Diabetic macular edema (DME) can be confusing. We are focused on helping you understand DME and how LUCENTIS may be able to help. LUCENTIS is a prescription medication indicated for the treatment of patients with DME.
Diabetic macular edema (DME) is directly linked to diabetes. DME is a progressive disease and, if left untreated, may result in vision loss.

This brochure will walk through what DME is, how LUCENTIS may help, and what you can do to help maintain or improve your vision.

Talk to your Retina Specialist to see if LUCENTIS is right for you

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.

Who is LUCENTIS for?

LUCENTIS® (ranibizumab injection) is a prescription medicine for the treatment of patients with diabetic macular edema (DME).

What important safety information should I know about LUCENTIS?

You should not use LUCENTIS if you have an infection in or around the eye or are allergic to LUCENTIS or any of its ingredients.

Table of contents

- How can uncontrolled blood sugar from diabetes and DME affect my vision? ........................................... 4-7
- What can I expect at my doctor’s appointments? ........ 8-15
- What tools and support are available to help? ............. 16-28
How can DME affect my vision?

Diabetes is a chronic condition that affects the way your body processes blood sugar. This can lead to higher levels of blood sugar which, over a long period of time, can damage your eyes.

One type of damage that can happen from high blood sugar levels is called diabetic retinopathy (DR). DR occurs when blood vessels in a part of your eye called the retina swell and weaken.

When DR worsens, it can lead to another condition called diabetic macular edema or DME. DME occurs when the damaged blood vessels from DR leak into a part of the retina called the macula.

The macula is responsible for sharp, central vision. DME can cause too much fluid to build up in the macula, which can lead to vision changes if left untreated.

DME occurs when DR worsens. When a patient has DME, the blood vessels in the back of the eye swell, weaken, and leak—often affecting vision.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.
What are the symptoms?

Often, people have DME without realizing it. That’s why it’s important to know the symptoms of DME. They are different for everyone.

<table>
<thead>
<tr>
<th>HEALTHY VISION</th>
<th>DME SYMPTOMS</th>
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<tbody>
<tr>
<td>Healthy Vision</td>
<td>Blurry vision</td>
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<td></td>
<td>Wavy lines</td>
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<tr>
<td></td>
<td>Dark spots</td>
</tr>
<tr>
<td></td>
<td>Dull colors</td>
</tr>
</tbody>
</table>

Compare healthy vision to DME vision symptoms

What can I do?

If you have DME, you can reduce the risk of eye complications by working with your doctor to control your diabetes.

- A₁c (blood sugar levels)
- Blood pressure
- Diet

How can you do this?

Follow your doctor’s advice to eat a healthy diet approved by your diabetes care team and use your medicine as directed. Getting regular eye exams with dilation is important because the doctor can better see the back of your eye and can tell if you have DME. The sooner you know, the more you can do together.

A doctor called a Retina Specialist can tell you if you have DME.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.
Your Retina Specialist is here to help

Your diabetes care team may have many different doctors and nurses. But when it comes to your eye health, your best ally is your Retina Specialist.

People may have DME for years and not know it. But there are treatments that can help you manage this condition over time, and your Retina Specialist can help. These doctors have extra training that can help manage DME.

How does my doctor know how I’m doing?
Your Retina Specialist can track your progress in many ways. One way is by measuring your vision. Here are 2 other common tests your doctor may use:

OCT Images
Your doctor may use a picture test called optical coherence tomography [tuh-MOG-ruh-fee] (OCT). It helps them take a picture of the back of the eye. This test is used to monitor changes to the retina.

Fundus Photography
[FUHN-duhz] photography is another kind of photo test. A light is shined into your eye. The reflection helps your doctor see and take a picture of the delicate tissues in the back of your eye.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.
What is LUCENTIS?

LUCENTIS® (ranibizumab injection) is a prescription medicine for the treatment of patients with DME.

Your Retina Specialist may give you LUCENTIS if you have DME

Remember how DME is caused by swelling and fluid leaking into the back of your eye? LUCENTIS may reduce the swelling and leaking of blood vessels.

Take care of the vision you have. With LUCENTIS you could maintain the vision you have now—or maybe even improve it. Everyone is different.

Select Important Safety Information

LUCENTIS is a prescription medication given by injection into the eye, and it has side effects. LUCENTIS is not for everyone. Some LUCENTIS patients have had detached retinas and serious eye infections.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.

How vision is tested in DME

Your Retina Specialist will keep track of how many letters you can see on an eye chart. The more letters you can read, the better you can see. That’s called visual acuity.

