2: Summary of Trial Outcomes – 12-Month Data

Study	ANCHOR			MARINA			PIER		
Study Design (including publication status)	DB RCT RB 0.3 mg monthly versus RB 0.5 mg monthly versus verteporfin PDT every three months (as needed) 24 months, Published			DB RCT RB 0.3 mg monthly versus RB 0.5 mg monthly versus sham monthly 24 months, Published			DB RCT RB 0.3 mg versus RB 0.5 mg versus sham, each administered monthly for three months then every three months 24 months, Unpublished		
Treatment Arm	**RB 0.3 mg**	**RB 0.5 mg**	**Verteporfin PDT**	**RB 0.3 mg**	**RB 0.5 mg**	**Sham**	**RB 0.3 mg**	**RB 0.5 mg**	**Sham**
Number of patients randomized	N=140	N=140	N=143	N=238	N=240	N=238	N=60	N=61	N=63
Total withdrawals (WDAEs)	N=10 (2) Deaths: 3	N=5 (1) Deaths: 2	N=10 (4) Deaths: 2	N=6 (0) Deaths: 1	N=6 (2) Deaths: 2	N=21 (5) Deaths: 0	N=1	N=2	N=8
Subjects with VA 20/200 or worse, n (%)	32 (23) ***p<0.0001***	23 (16) ***p<0.0001***	81 (57)	29 (12) ***p<0.0001***	28 (12) ***p<0.0001***	102 (43)	14 (23) ***p=0.0002***	15 (25) ***p=0.001***	33 (52)
QoL, mean change (SD) from baseline (VFQ-25 composite)	5.9 (14) ***p=0.0025***	8.1 (16) ***p<0.0001***	2.2 (15)	+5.2 (13.3) ***p<0.0001***	+5.6 (13.6) ***p<0.0001***	-2.8 (13.5)	1.0 (12.3) p=0.4944	-1.3 (15.3) p=0.9940	-1.3 (12.6)
Mean (SD) change from baseline in VA, letters	+7.2 (15) ***p<0.0001***	+11.0 (15) ***p<0.0001***	-8.5 (16)	+5.4 (13.4) ***p<0.0001***	+6.3 (14.1) ***p<0.0001***	-11.0 (17.9)	-1.6 (15.1) ***p=0.0001***	-0.2 (13.1) ***p<0.0001***	-16.3 (22.3)
Loss of <15 letters VA from baseline, subjects, n (%)	133 (95) ***p<0.0001***	136 (98) ***p<0.0001***	93 (66)	213 (93) ***p<0.0001***	209 (91) ***p<0.0001***	138 (60)	50 (83) ***p<0.0001***	55 (90) ***p<0.0001***	31 (49)
Gain of ≥15 letters VA from baseline, subjects, n (%)	37 (26) ***p=0.0003***	51 (37) ***p<0.0001***	15 (11)	42 (18) ***p<0.0001***	72 (31) ***p<0.0001***	14 (6)	7 (12) p=0.8674	8 (13) p=0.7080	6 (10)
Mean (SD) change from baseline in size of lesion, DA	0.36 (1.1)	0.28 (1.3)	2.56 (3.1)	+0.11(2.1) ***p<0.0001***	+0.14(2.0) ***p<0.0001***	+2.33 (2.9)	0.05 (1.8) ***p<0.0001***	0.24 (1.9) ***p<0.0001***	2.42 (2.9)
Subjects with an ocular SAE, n (%)	6 (4) p=0.94	8 (6) p=0.56	6 (4)	15 (6) p=0.55	15 (6) p=0.57	12 (5)	5 (9) p=0.31	3 (5) p=0.09	9 (15)
Non-ocular SAE (%)	20 (15) p=0.27	28 (20) p=0.93	28 (20)	43 (18) p=0.63	44 (18) p=0.57	39 (17)	8 (14) p=0.51	7 (12) p=0.75	6 (10)
Subjects with an ocular AE, n (%)	129 (94) p=0.35	132 (94) p=0.37	138 (97)	233 (98) p=0.55	233 (98) p=0.76	229 (97)	51 (86) p=0.33	47 (77) ***p=0.03***	57 (92)
Non-ocular AE (%)	103 (75) p=0.37	119 (85) p=0.24	114 (80)	212 (89) ***p=0.02***	200 (84) p=0.50	192 (81)	46 (78) p=0.11	40 (66) p=0.90	40 (65)

