HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)
Intravitreal Injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------
- Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.2), 6/2010
- Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2.3), 6/2010
- Warnings and Precautions, Thromboembolic Events (5.3), 6/2010

----------INDICATIONS AND USAGE----------
LUCENTIS is indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)

----------DOSAGE AND ADMINISTRATION----------
FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2.1)

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) (2.2).
- Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly (2.2).

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). In the RVO clinical studies, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly (2.3).

----------DOSAGE FORMS AND STRENGTHS----------
- 10 mg/mL solution in a single-use vial for intravitreal injection (3)

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored during the week following the injection (5.1).
- Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection (5.2).

----------ADVERSE REACTIONS----------
- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure, and intraocular inflammation (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 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 less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly [*see Clinical Studies (14.2)*].

2.3 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).

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly [*see Clinical Studies (14.2)*].

2.4 Preparation for Administration

Using aseptic technique, all (0.2 mL) of the LUCENTIS vial contents are withdrawn through a 5-micron, 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

2.5 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before LUCENTIS is administered to the other eye.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use glass vial designed to provide 0.05 mL of 10 mg/mL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored during the week following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.4, 2.5) and Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection with LUCENTIS. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.5)*].

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration

The ATE rate in the three controlled neovascular AMD studies during the first year was 1.9% (17 out of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 out of 441) in patients from the control arms [*see Clinical Studies (14.1)*]. In the second year of studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 out of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 out of 344) in patients from the control arms.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2 and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 out of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 out of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion

The ATE rate in the two controlled RVO studies during the first six months was 0.8% in both the LUCENTIS and control arms of the studies (4 out of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 out of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 out of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 out of 260) in the control arms.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis [*see Warnings*

and Precautions (5.1)], rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts.

6.2 Clinical Studies Experience

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in three double-masked, controlled studies (AMD-1, AMD-2, and AMD-3) [*see Clinical Studies (14.1)*] as well as exposure to 0.5 mg LUCENTIS in 259 patients with macular edema following RVO in two double-masked, controlled studies (RVO-1 and RVO-2) [*see Clinical Studies (14.2)*].

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS treated patients compared with the control group.

Table 1
Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS n=379	Control n=379	LUCENTIS n=440	Control N=441	LUCENTIS n=259	Control n=260
Conjunctival hemorrhage	74%	60%	64%	50%	48%	37%
Eye pain	35%	30%	26%	20%	17%	12%
Vitreous floaters	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	24%	7%	17%	5%	7%	2%
Vitreous detachment	21%	19%	15%	15%	4%	2%
Intraocular inflammation	18%	8%	13%	7%	1%	3%
Cataract	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	16%	14%	13%	10%	7%	5%
Eye irritation	15%	15%	13%	12%	7%	6%
Lacrimation increased	14%	12%	8%	8%	2%	3%
Blepharitis	12%	8%	8%	5%	0%	1%
Dry eye	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	18%	15%	13%	10%	5%	3%
Eye pruritis	12%	11%	9%	7%	1%	2%
Ocular hyperemia	11%	8%	7%	4%	5%	3%
Retinal disorder	10%	7%	8%	4%	2%	1%
Maculopathy	9%	9%	6%	6%	11%	7%
Retinal degeneration	8%	6%	5%	3%	1%	0%
Ocular discomfort	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Table 2 shows frequently reported non-ocular adverse reactions in LUCENTIS treated patients compared with the control group.

Table 2
Non-Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS n=379	Control n=379	LUCENTIS n=440	Control n=441	LUCENTIS n=259	Control n=260
Nasopharyngitis	16%	13%	8%	9%	5%	4%
Headache	12%	9%	6%	5%	3%	3%
Arthralgia	11%	9%	5%	5%	2%	1%
Bronchitis	11%	9%	6%	5%	0%	2%
Urinary tract infection	9%	9%	5%	5%	1%	2%
Cough	9%	8%	5%	4%	2%	2%
Nausea	9%	6%	5%	5%	1%	2%
Upper respiratory tract infection	9%	8%	5%	5%	2%	2%
Sinusitis	8%	7%	5%	5%	3%	2%
Anemia	8%	7%	4%	3%	1%	1%
Influenza	7%	5%	3%	2%	3%	2%
Chronic obstructive pulmonary disease	6%	3%	1%	0%	0%	0%
Hypercholesterolemia	5%	5%	3%	2%	1%	1%
Insomnia	5%	5%	3%	2%	1%	1%
Pain in extremity	5%	6%	3%	2%	1%	1%
Atrial fibrillation	5%	4%	2%	2%	1%	0%
Anxiety	4%	4%	3%	2%	1%	2%
Dyspnea	4%	3%	2%	2%	0%	0%
Gastroenteritis viral	4%	1%	3%	1%	1%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%–5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-8% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in the RVO patients with the highest levels of immunoreactivity.