In one study, where DME patients received monthly injections of LUCENTIS, 34% of patients had gained 3 lines (15 letters) after 2 years. In a second identical study, 45% of patients had gained 3 lines after 2 years. On average, patients gained 2 lines on the eye chart in both studies.*

Here is an example of a 3-line gain

Only 12-18% of patients who did not receive LUCENTIS experienced a 3-line improvement.

*Individual results may vary.
What else should I know about DME?

DME is a complication of diabetes, and because diabetes is a chronic condition that doesn’t go away, you need to partner with your doctor often. Visit your Retina Specialist regularly. Your doctor will determine how long you might need treatment.

Some common eye-related side effects from the injection include:
- Eye irritation
- Eye pain
- Small specs in vision
- Redness of the eye
- Increased eye pressure

Select Important Safety Information

Some patients have had increased eye pressure before and within 1 hour of an injection. Your eye doctor should check your eye pressure and eye health before and after your LUCENTIS injection.

Uncommonly, LUCENTIS patients have had serious, sometimes fatal, problems related to blood clots, such as heart attacks or strokes.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.
What can I expect from my LUCENTIS treatment?

LUCENTIS is an injection you receive in your eye. The idea of getting an injection might make you nervous. That’s normal. For most people, it feels like pressure on the eye. But it helps if you prepare yourself ahead of time.

Before your injection, ask your Retina Specialist:

☑️ Do I need to do anything or bring anyone?
☑️ Would you like to know about what vitamins, supplements, or medicines I’m taking?
☑️ How long will I be at the appointment?
☑️ Will I be able to see after the injection?
☑️ What are the possible side effects?

1 FIND MORE QUESTIONS AND TIPS IN THE DISCUSSION GUIDE

On the day you receive your injection:

- The area around your eye will be cleaned
- Your doctor will numb your eye prior to the administration of LUCENTIS, which may cause some initial pain and discomfort
- Your doctor may use a tool to help keep your eye open
- The LUCENTIS injection will be quick (only a few seconds)

After your injection you may:

- Have some redness in the white part of your eye
- See a few specks in your vision
- Receive antibiotic eye drops to use for a few days after the injection. Use the eye drops as directed to help prevent infection

Other injection-day tips:

- Arrange a ride home
- Talk with your doctor about what side effects to expect
- Ask what symptoms require you to check in with your doctor
- Ask your Retina Specialist if there are activities you should avoid

Select Important Safety Information

If your eye becomes red, sensitive to light, or painful, or if you have a change in vision, call or visit your eye doctor right away.

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What else should I know about DME?

DME is a complication of diabetes, and because diabetes is a chronic condition that doesn’t go away, you need to partner with your doctor often. Visit your Retina Specialist regularly. Your doctor will determine how long you might need treatment.

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• Eye irritation
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Do I need to do anything or bring anyone?

Would you like to know about what vitamins, supplements, or medicines I’m taking?

How long will I be at the appointment?

Will I be able to see after the injection?

What are the possible side effects?

LUCENTIS is an injection you receive in your eye. The idea of getting an injection might make you nervous. That’s normal. For most people, it feels like pressure on the eye. But it helps if you prepare yourself ahead of time.

What can I expect from my LUCENTIS treatment?

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.

How can I check my vision?

To monitor your vision changes, use your Amsler Grid at a set time each week. There’s an Amsler Grid for you inside this booklet.

To use your Amsler Grid, just follow these steps:

1. Cover one eye to check the other’s vision
2. Keep the grid at a normal reading distance—about 14 inches away
3. Look directly at the dot in the center of the grid with your other eye
4. If you normally wear glasses, keep them on while looking at the grid
5. Do the straight lines appear wavy, distorted, broken, or blurry?
   Take note of any abnormal or dark spots

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.

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What important safety information should I know about LUCENTIS?

You should not use LUCENTIS if you have an infection in or around the eye or are allergic to LUCENTIS or any of its ingredients.

LUCENTIS is a prescription medication given by injection into the eye, and it has side effects. LUCENTIS is not for everyone. Some LUCENTIS patients have had detached retinas and serious eye infections. If your eye becomes red, sensitive to light, or painful, or if you have a change in vision, call or visit your eye doctor right away.

Some patients have had increased eye pressure before and within 1 hour of an injection. Your eye doctor should check your eye pressure and eye health before and after your LUCENTIS injection.

Uncommonly, LUCENTIS patients have had serious, sometimes fatal, problems related to blood clots, such as heart attacks or strokes.

Fatal events were seen more often in patients with DME and DR with LUCENTIS compared with patients who did not receive LUCENTIS. Although there were only few fatal events which included causes of death typical of patients with advanced diabetic complications, these events may be caused by LUCENTIS.