AE=adverse event; DA=disc area; DB=double blind; PDT=photodynamic therapy; QoL=quality of life; RB=ranibizumab; RCT=randomized controlled trial; SAE=serious adverse event; SD=standard deviation; VA=visual acuity; WDAE=withdrawal due to adverse event.

Discussion

Neovascular AMD may be subdivided angiographically into PC, MC and pure OC forms. About 40% of neovascular AMD are of the classic subtype, while about 60% are of the occult subtype.

Efficacy

All double-blind RCTs of ranibizumab used a sham group as the control. While it would not be ethical to expose control arms to an IVT injection, the lack of a true IVT injection in the sham arm complicates the assessment of ocular AEs and SAEs, and also calls into question the integrity of the blinding. Since only subjects receiving ranibizumab received an IVT, the nature of the injection itself, including the appearance of vitreous floaters in some patients, might unblind subjects in the ranibizumab group.

The results from PIER were not consistent with those of the other two studies. Quality of life by VFQ-25 (as described in Appendix II) was not statistically different from sham, and subjects did not gain VA from baseline to 12 months, as they did in the other studies. Unlike the other studies, PIER increased the dosing interval after the first three injections to every three months, suggesting that a longer dosing interval may lead to reduced efficacy.

In the ANCHOR trial there were statistically significant improvements for ranibizumab versus verteporfin PDT and sham in overall, and through most individual components of a vision-specific quality of life instrument. However, the mean change in the composite score did not exceed the 10-point difference which is suggested to be clinically meaningful. Individual items that did approach or exceed the 12-point subscale difference deemed to be clinically meaningful, included vision-specific mental health and general vision. Although improvements in these items were also observed with verteporfin PDT, improvements with both doses of ranibizumab were significantly greater.

There is one single-blind RCT comparing the combination of ranibizumab and verteporfin PDT with verteporfin PDT alone.[14] Although it appears that the combination of these agents confers an efficacy advantage compared with PDT alone, it has not been established whether adding PDT to ranibizumab improves the efficacy of ranibizumab.

Bevacizumab, another monoclonal antibody targeting VEGF, is the closest pharmacological comparator to ranibizumab, but it is not approved for AMD despite being used off-label for this purpose. There are currently no trials comparing these two agents directly; however, there are several studies that are ongoing. While the adverse effects associated with the systemic use of bevacizumab are considerable yet accepted in the context of anticancer therapy, few controlled studies of bevacizumab in AMD were found. The largest source of safety data where bevacizumab has been used as an IVT injection is from a 2006 internet survey, in which mild increases in blood pressure were the most common AE and 5 cerebrovascular accidents were reported. The lack of a control group in this data as well as the longer half-life of bevacizumab compared with ranibizumab leave some important questions unanswered.

Harms

There were no statistically significant differences between ranibizumab and verteporfin PDT subjects in terms of ocular or non-ocular SAEs or other AEs. In both RCTs comparing ranibizumab with sham, there were no statistically significant differences in ocular or non-ocular SAEs, but the incidence of non-ocular AEs was higher in the ranibizumab 0.3 mg arm versus sham in MARINA and PIER, and this difference reached statistical significance in MARINA

(89% versus 81%; p=0.02 by CDR analysis). Such differences were not seen for the higher dose (0.5 mg) of ranibizumab, making these findings difficult to interpret. The incidence of ocular events in the study eye was either lower with ranibizumab or not statistically different between groups.