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (±2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ranibizumab. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LUCENTIS should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ranibizumab is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients has not been established.

8.5 Geriatric Use

In the clinical studies, approximately 82% (1146/1406) of the patients randomized to treatment with LUCENTIS were ≥65 years of age and approximately 55% (772/1406) were ≥75 years of age. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure in population pharmacokinetic analyses after correcting for creatinine clearance.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with renal impairment. In population pharmacokinetic analyses of patients, 54% (389/725) had renal impairment (39% mild, 12% moderate, and 2% severe). The reduction in ranibizumab clearance in patients with renal impairment is considered clinically insignificant. Dose adjustment is not expected to be needed for patients with renal impairment.

8.7 Patients with Hepatic Dysfunction

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with hepatic impairment. Dose adjustment is not expected to be needed for patients with hepatic dysfunction.

10 OVERDOSAGE

Planned initial single doses of ranibizumab injection 1 mg were associated with clinically significant intraocular inflammation in 2 of 2 neovascular AMD patients injected. With an escalating regimen of doses beginning with initial doses of ranibizumab injection 0.3 mg, doses as high as 2 mg were tolerated in 15 of 20 neovascular AMD patients.

11 DESCRIPTION

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

LUCENTIS is a sterile, colorless to pale yellow solution in a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL LUCENTIS aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the progression of neovascular AMD and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics

Increased center point thickness (CPT) as assessed by optical coherence tomography (OCT) is associated with neovascular AMD and macular edema following RVO. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography is associated with neovascular AMD.

Neovascular (Wet) Age-Related Macular Degeneration

In Study AMD-3, CPT was assessed by OCT in 118/184 patients. OCT measurements were collected at baseline, Months 1, 2, 3, 5, 8, and 12. In patients treated with LUCENTIS, CPT decreased, on average, more than the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of vascular leakage, on average, decreased by Month 3 as assessed by fluorescein angiography. The area of vascular leakage for an individual patient was not correlated with visual acuity.

Macular Edema Following Retinal Vein Occlusion

On average, CPT reductions were observed in Studies RVO-1 and RVO-2 beginning at Day 7 following the first LUCENTIS injection through Month 6. CPT was not evaluated as a means to guide treatment decisions [*see Clinical Studies (14.2)*].

12.3 Pharmacokinetics

In animal studies, following intravitreal injection, ranibizumab was cleared from the vitreous with a half-life of approximately 3 days. After reaching a maximum at approximately 1 day, the serum concentration of ranibizumab declined in parallel with the vitreous concentration. In these animal studies, systemic exposure of ranibizumab is more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration, maximum ranibizumab serum concentrations were low (0.3 ng/mL to 2.36 ng/mL). These levels were below the concentration of ranibizumab (11 ng/mL to 27 ng/mL) thought to be necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 1 mg/eye. Serum ranibizumab concentrations in RVO patients were similar to those observed in neovascular AMD patients.

Based on a neovascular AMD population pharmacokinetic analysis, maximum serum concentrations of 1.5 ng/mL are predicted to be reached at approximately 1 day after monthly intravitreal administration of LUCENTIS 0.5 mg/eye. Based on the disappearance of ranibizumab from serum, the estimated average vitreous elimination half-life was approximately 9 days. Steady-state minimum concentration is predicted to be 0.22 ng/mL with a monthly dosing regimen. In humans, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity data are available for ranibizumab injection in animals or humans.

No studies on the effects of ranibizumab on fertility have been conducted.

14 CLINICAL STUDIES

14.1 *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 1323 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) 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. 34%–40% of LUCENTIS-treated patients 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. Detailed results are shown in the Table 3, Table 4, and Figure 1 below.

Table 3

Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n=238	LUCENTIS 0.5 mg n=240	Estimated Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	12	62%	95%	32% (26%, 39%)
	24	53%	90%	37% (29%, 44%)
Gain of ≥ 15 letters in visual acuity (%)[b]	12	5%	34%	29% (22%, 35%)
	24	4%	33%	29% (23%, 35%)
Mean change in visual acuity (letters) (SD)[b]	12	−10.5 (16.6)	+7.2 (14.4)	17.5 (14.8, 20.2)
	24	−14.9 (18.7)	+6.6 (16.5)	21.1 (18.1, 24.2)

[a] Adjusted estimate based on the stratified model.
[b] $p < 0.01$.