Some LUCENTIS patients have serious side effects related to the injection. These include serious infections inside the eye, detached retinas, and cataracts. The most common eye-related side effects are increased redness in the white of the eye, eye pain, small specks in vision, and increased eye pressure. The most common non–eye-related side effects are nose and throat infections, anemia, nausea and cough.

LUCENTIS is for prescription use only.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

For additional Safety Information, please talk to your doctor and see the enclosed LUCENTIS full Prescribing Information.
To monitor your vision changes, use your Amsler Grid at a set time each week. There’s an Amsler Grid for you inside this booklet.

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5. Do the straight lines appear wavy, distorted, broken, or blurry?

Try Your Amsler Grid Tool

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**What if I have health insurance, but I’m concerned about treatment costs?**

**LUCENTIS Access Solutions** is a program that helps people who are taking LUCENTIS. Your insurance coverage and the cost of your medicine might keep you from getting the treatment you need. We might be able to help.

### Out-of-Pocket Expense Support

<table>
<thead>
<tr>
<th>Co-pay</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5</td>
<td>$0</td>
</tr>
</tbody>
</table>

Eligible patients pay as little as $5 per injection co-pay or co-insurance until the $10,000 yearly limit is reached*

Financial assistance provided by the program counts towards your annual deductible

Genentech Patient Foundation† provides free Genentech medicine to people who need it

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*This LUCENTIS Co-pay Program is valid ONLY for patients with commercial insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medication. Patients using Medicare, Medicaid or any other federal or state government program to pay for their medications are not eligible. Under the program, the patient will pay a co-pay. After reaching the maximum program benefit, the patient will be responsible for all out-of-pocket expenses.

All participants are responsible for reporting the receipt of all program benefits as required by any insurer or by law. No party may seek reimbursement for all or any part of the benefit received through this Program. The program is only valid in the United States and U.S. Territories. This program is void where prohibited by law and shall follow state restrictions in relation to AB-rated generic equivalents (e.g., MA, CA) where applicable. The patient, guardian, prescriber, hospital and any other person using the program agree not to seek reimbursement for all or any part of the benefit received by the patient through the offer of this program. Genentech reserves the right to rescind, revoke or amend the program without notice at any time. Additional terms and conditions apply. Please visit www.LUCENTISCopayProgram.com for the full list of Terms and Conditions.

†To be eligible for free Genentech medicine from the Genentech Patient Foundation, insured patients who have coverage for their medicine must have pursued all other forms of financial assistance and meet certain income requirements. Uninsured patients and insured patients without coverage for their medicine must meet different income requirements.
Genentech Access Solutions is here to help you. Just give us a call or go online

Genentech Access Solutions: More programs and services
Learn more about available programs and services for affording your medication.

To speak with a dedicated specialist, call 1-866-724-9394
Find us online! Genentech-Access.com/LUCENTIS/patients

Select Important Safety Information
Fatal events were seen more often in patients with DME and DR with LUCENTIS compared with patients who did not receive LUCENTIS. Although there were only few fatal events which included causes of death typical of patients with advanced diabetic complications, these events may be caused by LUCENTIS.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.
Terms to know

Sometimes, medical terms can be hard to understand. In this booklet (or at your doctor’s office), you might come across a word that’s unfamiliar. So we’ve put together a list of words to help.

**Cornea**
The cornea is like the front window of the eye. It transmits and focuses light into the eye. It has a complex structure that is made up of 5 layers.

**Dilation**
An examination wherein drops are placed in the eyes to widely open (dilate) the pupils, allowing a better view of the inside of the eye, especially the retina tissue.

**DME**
Diabetic macular edema (DME) [die-uh-BET-ik MAK-u-lur eh-DEE-ma] is when damaged blood vessels begin to leak fluid into the macula.

**DR**
Diabetic retinopathy (DR) [die-uh-BET-ik ret-ih-NOP-uh-thee] is a complication of diabetes that affects eyes. DR is caused by blood vessels swelling or getting blocked.

**Iris**
The iris is the colored part of the eye that controls the amount of light that enters the eye.

**Lens**
The lens is the transparent structure of the eye behind the iris. It focuses light rays onto the retina.

**Macula**
The macula [MAK-yuh-luh] is a small area in the back of the eye, located in the retina. The macula is responsible for sharp central vision. It allows people to see well enough to do things like reading and detailed work.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.
Learn how LUCENTIS can help

Diabetic macular edema (DME) can be confusing. We are focused on helping you understand DME and how LUCENTIS may be able to help. LUCENTIS is a prescription medication indicated for the treatment of patients with DME.

Speak to a LUCENTIS Specialist at 1-866-LUCENTIS (1-866-582-3684) Monday through Friday, 9/AM to 8/PM ET. Talk with a LUCENTIS Specialist for questions about what to expect with LUCENTIS or affording your medication. For medical questions or emergencies, call your Retina Specialist right away.