Numerically, there were a larger proportion of arterial thromboembolic events in ranibizumab subjects compared with sham after one year of the MARINA study. However, this imbalance was reduced after the second year of the study. After one year of the SAILOR study (this study did not meet the CDR inclusion criteria for systematic review because it had no comparator arm), a large RCT (>2,000 subjects) comparison of the 0.3 mg and 0.5 mg doses of ranibizumab, there was a larger proportion of 0.5 mg subjects who experienced a cerebrovascular accident (stroke) compared with the 0.3 mg arm (1.2% versus 0.3%; p=0.02). This finding prompted the manufacturer to send a letter to health care professionals advising them of the risk and also advising them that patients with previous history of strok appeared to be at increased risk of this event.[15] See Appendix III for additional harms data concerning cerebrovascular accidents.

Pharmacoeconomic Review

Context

The CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. The CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

Objective of the Manufacturer's Economic Evaluation

To assess the incremental cost-effectiveness and cost-utility of ranibizumab compared with verteporfin with PDT or best supportive care (BSC) in adults with wet AMD.

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a pharmacoeconomic evaluation: a cost-effectiveness and cost-utility analysis of ranibizumab compared with BSC and verteporfin with PDT in the treatment of adult patients with wet AMD. The manufacturer considered the forms of AMD (PC, OC, and MC) using separate analyses. The model was based on a Markov process with six health states (5 levels of visual acuity (VA); dead) with simulated patients modeled in 3 month cycles. Transition probabilities and the baseline distribution of VA were based on those observed in the clinical trials. Although follow-up in the three key clinical trials on which the model was based was two years or less, the time horizon selected for the model was 10 years. The model also assumed that the treatment effect of ranibizumab would be sustained at 100% for three months after its discontinuation, and at 50% for an additional 3 months. Costs and benefits were both discounted at 5% per annum. The outcome measures included vision years and quality-adjusted life years (QALYs). The key data sources were clinical studies for ranibizumab: ANCHOR;[16] MARINA;[4] PIER;[7] published ophthalmology literature; and expert opinion.

The manufacturer analyses were based on the assumption that the proposed Product Listing Agreement for ranibizumab (in which the cost of additional vials for patients requiring more than 9 vials in year 1, or 6 vials in years 2 and 3 of treatment) would be covered by the manufacturer and could be implemented by the drug plans. There are a number of conditions to this Agreement.

Cost Comparison

CDR produced the following table to provide a comparison of the cost of treatment of ranibizumab with comparator treatments deemed appropriate by clinical experts. Comparators may reflect recommended or actual practice and are not restricted to drugs, but may include devices or procedures where appropriate. Costs are manufacturer list prices, unless otherwise specified.

Table 3: Cost Comparison of Ranibizumab and Comparators

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended dose	Annual cost ($)
Ranibizumab (Lucentis)*	**3.0mg/ 0.3mL single use vial**	**injection**	**$1,575**	**0.5 mg monthly** **Based on Product Listing Agreement:** **Year 1** **Years 2 and 3**	**$18,900 (12 injections)** **$14,175 (9 injections)** **$9,450 (6 injections)**
Pegaptanib sodium (Macugen)	0.3mg/ 90uL single use syringe	pre-filled syringe	$995	0.3mg every 6 weeks	$7,960
Photodynamic therapy with verteporfin (Visudyne)	15mg/ single use vial	injection	$1,750	1 injection every 3 months[#] (1-3 courses typically observed)^	$7,000 $1,750 - $5,250

Source: Pharmaceutical Pricing System (PPS) Buyers' Guide, July 2007
* Manufacturer's (Novartis Pharmaceuticals Canada Inc.) submission binder
[#] According to the product monograph for verteporfin and information from Ontario Drug Benefit, the patient should be re-evaluated every 3 months and if choroidal neovascular leakage is detected on fluoroscein angiography, therapy should be repeated.
^ Ontario Drug Benefit Program, 2007.

Note: Bevacizumab (Avastin) is currently being used off label for the treatment of wet AMD. The price of a 100mg vial is $600. Doses have been reported at 1mg-2.5mg every 4 weeks.