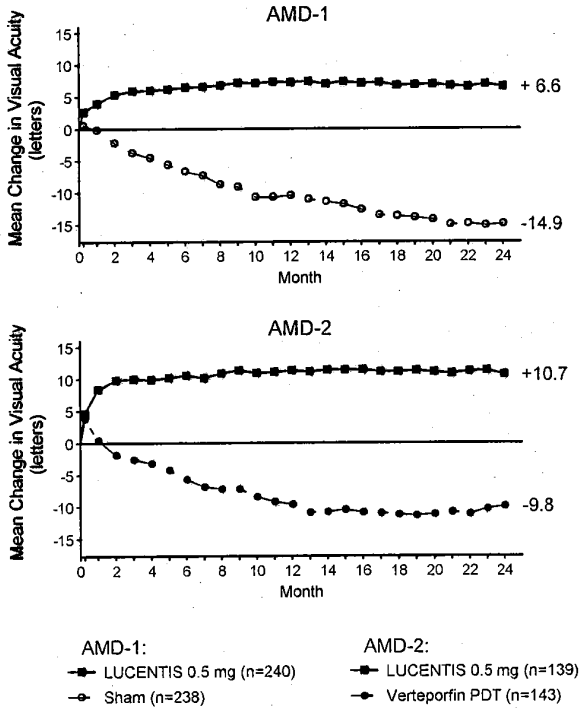
Table 4

Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n=143	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	12	64%	96%	33% (25%, 41%)
	24	66%	90%	25% (16%, 34%)
Gain of ≥ 15 letters in visual acuity (%)[b]	12	6%	40%	35% (26%, 44%)
	24	6%	41%	35% (26%, 44%)
Mean change in visual acuity (letters) (SD)[b]	12	−9.5 (16.4)	+11.3 (14.6)	21.1 (17.5, 24.6)
	24	−9.8 (17.6)	+10.7 (16.5)	20.7 (16.8, 24.7)

[7] [a] Adjusted estimate based on the stratified model.
[b] $p < 0.01$.

Figure 1
Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-1 and Study AMD-2

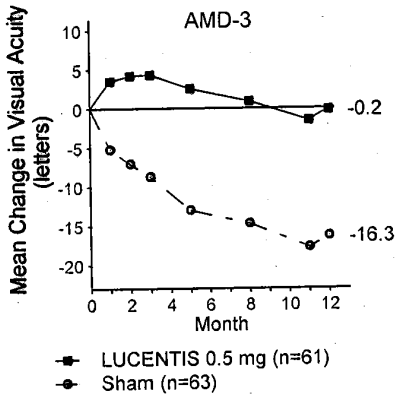


Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1–0.3 DA for LUCENTIS versus 2.3–2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3–0.4 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 (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with LUCENTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) maintained their visual acuity at Month 12.

Figure 2
Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)
The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, one-year studies in patients with macular edema following 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 rescue laser treatment beginning at Month 3 of the 6 month treatment period. Rescue laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 72 of 132 (55%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

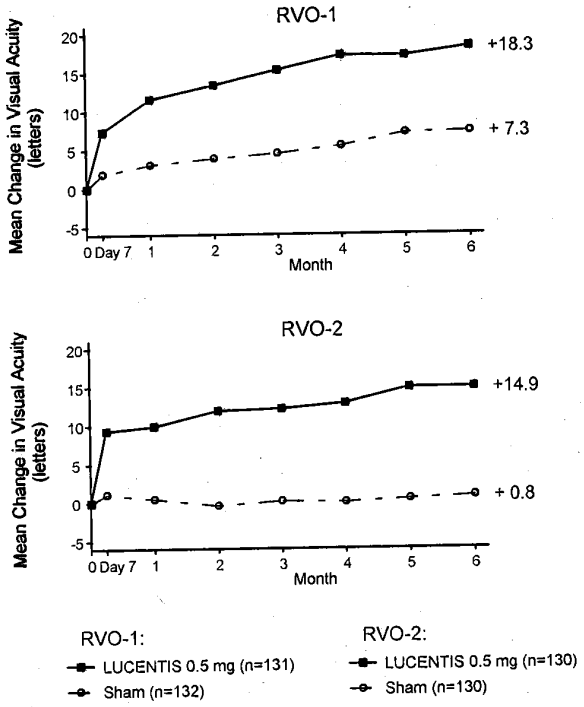
At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

Table 5
Percentage of Patients with Gain of ≥15 letters in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2

Study	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI)
RVO-1	29%	61%	31%[a] (20%, 43%)
RVO-2	17%	48%	30%[a] (20%, 41%)

[a] $p < 0.01$, adjusted estimate based on stratified model

Figure 3
Mean Change in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2



$p < 0.01$ for all time points

16 HOW SUPPLIED/STORAGE AND HANDLING
Each LUCENTIS carton, NDC 50242-080-01, contains a 0.2 mL fill of 10 mg/mL ranibizumab in a 2-cc glass vial; one 5-micron, 19-gauge × 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge × 1/2-inch injection needle for the intravitreal injection; and one package insert [*see Dosage and Administration (2.5)*]. VIALS ARE FOR SINGLE EYE USE ONLY.

LUCENTIS should be refrigerated at 2°–8°C (36°–46°F). DO NOT FREEZE. Do not use beyond the date stamped on the label. LUCENTIS

vials should be protected from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

LUCENTIS® [ranibizumab injection]
Manufactured by:
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A Member of the Roche Group
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