With the LUCENTIS Helpline, support is just a phone call away.

For Important Safety Information, please see safety information throughout, on pages 18-19, and the enclosed Prescribing Information.

Ophthalmologist
An ophthalmologist [oph-thal-MOL-o-gist] is a doctor who treats eye disease and injury.

Pupil
The pupil is the opening at the center of the iris. It contracts in bright light, and expands in dark light.

Retina
The light-sensitive layer that lines the back of the eye. The retina receives images and sends them through the optic nerve to the brain.

Retina Specialist
An ophthalmologist who specializes in treating a variety of diseases in the back of the eye (or retina). Compared to an ophthalmologist, a Retina Specialist has completed 1 to 2 additional years of training that focuses on the retina.

Visual Acuity
The ability to see details clearly at different distances.

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Learn how LUCENTIS can help
DME can affect what you see

Diabetic macular edema (DME) can be confusing. We are focused on helping you understand DME and how LUCENTIS may be able to help. LUCENTIS is a prescription medication indicated for the treatment of patients with DME.

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3. Look directly at the dot in the center of the grid with your other eye
4. If you normally wear glasses, keep them on while looking at the grid
5. Do the straight lines appear wavy, distorted, broken, or blurry? Take note of any abnormal or dark spots

If you notice any changes or if the appearance of the lines start to get worse, notify your Retina Specialist right away
Check your vision with an Amsler Grid

To monitor your vision changes, use your Amsler Grid at a set time each week. Instructions are on the back.
What can I expect from my first injection?

Do I need to do anything or bring anyone?

How long will I be at the appointment?

What side effects should I expect?

What activities should I avoid?
Get organized before your injection

Before you go to your Retina Specialist’s office, you may want to (check all that apply):

- Arrange a ride home from the doctor’s office
- Pack sunglasses
- Bring insurance card or Medicaid card
- Bring ID
- Remove any eye makeup
- Bring a list of vitamins, supplements, and medicines you are taking

After your injection, call your doctor right away if:
- Your eye becomes red
- Your eye becomes sensitive to light
- Your eye becomes painful
- Your vision changes after you get home

If you experience any of the above symptoms, you could be at risk of developing a serious eye condition.
LUCENTIS® (ranibizumab injection) for intravitreal injection

Initial U.S. Approval: 2006

--- RECENT MAJOR CHANGES ---
- Indications and Usage, Diabetic Retinopathy (1.4) 04/2017
- Dosage and Administration (2) 03/2018
- Dosage Forms and Strengths (3) 03/2018

--- INDICATIONS AND USAGE ---
LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, 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)
- Diabetic Retinopathy (DR) (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

--- 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 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) (2.3): 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) (2.4): LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

--- ADVERSE REACTIONS ---
- Myopic Choroidal Neovascularization (mCNV) (2.5): 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.
- Single-use prefilled syringe 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)
- 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 patients with DME and DR at baseline, who were 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 1-888-635-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2018
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)
1.4 Diabetic Retinopathy (DR)
1.5 Myopic Choroidal Neovascularization (mCNV)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION.

Vials: A 5-micron sterile filter needle (19-gauge x 1-1/2 inch), a 1-mL Luer lock syringe and a 30-gauge x ½ inch sterile injection needle are needed but not included.

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

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL solution) 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. In the 9 months after three initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly [see Clinical Studies (14.1)].

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed 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 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) and Diabetic Retinopathy (DR)

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

2.5 Myopic Choroidal Neovascularization (mCNV)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to 3 months. Patients may be retreated if needed [(see Clinical Studies 14.5)].
2.6 Preparation for Administration

**Prefilled Syringe:**

The prefilled syringe is sterile and is for single use only. **Do not** use the product if the packaging is damaged or has been tampered with.

To prepare LUCENTIS for intravitreal administration, please adhere to these instructions for use. Read all the instructions carefully before using the prefilled syringe.

The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.

For the intravitreal injection, a 30-gauge x ½ inch sterile injection needle should be used (not provided).

**Note:** the dose must be set to 0.05 mL.

---

**Device description**

LUCENTIS prefilled syringes are available in 2 dose strengths:

- **LUCENTIS 0.5 mg prefilled syringe with a CLEAR finger grip.**

![Clear syringe and needle](image)

- **LUCENTIS 0.3 mg prefilled syringe with an ORANGE finger grip.**

![Orange syringe and needle](image)

Check the labels on the LUCENTIS carton, syringe tray and prefilled syringe to make sure you have the correct dose strength.
Step 1: Prepare

- Make sure that your pack contains a sterile prefilled syringe in a sealed tray.
- Peel the lid off the syringe tray and, using aseptic technique, remove the syringe.