Results (as submitted by the manufacturer)

The manufacturer's reference case suggests that ranibizumab is associated with:

- Incremental costs per QALY of:
  - $4,167 compared to verteporfin with PDT
  - $12,900 to $38,150 compared with BSC
- Incremental costs per vision year gained of:
  - $952 compared to verteporfin with PDT
  - $4,170 to $38,151 compared to BSC

Table 4: Results of Manufacturer's Reference Case (costs reported in 2007 Canadian $)								
Treatment Strategy	**AMD Type**	**Trial**	**Treatment Duration**	**Total Cost**	**QALYs**	**VYs**	**ICUR ($/QALY)**	**ICER ($/VY)**
Ranibizumab	PC	ANCHOR	1year	79,512	5.37	2.86	4,167	952
Verteporfin with PDT				78,686	5.17	1.99		
Ranibizumab	PC	ANCHOR	1year	79,512	5.37	2.86	21,857	5,238
BSC				74,058	5.12	1.81		
Ranibizumab	PC	PIER	1year	75,875	5.01	2.68	12,871	4,166
BSC				72,720	4.77	1.93		
Ranibizumab	MC	MARINA	2year	73,158	5.71	4.48	37,363	9,542
BSC				60,445	5.37	3.14		
Ranibizumab	OC	MARINA	2year	64,864	5.93	5.33	38,151	10,345
BSC				51,158	5.57	4.00		

AMD=age-related macular degeneration; BSC=best supportive care; ICER=incremental cost-effectiveness ratio; ICUR=incremental cost-utility ratio; MC=minimally classic; OC=occult with no classic; PC=predominantly classic; PDT=photodynamic therapy; QALY=quality-adjusted life year; VY(s)s=vision year(s).
Source: *Manufacturer's (Novartis Pharmaceuticals Canada Inc.) submission binder (Pharmacoeconomic Evaluation)*

Results (based on CDR re-analysis)

The CDR conducted a re-analysis of the manufacturer's model where the assumptions used in the Reference Case were altered to describe an alternative reference case with more conservative estimates for mortality, utility, and clinical benefit by the CDR. The results show that the cost per QALY for ranibizumab is less than $30,000 for the treatment of PC AMD, when compared to BSC or verteporfin PDT; $49,000 for the treatment of MC when compared to BSC; and, $53,000 for the treatment of OC compared to BSC.

In addition, if the Product Listing Agreement does not hold or cannot be implemented, the cost per QALY estimates increase to: $36,000 for the treatment of PC compared to verteporfin PDT; $50,000 to $78,000 for the treatment of PC compared to BSC; and, over $100,000 for the treatment of MC or OC compared to BSC.

Table 5: Results of CDR Re-analysis (costs reported in 2007 Canadian $)					
Treatment strategy	**AMD type**	**Trial**	**Treatment duration**	**Alternative ICUR ($/QALY)**	**Alternative ICUR – where PLA does not hold ($/QALY)**
RB vs verteporfin with PDT	PC	ANCHOR	1 year	5,191	36,003
RB vs BSC	PC	ANCHOR	1 year	26,619	51,781
RB vs BSC	PC	PIER	1 year	21,148	77,787
RB vs BSC	MC	MARINA	2 year	48,917	101,199
RB vs BSC	OC	MARINA	2 year	52,678	105,184

AMD=age-related macular degeneration; BSC=best supportive care; ICUR=incremental cost-utility ratio; MC=minimally classic; OC=occult with no classic; PC=predominantly classic; PDT=photodynamic therapy; PLA=product listing agreement; QALY=quality-adjusted life year; RB=ranibizumab.

Pharmacoeconomic Analysis Discussion Points

In reviewing the manufacturer's submission, the reviewers noted the following:

- *Product Listing Agreement.* The results presented by the manufacturer are based on the manufacturer adhering to their proposed Product Listing Agreement and the drug plans being able to implement it. Where the Product Listing Agreement does not hold, and patients require monthly injections of ranibizumab for the duration of treatment (1 year for PC AMD, and 2 years for OC and MC AMD), the cost per QALY estimates increase significant, as presented in the Alternative Reference Case above.

