CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
2Q17 April – May

BRAND NAME
Lucentis®

GENERIC NAME
ranibizumab

MANUFACTURER
Genentech, Inc.

DATE OF APPROVAL
June 30, 2006

PRODUCT LAUNCH DATE
July 13, 2006

REVIEW TYPE

☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

FDA APPROVED INDICATION(S)
Lucentis is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy in patients with DME
- Myopic Choroidal Neovascularization (mCNV)

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OFF-LABEL USES
Not applicable

CLINICAL EFFICACY[12]
Neovascular (Wet) Age-Related Macular Degeneration (AMD)
The safety and efficacy of Lucentis were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1,323 patients (Lucentis 879, control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2
In Study AMD-1, patients with minimally classic or occult (without classic) choroidal neovascularization (CNV) lesions received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with Lucentis in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly Lucentis 0.3 mg intravitreal injections and sham PDT; 2) monthly Lucentis 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham PDT (or active verteporfin PDT) was given with the initial Lucentis (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with Lucentis in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all Lucentis -treated patients (approximately 95%) maintained their visual acuity. Among Lucentis -treated patients, 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results.

Patients in the group treated with Lucentis had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3 disc areas (DA) for Lucentis versus 2.3-2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3-0.4 DA for Lucentis versus 2.9-3.1 DA for the control arms.

Study AMD-3
Study AMD-3 was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of Lucentis in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received Lucentis 0.3

mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (Lucentis 0.3 mg, 60; Lucentis 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with Lucentis in Study AMD-3 received a mean of 6 total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline. After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every 3 months with Lucentis lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all Lucentis -treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

Study AMD-4
Study AMD-4 was a randomized, double-masked, active treatment-controlled, two-year study designed to assess the safety and efficacy of Lucentis 0.5 mg administered monthly or less frequently than monthly in patients with neovascular AMD. Patients randomized to the Lucentis 0.5 mg less frequent dosing arm received 3 monthly doses followed by monthly assessments where patients were eligible to receive Lucentis injections guided by pre-specified re-treatment criteria. A total of 550 patients were enrolled in the two 0.5 mg treatment groups with 467 (85%) completing through Month 24. Data are available through Month 24. Clinical results at Month 24 remain similar to that observed at Month 12.

From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm. Over this 21 month period, patients in the 0.5 mg less frequent dosing and the 0.5 mg monthly arms averaged 10.3 and 18.5 injections, respectively.

<u>Macular Edema Following Retinal Vein Occlusion (RVO)</u>
The safety and efficacy of Lucentis were assessed in two randomized, double-masked, 1-year studies in patients with macular edema following retinal vein occlusion (RVO). Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (Lucentis 0.3 mg, 266 patients; Lucentis 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were eligible to receive Lucentis injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 6-month treatment period. Macular focal/grid laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg Lucentis and 71 of 132 (54%) patients treated with sham. The primary endpoint studied was mean change from baseline in BVCA score at 6 months.

The results of RVO-1 showed that patients who received Lucentis showed a significant improvement in the mean change in VA from baseline at Months 6 (primary endpoint) and 12 compared with sham ($p<0.01$ and $p<0.0001$, respectively). At Month 6, patients in the Lucentis 0.5 mg group gained a mean of 18.3 letters compared with a mean gain of 7.3 letters in the sham group. At Month 12, the Lucentis 0.5 mg group maintained this gain. At Month 6, 61.1% of patients in the Lucentis 0.5 mg group had experienced a clinical improvement in VA (gained ≥15 letters from baseline) compared with 28.8% of patients in the sham group. At Month 12, the Lucentis 0.5 mg group maintained clinical improvement, with 60.3% having a gain in VA (gained ≥15 letters from baseline). Fewer patients who were treated with Lucentis 0.5 mg required rescue laser therapy at Months 6 and 12 (19.8% and 34.4%, respectively) compared with the sham-treated patients (54.5% and 61.4%, respectively). The improvements in BCVA at Month 6 were maintained through Month 12 with the initiation of as-needed (PRN) Lucentis treatment from Month 6 through Month 12. Patients who switched from the sham treatment group to PRN Lucentis during Months 6 through 12 gained a cumulative 12.1 letters; however, patients who switched treatment gained fewer letters than those who received Lucentis throughout the entire study period.