Step 2: Inspect syringe

- LUCENTIS should be colorless to pale yellow.
- **Do not** use the prefilled syringe if:
  - the syringe cap is detached from the Luer lock.
  - the syringe is damaged.
  - particulates, cloudiness, or discoloration are visible.

Step 3: Remove syringe cap

- Snap off (do not turn or twist) the syringe cap (see Figure 2).
Step 4: Attach needle

- Attach a 30G x ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock (see Figure 3).
- Carefully remove the needle cap by pulling it straight off.

*Note: Do not wipe the needle at any time.*

Step 5: Dislodge air bubbles

- Hold the syringe with the needle pointing up.
- If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

Step 6: Expel air and adjust drug dose

- Hold the syringe at eye level, and carefully push the plunger rod until the edge below the dome of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5).

*Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.*
Step 7: Inject

- The injection procedure should be carried out under aseptic conditions.
- Insert the needle into the injection site.
- Inject slowly until rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL.
- After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.
**Vial:**

Using aseptic technique, all of the LUCENTIS vial contents are withdrawn through a 5-micron (19-gauge x 1-1/2 inch), sterile filter needle attached to a 1 mL syringe (not included). 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 ½ inch needle for the intravitreal injection.

Use aseptic technique to carry out the following preparation steps:

1. Prepare for intravitreal injection with the following medical devices for single use (not included):
   - a 5-micron sterile filter needle (19-gauge x 1-1/2 inch)
   - a 1 mL sterile Luer lock syringe (with marking to measure 0.05 mL)
   - a sterile injection needle (30-gauge x 1/2-inch)

2. Before withdrawal, disinfect the outer part of the rubber stopper of the vial.

3. Place a 5-micron filter needle (19-gauge x 1-1/2 inch) onto a 1 mL Luer lock syringe using aseptic technique.

4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.

5. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. The filter needle should be discarded after withdrawal of the vial contents and must not be used for the intravitreal injection.

8. Attach a 30-gauge x 1/2-inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.

9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.
10. Hold the syringe at eye level, and carefully push the plunger rod until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

2.7 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 prefilled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle (vial only), 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 prefilled syringe designed to provide 0.05 mL for intravitreal injection.
- Colorless to pale yellow 10 mg/mL solution (LUCENTIS 0.5 mg)
- Colorless to pale yellow 6 mg/mL solution (LUCENTIS 0.3 mg)

Single-use glass vial designed to provide 0.05 mL for intravitreal injection.
- Colorless to pale yellow 10 mg/mL solution (LUCENTIS 0.5 mg)
- Colorless to pale yellow 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 (2.6, 2.7) 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 (2.7)].

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. Arterial thromboembolic events 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 (AMD-1, AMD-2, AMD-3) 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 Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies [AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy (PDT)], 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 and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [see Clinical Studies (14.3, 14.4)].

In a pooled analysis of Studies D-1 and D-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 Patients with Diabetic Macular Edema and Diabetic Retinopathy at Baseline

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [see Clinical Studies (14.3, 14.4)].
A pooled analysis of Studies D-1 and D-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 other sections of the label:

- Endophthalmitis and Retinal Detachments [see Warnings and Precautions (5.1)]
- Increases in Intraocular Pressure [see Warnings and Precautions (5.2)]
- Thromboembolic Events [see Warnings and Precautions (5.3)]
- Fatal Events in patients with DME and DR at baseline [see Warnings and Precautions (5.4)]