- *Estimates of efficacy for ranibizumab.* The results of the pivotal trials are robust. However, the results of the economic analysis were highly sensitive to the horizon selected, and shorter time horizons appear to be more appropriate given the lack of supporting data. Given the high cost of ranibizumab, if relapses require prolonged treatment (treatment beyond three years) or repeated courses of treatment, the cost per QALY associated with ranibizumab would likely be substantially higher.

- *Failure to consider VA in contralateral eye.* The manufacturer's model used utility estimates based on VA in the better-seeing eye. The incremental utility benefit associated with also preserving vision in the worse-seeing eye was not presented or discussed. This is acceptable as long as the manufacturer's current Product Listing Agreement applies (i.e., the manufacturer would reimburse the drug plans for treatment of the other eye, if required for a three year period). If the Product Listing Agreement is modified or expires, bilateral treatment with ranibizumab might be much less economically attractive than treatment of the better-seeing eye alone.

- *Estimates of utility associated with blindness*. The estimates of utility used in the reference case are based on a study sponsored by the manufacturer.[17] The methodology employed in the study appears to have some significant limitations (such as the design of the study and the study population), which casts some question on the applicability of the estimates. The conclusions of the model are sensitive to the estimate of utility that is used.

- *Limited use of sensitivity analysis*. Although multiple sensitivity analyses were performed, the report did not fully test the impact of key assumptions on the economic attractiveness of ranibizumab, e.g., efficacy of ranibizumab after treatment, alternative published utility estimates, or shorter time horizons. CDR conducted additional sensitivity analyses to help address this limitation, as presented above.

CEDAC Final Recommendation — Issued March 27, 2008

Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, 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.

APPENDIX I: METHODOLOGY FOR THE FULL CDR CLINICAL REVIEW

Methods

Reviewer Information

- The Systematic Review of Clinical Trials and Executive Summary were prepared by two CDR clinical reviewers in consultation with a retinal specialist.
- Supplemental Issues were prepared by two CDR reviewers.
- Background Information on the condition was prepared by a retinal specialist.

Systematic Review Methods

Review Protocol

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert, in consultation with the internal and external pharmacoeconomic reviewers. Members of CEDAC also provided input and comments.

Literature Search Methods

- The literature search was performed by an internal CDR information specialist, using a peer-reviewed search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews; EMBASE and Medline through OVID; and The Cochrane Library (2007, Issue 3) through Wiley InterScience.
- Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The initial search was completed on July 17, 2007. Regular alerts were established to update the search until CEDAC's meeting scheduled for November 21, 2007.
- Grey literature was obtained by searching the web sites of regulatory, health technology assessment, and near-technology assessment agencies, as well as clinical trial registries. Google™ and other online search engines were used to search for a variety of web-based information, including conference abstracts.
- In addition, the drug manufacturer was contacted for additional information regarding trial data.

Selection of Studies

- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Quality Assessment

- Study bias was critically assessed independently by two CDR reviewers.

Data Analysis Methods

- Data analysis was carried out using the Review Manager 4.2 software. Where appropriate CDR reviewers calculated NNT, RR, MD of change between ranibizumab arms and VP PDT or sham.

Supplemental Issue(s) Methods

In addition to the systematic review, a number of supplemental issues were extensively considered and reported within a 22-page supplemental issue section.

Issues included:

- additional harms information
- information on comparator medications (bevacizumab)
- validity of outcome measures employed in the reviewed trials
- mechanisms and consequences of anti-VEGF therapy
- combination of ranibizumab and verteporfin PDT: FOCUS study
- additional detailed data from included trials.

APPENDIX II: ADDITIONAL HARMS DATA

The international birth date for ranibizumab was June 30, 2006 (USA). The most recent Periodic Safety Update Report (PSUR) covers the period from Jan 1, 2007 to June 30, 2007.[18] As of this time, the product had been approved in 48 countries, and had just been approved in Canada (June 26, 2007). At this time, 6168 patients had received ranibizumab in clinical trials, and based on sales data, patient exposure was approximated at 150000 patient treatment-years.

