

sBLA 125156/S-069  
sBLA 125156/S-076  
Page 6

## 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<sup>®</sup> (ranibizumab injection)**  
**Intravitreal Injection**  
**Initial U.S. Approval: 2006**

### RECENT MAJOR CHANGES

- Indications and Usage, Diabetic Macular Edema (DME) (1.3) 08/2012
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 08/2012
- Dosage and Administration, Administration (2.6) 08/2012
- Warnings and Precautions, Endophthalmitis and Retinal Detachments (5.1) 08/2012
- Warnings and Precautions, Increases in Intraocular Pressure (5.2) 08/2012
- Warnings and Precautions, Thromboembolic Events (5.3) 08/2012
- Warnings and Precautions, Fatal Events in DME Patients (5.4) 08/2012

### 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)
- Diabetic Macular Edema (DME) (1.3)

### DOSAGE AND ADMINISTRATION

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2.1)

#### Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)

- 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 3 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.

#### Macular Edema Following Retinal Vein Occlusion (RVO) (2.3)

- 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 6 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.

#### Diabetic Macular Edema (DME) (2.4)

- LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

### DOSAGE FORMS AND STRENGTHS

Single-use glass vial designed to provide 0.05 mL for intravitreal injections:

- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
- 6 mg/mL solution (LUCENTIS 0.3 mg) (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 following the injection (5.1).
- Increases in intraocular pressure (IOP) have been noted both pre- and post-intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors (5.3).
- Fatal events occurred more frequently in DME patients treated monthly with LUCENTIS compared with control (5.4).

### 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 (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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2012

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)

### 2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
- 2.4 Diabetic Macular Edema (DME)
- 2.5 Preparation for Administration
- 2.6 Administration

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

- 4.1 Ocular or Periocular Infections
- 4.2 Hypersensitivity

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Endophthalmitis and Retinal Detachments
- 5.2 Increases in Intraocular Pressure
- 5.3 Thromboembolic Events
- 5.4 Fatal Events in DME Patients

### 6 ADVERSE REACTIONS

- 6.1 Injection Procedure
- 6.2 Clinical Studies Experience

- 6.3 Immunogenicity
- 6.4 Postmarketing Experience

### 7 DRUG INTERACTIONS

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

### 14 CLINICAL STUDIES

- 14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 14.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 14.3 Diabetic Macular Edema (DME)

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the Full Prescribing Information are not listed

sBLA 125156/S-069

sBLA 125156/S-076

Page 7

## 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)

#### 1.3 Diabetic Macular Edema (DME)

### 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 of 10 mg/mL LUCENTIS solution) 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 3 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 (14.1)*].

#### 2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) 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 6 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 Diabetic Macular Edema (DME)

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

#### 2.5 Preparation for Administration

Using aseptic technique, all 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 x 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.

#### 2.6 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.

Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion

of the optic nerve head immediately after the injection [see *Warnings and Precautions (5.2)*]. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection [see *Warnings and Precautions (5.1)*].

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 for intravitreal injection.

- 10 mg/mL solution (LUCENTIS 0.5 mg)
- 6 mg/mL solution (LUCENTIS 0.3 mg)

### 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 following the injection to permit early treatment should an infection occur [see *Dosage and Administration (2.5, 2.6)* and *Patient Counseling Information (17)*].

#### 5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately [see *Dosage and Administration (2.6)*].

#### 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 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 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 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 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 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 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 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) [see *Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

**Diabetic Macular Edema**

In a pooled analysis of Studies DME-1 and DME-2 [see *Clinical Studies (14.3)*], the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

**5.4 Fatal Events in DME Patients**

A pooled analysis of Studies DME-1 and DME-2 [see *Clinical Studies (14.3)*] showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

**6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the label:

- Endophthalmitis and Retinal Detachments
- Increases in Intraocular Pressure
- Thromboembolic Events
- Fatal Events in DME Patients

**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 detachment, and iatrogenic traumatic cataract.

**6.2 Clinical Studies Experience**

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.

**Ocular Reactions**

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

**Table 1**  
Ocular Reactions in the DME, AMD, and RVO Studies

Adverse Reaction	DME 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

**Non-Ocular Reactions**

Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DME, AMD, and/or RVO and which

sBLA 125156/S-069  
sBLA 125156/S-076  
Page 9

occurred at a  $\geq 1\%$  higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

**Table 2**  
Non-Ocular Reactions in the DME, AMD and RVO Studies

Adverse Reaction	DME 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg n=25 0	Control n=25 0	LUCENTIS 0.5 mg n=37 9	Control n=37 9	LUCENTIS 0.5 mg n=44 0	Control n=44 1	LUCENTIS 0.5 mg n=25 9	Control n=26 0
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	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 DME or RVO patients with the highest levels of immunoreactivity.