Study RVO-2 evaluated the efficacy and safety of Lucentis in patients with macular edema following central RVO (CRVO). Patients received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

The results of RVO-2 showed that patients who received Lucentis showed significant improvement in the mean change in VA from baseline at Month 6 (primary endpoint) compared with sham ($p<0.01$). At Month 6, patients in the Lucentis 0.5 mg group gained a mean of 14.9 letters compared with a mean 0.8 letter gain in the sham treatment group. At Month 6, 47.7% of patients in the Lucentis 0.5 mg group experienced a clinically significant improvement in vision (gained ≥15 letters from baseline) compared with 16.9% of patients in the sham treatment group. The improvements in BCVA at Month 6 were maintained through Month 12 with the initiation of PRN Lucentis treatment from Month 6 through Month 12. Patients who switched from the sham treatment group to PRN Lucentis during Months 6 through 12 gained fewer letters than those who received Lucentis throughout the entire study period.

Additional analyses of patients from the RVO-1 and RVO-2 studies showed that patients who were treated with Lucentis had greater improvements in vision-related patient-reported outcomes than did sham-treated patients. Lucentis-treated patients had improvements in the near and distance activities subscale scores of the NEI VFQ-25 at 6 months and maintained this improvement through Month 12. Near activities evaluated by the NEI VFQ-25 included items such as reading or seeing up close, whereas distance activities included tasks such as seeing movies, television, or sporting events and reading road signs. An analysis of reading speed in the RVO-1 and RVO-2 studies also demonstrated that Lucentis-treated patients experienced significantly greater improvements from baseline to Month 6 than did sham-treated patients.

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Diabetic Macular Edema (DME) & Diabetic Retinopathy in Patients with Diabetic Macular Edema (DME)

Efficacy and safety data of Lucentis for diabetic macular edema (DME) diabetic retinopathy (DR) in patients with DME are derived from studies D-1 and D-2. Studies D-1 and D-2 were two identically designed, Phase III, 36-month, randomized, multicenter, double-masked, sham-controlled, parallel-group clinical trials. These studies included 759 patients with DME who were randomized to Lucentis 0.3 mg, Lucentis 0.5 mg, or sham injections monthly in one eye for 24 months. After Month 24, patients from the sham-control group could cross over and receive Lucentis 0.5 mg monthly based on prespecified criteria, while Lucentis-treated patients continued with monthly dosing of their assigned dose. All patients were followed for an additional 12 months (36 months total). The primary endpoint studied in studies D-1 and D-2 was the percentage of patients with gains of ≥15 letters of BCVA at Month 24. All enrolled patients had DR and DME at baseline.

Of the 759 patients enrolled, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study (ETDRS) Retinopathy Severity Scores (ETDRS-RSS) ranging from 10 to 75. At baseline, 62% of patients had non-proliferative diabetic retinopathy (NPDR) (ETDRS-RSS less than 60) and 31% had PDR (ETDRS-RSS greater than or equal to 60). The ETDRS-RSS could not be graded in 5% of patients at baseline, and 2% of patients had absent or questionable DR at baseline. Approximately 20% of the overall population had prior PRP.

The results from these two individual studies were consistent with each other, with the benefits of Lucentis relative to sham-control treatment confirmed in both studies. The studies met the primary endpoint, where a significantly greater proportion of patients who received Lucentis were able to read ≥15 more letters (3 lines) on the eye chart at Month 24 compared to baseline. Benefits were sustained at Month 36. At Month 24, DR improvement by ≥3-steps in ETDRS-RSS from baseline in subgroups examined (e.g., age, gender, race, baseline visual acuity, baseline HbA1c, prior DME therapy at baseline, baseline DR severity (NPDR, PDR)) were generally consistent with the results in the overall population.

Compared to monthly Lucentis 0.3 mg, no additional benefit was observed with monthly treatment with Lucentis 0.5 mg.

The difference in the proportion of patients treated with Lucentis 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-RSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.

Myopic Choroidal Neovascularization (mCNV)

The efficacy and safety data of Lucentis were assessed in a randomized, double-masked, active-controlled 12- month study in patients with mCNV. Patients were randomized 2:2:1 to 1 of the 3

treatment groups: Lucentis 0.5 mg Group 1 (n=106), Lucentis 0.5 mg Group 2 (n=116), or vPDT (n=55). The study had an active control (vPDT) through Month 3. Patients' age ranged from 18 to 87 years, with a mean age of 55 years. A total of 276 patients (222 patients in the Lucentis treated Groups I and II; 55 patients in the active control verteporfin photodynamic therapy (vPDT) group) were enrolled.