During the reporting period of this PSUR, there were 6 reports of endophthalmitis, and one report each of eye infection, vitritis, and uveitis.

There were 21 spontaneous reports of CVAs provided by health care professionals as well as 6 spontaneous reports of CVAs provided by non-health care professionals, 3 solicited reports, and one literature report. There was also one ischemic stroke and one hemorrhagic stroke. The details of these events are provided in the following table, although only the reports that provide information are listed. Patients were generally elderly (>75 years of age) females, and most had previous cardiovascular history, including hypertension, hypercholesterolemia, diabetes mellitus, as well as various events such as MI and CVA. Many of the patients had their reported event after their first or second ranibizumab injection. Causality was most often either unreported or unknown, although there were 6 events where a causal link was suspected. It was not clear why a causal link was suspected in these cases, as some were in very elderly individuals (83, 87, and 87 years old) with previous cardiovascular history.

There were 8 reports of myocardial infarction during the period of this PSUR. Ages were reported in 7 cases, and the patients were all elderly (range 74-96 years of age). Of the 8 reports, 6 cases were reported to have a suspected causal link, although in one of these cases the reporter was a non-health care professional.

APPENDIX III: NATIONAL EYE INSTITUTE VISUAL FUNCTION QUESTIONNAIRE (NEI VFQ)

The NEI-VFQ measures vision-targeted quality of life. The original 51-item questionnaire was developed based on focus groups comprised of persons with a number of common eye conditions (e.g., age-related cataracts, age-related macular degeneration, and diabetic retinopathy).[19] It is comprised of 12 vision-specific, mostly multi-item, subscales related to: general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, color vision, expectations for future vision, and one general health subscale.[20] A shorter version of the original instrument, the VFQ-25, was subsequently developed, and is far more practical and efficient to administer.[21] With the exception of the expectations for future vision, all the constructs listed above were retained. Thus, the VFQ-25 includes 25 items relevant to 11 vision-related constructs in addition to a single item general health question.

Responses for each item are converted to a 0 to 100 scale, with 0 representing the worst, and 100 the best visual functioning. Both versions of the NEI-VFQ has been shown to be a valid and reliable in the assessment of health-related quality of life among patients with a wide range of eye conditions.[20,21] Determination of what constitutes a clinically meaningful change in the NEI-VFQ appears to be linked to its correlation with visual acuity. A 3-line change in visual acuity has been employed as the outcome of interest in clinical trials, and thus, corresponding changes in the NEI-VFQ are suggested as clinically meaningful endpoints; specifically a 10 point change in overall score and 12-13 points in the subscales (excluding color vision and ocular pain).[13,22]