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.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline [see Clinical Studies (14)]. Safety data observed in 224 patients with mCNV, as well as Studies AMD-4 and D-3, were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DME and DR 2-year</th>
<th>AMD 2-year</th>
<th>AMD 1-year</th>
<th>RVO 6-month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LUCENTIS 0.3 mg</td>
<td>LUCENTIS 0.5 mg</td>
<td>LUCENTIS 0.5 mg</td>
<td>LUCENTIS 0.5 mg</td>
</tr>
<tr>
<td>Con. hemorrhage</td>
<td>47% 32% n=250</td>
<td>74% 60% n=379</td>
<td>64% 50% n=440</td>
<td>48% 37% n=259</td>
</tr>
<tr>
<td>Eye pain</td>
<td>17% 13% n=250</td>
<td>35% 30% n=379</td>
<td>26% 20% n=440</td>
<td>17% 12% n=259</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>10% 4% n=250</td>
<td>27% 8% n=379</td>
<td>19% 5% n=440</td>
<td>7% 2% n=259</td>
</tr>
<tr>
<td>Intracocular pressure increased</td>
<td>18% 7% n=250</td>
<td>24% 7% n=379</td>
<td>17% 5% n=440</td>
<td>7% 2% n=259</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>11% 15% n=250</td>
<td>21% 19% n=379</td>
<td>15% 15% n=440</td>
<td>4% 2% n=259</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>4% 3% n=250</td>
<td>18% 8% n=379</td>
<td>13% 7% n=440</td>
<td>1% 3% n=259</td>
</tr>
<tr>
<td>Cataract</td>
<td>28% 32% n=250</td>
<td>17% 14% n=379</td>
<td>11% 9% n=440</td>
<td>2% 2% n=259</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>10% 5% n=250</td>
<td>16% 14% n=379</td>
<td>13% 10% n=440</td>
<td>7% 5% n=259</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>8% 5% n=250</td>
<td>15% 15% n=379</td>
<td>13% 12% n=440</td>
<td>7% 6% n=259</td>
</tr>
<tr>
<td>Lacration increased</td>
<td>5% 4% n=250</td>
<td>14% 12% n=379</td>
<td>8% 8% n=440</td>
<td>2% 3% n=259</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>3% 2% n=250</td>
<td>12% 8% n=379</td>
<td>8% 5% n=440</td>
<td>0% 1% n=259</td>
</tr>
<tr>
<td>Dry eye</td>
<td>5% 3% n=250</td>
<td>12% 7% n=379</td>
<td>7% 7% n=440</td>
<td>3% 3% n=259</td>
</tr>
<tr>
<td>Visual disturbance or vision blurred</td>
<td>8% 4% n=250</td>
<td>18% 15% n=379</td>
<td>13% 10% n=440</td>
<td>5% 3% n=259</td>
</tr>
<tr>
<td>Eye pruritis</td>
<td>4% 4% n=250</td>
<td>12% 11% n=379</td>
<td>9% 7% n=440</td>
<td>1% 2% n=259</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>9% 9% n=250</td>
<td>11% 8% n=379</td>
<td>7% 4% n=440</td>
<td>5% 3% n=259</td>
</tr>
<tr>
<td>Retinal disorder</td>
<td>2% 2% n=250</td>
<td>10% 7% n=379</td>
<td>8% 4% n=440</td>
<td>2% 1% n=259</td>
</tr>
<tr>
<td>Maculopathy</td>
<td>5% 7% n=250</td>
<td>9% 9% n=379</td>
<td>6% 6% n=440</td>
<td>11% 7% n=259</td>
</tr>
<tr>
<td>Retinal degeneration</td>
<td>1% 0% n=250</td>
<td>8% 6% n=379</td>
<td>5% 3% n=440</td>
<td>1% 0% n=259</td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>2% 1% n=250</td>
<td>7% 4% n=379</td>
<td>5% 2% n=440</td>
<td>2% 2% n=259</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>1% 2% n=250</td>
<td>7% 6% n=379</td>
<td>5% 4% n=440</td>
<td>0% 0% n=259</td>
</tr>
<tr>
<td>Posterior capsule opacification</td>
<td>4% 3% n=250</td>
<td>7% 4% n=379</td>
<td>2% 2% n=440</td>
<td>0% 1% n=259</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>1% 0% n=250</td>
<td>5% 2% n=379</td>
<td>3% 1% n=440</td>
<td>0% 0% n=259</td>
</tr>
</tbody>
</table>
Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 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 and DR, AMD, and RVO Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DME and DR 2-year</th>
<th>AMD 2-year</th>
<th>AMD 1-year</th>
<th>RVO 6-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUCENTIS 0.5 mg Control</td>
<td>n=250</td>
<td>n=379</td>
<td>n=440</td>
<td>n=259</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12% 6%</td>
<td>16% 13%</td>
<td>8% 9%</td>
<td>5% 4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>11% 10%</td>
<td>8% 7%</td>
<td>4% 3%</td>
<td>1% 1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10% 9%</td>
<td>9% 6%</td>
<td>5% 5%</td>
<td>1% 2%</td>
</tr>
<tr>
<td>Cough</td>
<td>9% 4%</td>
<td>9% 8%</td>
<td>5% 4%</td>
<td>1% 2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8% 4%</td>
<td>5% 7%</td>
<td>3% 4%</td>
<td>0% 1%</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>8% 4%</td>
<td>4% 4%</td>
<td>2% 2%</td>
<td>0% 2%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7% 5%</td>
<td>5% 5%</td>
<td>3% 2%</td>
<td>1% 1%</td>
</tr>
<tr>
<td>Influenza</td>
<td>7% 3%</td>
<td>7% 5%</td>
<td>3% 2%</td>
<td>3% 2%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>7% 6%</td>
<td>1% 1%</td>
<td>0% 0%</td>
<td>0% 0%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7% 7%</td>
<td>9% 8%</td>
<td>5% 5%</td>
<td>2% 2%</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>6% 4%</td>
<td>4% 6%</td>
<td>3% 4%</td>
<td>1% 0%</td>
</tr>
<tr>
<td>Headache</td>
<td>6% 8%</td>
<td>12% 9%</td>
<td>6% 5%</td>
<td>3% 3%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>6% 4%</td>
<td>3% 5%</td>
<td>2% 3%</td>
<td>0% 1%</td>
</tr>
<tr>
<td>Renal failure chronic</td>
<td>6% 2%</td>
<td>0% 1%</td>
<td>0% 0%</td>
<td>0% 0%</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>5% 3%</td>
<td>1% 1%</td>
<td>1% 0%</td>
<td>0% 0%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5% 8%</td>
<td>8% 7%</td>
<td>5% 5%</td>
<td>3% 2%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4% 4%</td>
<td>11% 9%</td>
<td>6% 5%</td>
<td>0% 2%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3% 3%</td>
<td>5% 4%</td>
<td>2% 2%</td>
<td>1% 0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3% 3%</td>
<td>11% 9%</td>
<td>5% 5%</td>
<td>2% 1%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1% 1%</td>
<td>6% 3%</td>
<td>3% 1%</td>
<td>0% 0%</td>
</tr>
<tr>
<td>Wound healing complications</td>
<td>1% 0%</td>
<td>1% 1%</td>
<td>1% 0%</td>
<td>0% 0%</td>
</tr>
</tbody>
</table>