### 6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LUCENTIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

## 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 ( $\pm 2$  days) after verteporfin PDT.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. There are no studies of LUCENTIS in pregnant women. In a study of placental and embryo-fetal development in pregnant cynomolgus monkeys, skeletal abnormalities were seen in fetuses at the highest dose tested of 1 mg/eye which resulted in trough exposures up to 13 times higher than predicted  $C_{max}$  levels with single eye treatment in humans [see *Nonclinical Toxicology* (13.2)]. Skeletal abnormalities were not seen in monkeys at 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. Animal reproduction studies are not always predictive of human response. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab [see *Clinical Pharmacology* (12.1)], treatment with LUCENTIS may pose a risk to embryo-fetal development (including teratogenicity) and reproductive 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 have not been established.

sBLA 125156/S-069

sBLA 125156/S-076

Page 10

### 8.5 Geriatric Use

In the clinical studies, approximately 72% (1366 of 1908) of patients randomized to treatment with LUCENTIS were  $\geq 65$  years of age and approximately 43% (822 of 1908) were  $\geq 75$  years of age [see *Clinical Studies (14)*]. 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.

### 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<sup>®</sup> (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, which lacks an Fc region, 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 (0.5 mg dose vial) or 6 mg/mL LUCENTIS (0.3 mg dose vial) aqueous solution with 10 mM histidine HCl, 10%  $\alpha$ , $\alpha$ -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<sub>110</sub>. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and DME. 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, macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD.

#### *Neovascular (Wet) Age-Related Macular Degeneration*

In Study AMD-3, CPT was assessed by OCT in 118 of 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 in 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 FA. 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)*].

#### *Diabetic Macular Edema*

On average, CPT reductions were observed in Studies DME-1 and DME-2 beginning at Day 7 following the first LUCENTIS injection through Month 36. CPT data did not provide information useful in influencing treatment decisions [see *Clinical Studies (14.3)*].

### 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 was 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 and DME patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, 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.

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

### 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. Although systemic exposure following ocular administration is expected to be low, effects on female fertility are possible due to the anti-VEGF mechanism of action for ranibizumab [see *Clinical Pharmacology (12.1)*].

sBLA 125156/S-069  
sBLA 125156/S-076  
Page 11

### 13.2 Animal Toxicology and/or Pharmacology

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted  $C_{max}$  levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

### 14 CLINICAL STUDIES

Unless otherwise noted, visual acuity was measured at a distance of 4 meters.

#### 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. 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. Detailed results are shown in Table 3, Table 4, and Figure 1 below.

**Table 3**

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

Outcome Measure	Month	Sham n=229	LUCENTIS 0.5 mg n=230	Estimated Difference (95% CI) <sup>a</sup>
Loss of <15 letters in visual acuity (%)	12	60%	91%	30% (23%, 37%)
	24	56%	89%	33% (26%, 41%)
Gain of ≥15 letters in visual acuity (%)	12	6%	31%	25% (18%, 31%)
	24	4%	30%	25% (18%, 31%)
Mean change in visual acuity (letters) (SD)	12	-11.0 (17.9)	+6.3 ( 14.1)	17.1 (14.2, 20.0)
	24	-15.0 (19.7)	+5.5 ( 15.9)	20.1 (16.9, 23.4)

<sup>a</sup> Adjusted estimate based on the stratified model;  $p < 0.01$

**Table 4**

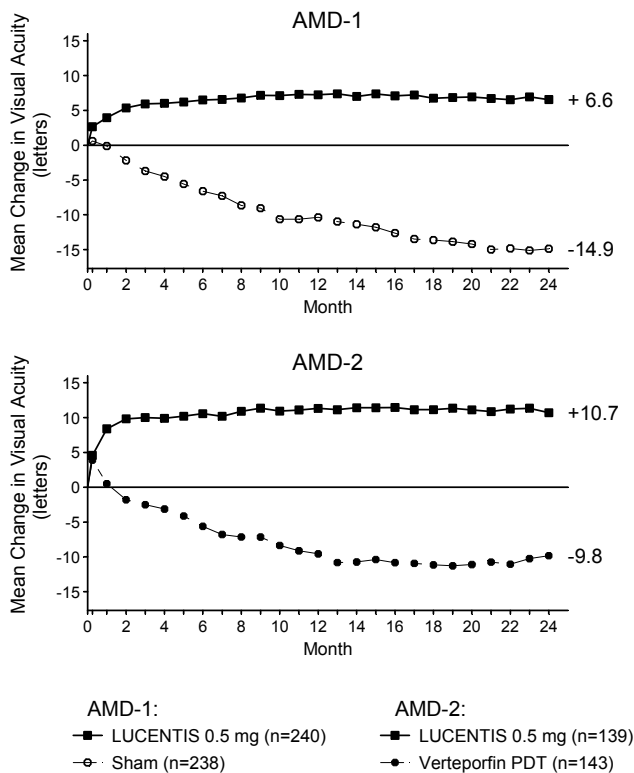
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfi n PDT n=141	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI) <sup>a</sup>
Loss of <15 letters in visual acuity (%)	12	66%	98%	32% (24%, 40%)
	24	65%	93%	28% (19%, 37%)
Gain of ≥15 letters in visual acuity (%)	12	11%	37%	26% (17%, 36%)
	24	9%	37%	29% (20%, 39%)
Mean change in visual acuity (letters) (SD)	12	-8.5 (17.8)	+11.0 (15.8)	19.8 (15.9, 23.7)
	24	-9.1 (18.7)	+10.9 (17.3)	20 (16.0, 24.4)

<sup>a</sup> Adjusted estimate based on the stratified model;  $p < 0.01$

sBLA 125156/S-069  
sBLA 125156/S-076  
Page 12

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



Visual acuity was measured at a distance of 2 meters

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.