REFERENCES

1. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984;102(11):1640-2.
2. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1432-44.
3. *Clinical study report addendum: CSR FVF2587g/CRFB002A2301: A phase III, multicenter, randomized, double-masked, active treatment-controlled study of the efficacy and safety of rhuFab V2 (ranibizumab) compared with verteporfin (Visudyne®) photodynamic therapy in subjects with predominantly classic subfoveal neovascular age-related macular degeneration* [**CONFIDENTIAL** additional manufacturer's information]. South San Francisco (CA): Genentech, Inc.; 2007 Mar 27.
4. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1419-31.
5. Kaiser PK, Blodi BA, Shapiro H, Acharya NR, MARINA Study Group. Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 2007;114(10):1868-75.
6. *Clinical study report addendum: CSR FVF2598g: A phase III, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of rhuFab V2 (ranibizumab) in subjects with minimally classic or occult subfoveal neovascular age-related macular degeneration* [**CONFIDENTIAL** additional manufacturer's information]. South San Francisco (CA): Genentech, Inc.; 2006 Mar 29.
7. *Clinical study report: CSR FVF3192g: A phase IIIb, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal choroidal neovascularization (CNV) with or without classic CNV secondary to age-related macular degeneration* [**CONFIDENTIAL** additional manufacturer's information]. South San Francisco (CA): Genentech, Inc.; 2006 Jul 14.
8. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: *Lucentis (ranibizumab) injection. Company: Genentech, Inc. Application no.: 125156. Approval date: 06/30/2006* [FDA approval package]. Rockville (MD): The Center; 2006. Available: http://www.fda.gov/cder/foi/nda/2006/125156s0000_LucentisTOC.htm (accessed 2008 May 22).
9. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: *Lucentis (ranibizumab) injection. Company: Genentech, Inc. Application no.: 125156. Approval date: 06/30/2006* [FDA approval package]. Rockville (MD): The Center; 2006. Available: http://www.fda.gov/cder/foi/nda/2006/125156s0000_LucentisTOC.htm (accessed 2008 May 22).
10. *Health Canada reviewer's report: Lucentis (ranibizumab)* [**CONFIDENTIAL** internal report]. Ottawa: Health Products and Food Branch, Health Canada; 2007 Jun 27.
11. *CDR submission binder: Lucentis (ranibizumab) 10 mg/mL solution for injection; Company: Novartis Pharmaceuticals Canada Inc.* [**CONFIDENTIAL** internal manufacturer's report]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2007 Jul.
12. *Clinical study report: CSR FVF2598g: A phase III, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of rhuFab V2 (ranibizumab) in subjects with minimally classic or occult subfoveal neovascular age-related macular degeneration* [**CONFIDENTIAL** additional manufacturer's information]. South San Francisco (CA): Genentech, Inc.; 2005 Oct 21.

13. Miskala PH, Hawkins BS, Mangione CM, Bass EB, Bressler NM, Dong LM, et al. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity: findings in patients with subfoveal choroidal neovascularization--SST report no. 1. *Arch Ophthalmol* 2003;121(4):531-9.

14. Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol* 2006;124(11):1532-42.

15. Barron H. *Dear health care provider letter [Lucentis]*. South San Francisco (CA): Genentech, Inc.; 2007 Jan 24. Available: http://www.fda.gov/medwatch/safety/2007/Lucentis_DHCP_01-24-2007.pdf (accessed 2008 May 22).

16. *Clinical study report: CSR FVF2587g/CRFB002A2301: A phase III, multicenter, randomized, double-masked, active treatment-controlled study of the efficacy and safety of rhuFab V2 (ranibizumab) compared with verteporfin (Visudyne®) photodynamic therapy in subjects with predominantly classic subfoveal neovascular age-related macular degeneration* [**CONFIDENTIAL** additional manufacturer's information]. South San Francisco (CA) / Basel, Switzerland: Genentech, Inc. / Novartis Pharma AG; 2005 Dec 26.

17. Czoski-Murray C, Carlton J, Brazier J, Kang HK, Young T, Papo NL. Appendix D - Valuing condition specific health states using simulation. In: *CDR submission binder, pharmacoeconomic report: Lucentis (ranibizumab) 10 mg/mL solution for injection; Company: Novartis Pharmaceuticals Canada Inc.* [**CONFIDENTIAL** internal manufacturer's report]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2007.

18. *Periodic safety update report 2 (PSUR 2) for Lucentis® (ranibizumab): 01 Jan 2007 - 30 Jun 2007* [**CONFIDENTIAL** internal manufacturer's report]. Basel, Switzerland: Novartis; 2007 Aug 15.

19. Mangione CM, Berry S, Spritzer K, Janz NK, Klein R, Owsley C, et al. Identifying the content area for the 51-item National Eye Institute Visual Function Questionnaire: results from focus groups with visually impaired persons. *Arch Ophthalmol* 1998;116(2):227-33.

20. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). *Arch Ophthalmol* 1998;116(11):1496-504.

21. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001;119(7):1050-8.

22. Slakter JS, Stur M. Quality of life in patients with age-related macular degeneration: impact of the condition and benefits of treatment. *Surv Ophthalmol* 2005;50(3):263-73.