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%-9% 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 patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the 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 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 PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels \([C_{\text{max}}]\)) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose [see Animal Data].

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab [see Clinical Pharmacology (12.1)], treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
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 \(C_{\text{max}}\) 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.
8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

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.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential

Infertility

No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 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

More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

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, 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 prefilled syringe or a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use container designed to deliver 0.05 mL of 10 mg/mL LUCENTIS (0.5 mg dose prefilled syringe or vial) or 6 mg/mL LUCENTIS (0.3 mg dose prefilled syringe or vial) 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<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, mCNV, DR, DME 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 retinal thickness (i.e., center point thickness (CPT) or central foveal thickness (CFT)), as assessed by optical coherence tomography (OCT) is associated with neovascular AMD, mCNV, macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD and mCNV. Microvascular retinal changes and neovascularization, as assessed by color fundus photography, are associated with diabetic retinopathy.

Neovascular (Wet) Age-Related Macular Degeneration

In Study AMD-3, CPT was assessed by time domain (TD)-OCT in 118 of 184 patients. TD-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. In this study, CPT data did not provide information useful in influencing treatment decisions [see Clinical Studies (14.1)].

In Study AMD-4, CFT was assessed by spectral domain (SD)-OCT in all patients; on average, CFT reductions were observed beginning at Day 7 following the first LUCENTIS injection through Month 24. CFT data did not provide information capable of predicting final visual acuity results [see Clinical Studies (14.1)].

In patients treated with LUCENTIS, the area of CNV leakage, on average, decreased by Month 3 as assessed by FA. The area of CNV 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 D-1 and D-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)].

Diabetic Retinopathy

Improvements from baseline in DR severity as assessed on fundus photography were observed in Studies D-1 and D-2 at Month 3 (first scheduled DR photographic assessment after randomization) through Month 36 [see Clinical Studies (14.4)].

Myopic Choroidal Neovascularization

On average CFT reductions were observed as early as Month 1, and were greater in the LUCENTIS groups compared to PDT [see Clinical Studies (14.5)].

12.3 Pharmacokinetics

In patients with neovascular AMD, following monthly intravitreal administration of 0.5 mg LUCENTIS, mean (±SD) maximum ranibizumab serum concentrations were 1.7 (± 1.1) ng/mL. These concentrations were below the concentration range of ranibizumab (11 to 27 ng/mL) that was necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay (based on human umbilical vein endothelial cells (HUVEC)). No significant change from baseline was observed in the mean plasma VEGF concentrations following three monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 2 mg/eye. Serum ranibizumab concentrations in RVO and DME and DR patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, maximum serum concentrations 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

Animal studies have not been conducted to determine the carcinogenic potential of ranibizumab. Based on the anti-VEGF mechanism of action of ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity [see Females and Males of Reproductive Potential (8.3)].

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 PDT. Sham PDT (or active PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if FA 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

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

*a 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

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

*a Adjusted estimate based on the stratified model; p < 0.01
Patients in the group treated with LUCEPTIS 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 LUCEPTIS 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 LUCEPTIS versus 2.9-3.1 DA for the control arms.