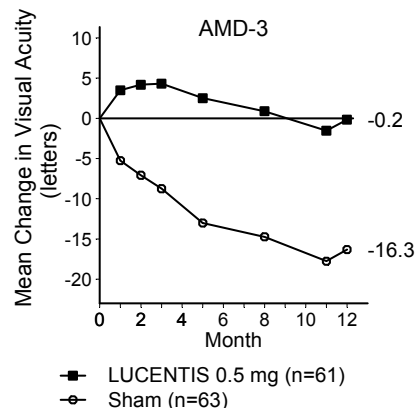
**Study AMD-3**

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 (see Figure 2). 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%) 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, 1-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 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.

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:

sBLA 125156/S-069  
sBLA 125156/S-076  
Page 13

**Table 5**

Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

Outcome Measure	Study <sup>a</sup>	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI) <sup>b</sup>
Gain of ≥15 letters in visual acuity (%)	RVO-1	29%	61%	31% (20%, 43%)
Gain of ≥15 letters in visual acuity (%)	RVO-2	17%	48%	30% (20%, 41%)

<sup>a</sup> RVO-1: Sham, n=131; LUCENTIS 0.5 mg, n=132

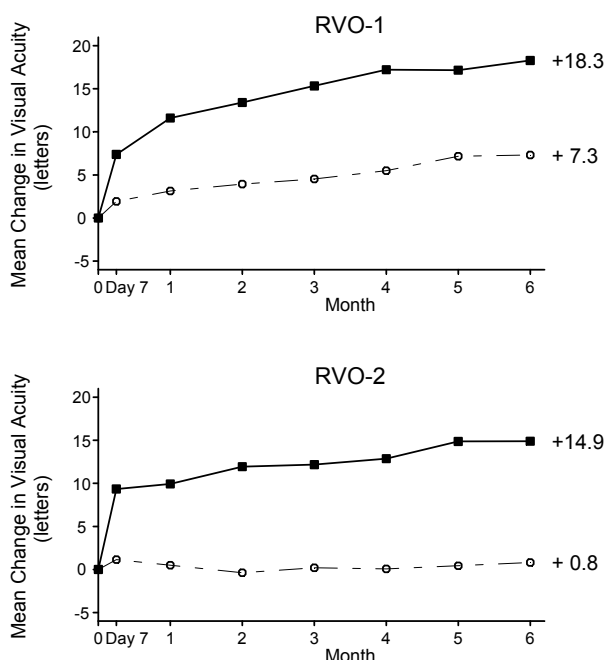
RVO-2: Sham, n=130; LUCENTIS 0.5 mg, n=130

<sup>b</sup> Adjusted estimate based on stratified model; p < 0.01

In Studies DME-1 and DME-2, patients received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly LUCENTIS 0.5 mg and patients originally randomized to monthly LUCENTIS 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with LUCENTIS 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with LUCENTIS 0.3 mg and 30 of 257 (12%) patients treated with sham.

Compared to monthly LUCENTIS 0.3 mg, no additional benefit was observed with monthly treatment with LUCENTIS 0.5 mg. At Month 24, after monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed:

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



RVO-1: LUCENTIS 0.5 mg (n=131) Sham (n=132)  
RVO-2: LUCENTIS 0.5 mg (n=130) Sham (n=130)  
p < 0.01 for all time points

**Table 6**

Visual Acuity Outcomes at Month 24 in Study DME-1 and Study DME-2

Outcome Measure	Study <sup>a</sup>	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI) <sup>b</sup>
Gain of ≥15 letters in visual acuity (%)	DME-1	12%	34%	21% (11%, 30%)
	DME-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	DME-1	92%	98%	7% (2%, 13%)
	DME-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	DME-1	2.3	10.9	8.5 (5.4, 11.5)
	DME-2	2.6	12.5	9.6 (6.1, 13.0)

<sup>a</sup> DME-1: Sham, n=130; LUCENTIS 0.3 mg, n=125

DME-2: Sham, n=127; LUCENTIS 0.3 mg, n=125

<sup>b</sup> Adjusted estimate based on stratified model; p ≤ 0.01

### 14.3 Diabetic Macular Edema (DME)

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 3-year studies in patients with DME. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (LUCENTIS 0.3 mg, 250 patients; LUCENTIS 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.