Patients randomized to the Lucentis groups received injections guided by pre-specified re-treatment criteria. The retreatment criteria in Group I were vision stability guided, with the BCVA at the current visit being assessed for changes compared with the two preceding monthly BCVA values. The retreatment criteria in Group II were disease activity guided, based on BCVA decrease from the previous visit that was attributable to intra- or sub-retinal fluid or active leakage secondary to mCNV as assessed by OCT and/or FA compared to the previous monthly visit.

The primary endpoint was the mean average change in BCVA from baseline to Month 1 through Month 3. Secondary endpoints were the mean change in BCVA from baseline to Month 1 through Month 6, the mean change in BCVA from baseline over time, the proportion of patients with ≥10 and ≥15 letters ETDRS letters gained (or reaching 84 letters) at Month 12, the proportion of patients with ≥10 and ≥15 letters lost at Month 12. Additionally, the mean change in CRT from baseline over time was measured by OCT on anatomical outcomes. Safety endpoints included incidence of ocular and non-ocular AEs over the 12-month study period.

The results showed that visual gains for the two Lucentis 0.5 mg treatment arms were superior to the active control arm. The mean change in BCVA from baseline at Month 3 was: +12.1 letters for Group I, +12.5 letters for Group II and +1.4 letters for the vPDT group. Efficacy was comparable between Group I and Group II.

The proportion of patients who gained ≥15 letters (ETDRS) by Month 3 was 37.1% and 40.5% for Lucentis Groups I and II, respectively and 14.5% for the vPDT group. The mean number of injections between baseline and Month 3 was 2.5 and 1.8 for Groups I and II, respectively. Forty-one percent of patients received 1, 2 or 3 injections between baseline and Month 3 with no injections afterwards.

CONTRAINDICATIONS
Lucentis is contraindicated in patients with ocular or periocular infections.

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
Not applicable

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ADVERSE REACTIONS
The most common adverse reactions (reported more frequently in Lucentis-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, and increased IOP.

More serious adverse reactions include:
- Endophthalmitis and rhegmatogenous retinal detachment (<0.1%)
- Iatrogenic traumatic cataract (<0.1%)
- Thromboembolic events (7.2%)
- Fatal events in patients with DME and DR at baseline (4.4%)

DOSAGE AND ADMINISTRATION
Neovascular (Wet) Age-Related Macular Degeneration (AMD)
Lucentis 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).
- Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment.
- Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly.

Macular Edema Following Retinal Vein Occlusion (RVO)
Lucentis 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema
Lucentis 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Myopic Choroidal Neovascularization (mCNV)
Lucentis 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months.
- Patients may be retreated if needed.

PRODUCT AVAILABILITY
Single-use prefilled syringe: 0.05 mL of 10mg/mL solution
Single-use glass vial: 0.05 mL of either 10mg/mL or 6mg/mL solution

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN	COMMENTS

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	(route of admin/frequency of use)	
bevacizumab (Avastin)	AMD: 1.25 to 2.5 mg administered by intravitreal injection every 4 weeks	
	Neovascular glaucoma: 1.25 mg administered by intravitreal injection every 4 weeks	
	ME secondary to RVO: 1 mg to 2.5 mg administered by intravitreal injection every 4 weeks	
	Proliferative DR: 1.25 mg administered by intravitreal injection 5 to 20 days before vitrectomy	
	DME: 1.25 mg administered by intravitreal injection	
verteporfin (Visudyne)	AMD or mCNV: 6 mg/m^2 of body surface area intravenously, followed by activation of verteporfin with a nonthermal diode laser; may repeat at 3-month intervals	
aflibercept (Eylea)	AMD: 2 mg (0.05 mL) via intravitreal injection once every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks	
	ME following RVO: 2 mg (0.05 mL) via intravitreal injection once every 4 weeks	
	DME or DR in patients with DME: 2 mg (0.05 mL) via intravitreal injection once every 4 weeks for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks	
pegaptanib (Macugen)	AMD:	

	0.3 mg (0.9 mL) via intravitreal injection every 6 weeks	

Boldface indicates generic availability

Utilization Management Recommendation
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): (1) To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes. (2) Lucentis is currently being evaluated in clinical trials for many uses, including retinoblastoma, telangiectasia, polypoidal choroidal vasculopathy, port wine stain birthmark, and pigment epithelial detachment. ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
• It would not be clinically appropriate to require a trial of Avastin prior to initiation of Lucentis for mCNV.

REFERENCES

[1] Lucentis Prescribing Information. South San Francisco, CA: Genentech, Inc.; January 2017. Available at www.lucentis.com. Accessed January 31, 2017.
[2] Lucentis Formulary Dossier. In: AMCP eDossier System [internet database]. Updated periodically. Accessed January 31 2017.