Study AMD-3

Study AMD-3 was a randomized, double-masked, sham-controlled, 2-year study designed to assess the safety and efficacy of LUCEPTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received LUCEPTIS 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for three consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (LUCEPTIS 0.3 mg, 60; LUCEPTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with LUCEPTIS in Study AMD-3 received a mean of six total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was the 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 LUCEPTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCEPTIS-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 three 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 (see Figure 3). 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. The distribution of injections received in the less frequent dosing arm is shown in Figure 4.
14.2 Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of LUVENTIS 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 (LUVENTIS 0.3 mg, 266 patients; LUVENTIS 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 LUVENTIS 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 LUVENTIS 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 LUVENTIS and 71 of 132 (54%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUVENTIS 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 LUVENTIS, the following clinical results were observed:

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Study</th>
<th>Sham</th>
<th>LUVENTIS 0.5 mg</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain of ≥15 letters in visual acuity (%)</td>
<td>RVO-1</td>
<td>29%</td>
<td>61%</td>
<td>31% (20%, 43%)</td>
</tr>
<tr>
<td>Gain of ≥15 letters in visual acuity (%)</td>
<td>RVO-2</td>
<td>17%</td>
<td>48%</td>
<td>30% (20%, 41%)</td>
</tr>
</tbody>
</table>

* RVO-1: Sham, n=131; LUVENTIS 0.5 mg, n=132
  RVO-2: Sham, n=130; LUVENTIS 0.5 mg, n=130

b Adjusted estimate based on stratified model; p < 0.01
Figure 5
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

14.3 Diabetic Macular Edema (DME)

Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 (See Section 14.4 Diabetic Retinopathy below). All enrolled patients had DR and DME at baseline.

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 3-year studies. 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.

In Studies D-1 and D-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:
Table 6
Visual Acuity Outcomes at Month 24 in Study D-1 and D-2

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

<sup>a</sup> D-1: Sham, n=130; LUCENTIS 0.3 mg, n=125
D-2: Sham, n=127; LUCENTIS 0.3 mg, n=125
<sup>b</sup> Adjusted estimate based on stratified model; p ≤ 0.01

Figure 6
Mean Change in Visual Acuity from Baseline to Month 36 in Study D-1 and Study D-2

Visual acuity outcomes observed at Month 24 in patients treated with LUCENTIS 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received LUCENTIS 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with LUCENTIS at the beginning of the studies.
In Studies D-1 and D-2, patients received monthly injections of LUCENTIS for 12 or 36 months, after which 500 patients opted to continue in the long-term follow-up study. Of 298 patients who had at least 12 months of follow-up from Month 36, 58 (19.5%) patients maintained vision with no further therapy. The remaining 202 patients were followed for less than 12 months.

### 14.4 Diabetic Retinopathy (DR)

Efficacy and safety data of LUCENTIS are derived from Studies D-1 and D-2 [see Clinical Studies (14.3)] and D-3. All enrolled patients in Studies D-1 and D-2 had DR and DME at baseline. Study D-3 enrolled DR patients both with and without DME at baseline.

Of the 759 patients enrolled in Studies D-1 and D-2, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scores (ETDRS-DRSS) ranging from 10 to 75. At baseline, 62% of patients had non-proliferative diabetic retinopathy (NPDR) (ETDRS-DRSS less than 60) and 31% had proliferative diabetic retinopathy (PDR) (ETDRS-DRSS greater than or equal to 60). The ETDRS-DRSS 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.

After monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed (Table 7; Figure 7):

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Study(^a)</th>
<th>Sham</th>
<th>LUCENTIS 0.3 mg</th>
<th>Estimated Difference (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3-step improvement from baseline in ETDRS-DRSS (^c)</td>
<td>D-1</td>
<td>2%</td>
<td>17%</td>
<td>15% (7%, 22%)</td>
</tr>
<tr>
<td></td>
<td>D-2</td>
<td>0%</td>
<td>9%</td>
<td>9% (4%, 14%)</td>
</tr>
<tr>
<td>≥2-step improvement from baseline in ETDRS-DRSS (^d)</td>
<td>D-1</td>
<td>4%</td>
<td>39%</td>
<td>35% (26%, 44%)</td>
</tr>
<tr>
<td></td>
<td>D-2</td>
<td>7%</td>
<td>37%</td>
<td>31% (21%, 40%)</td>
</tr>
</tbody>
</table>

\(^a\) D-1: Sham, n=124; LUCENTIS 0.3 mg, n=117  
D-2: Sham, n=115; LUCENTIS 0.3 mg, n=117  

\(^b\) Adjusted estimate based on stratified model  

\(^c\) \(p < 0.05\) for all time points comparing LUCENTIS 0.3 mg to sham from Month 12 through Month 24  

\(^d\) \(p < 0.05\) for all time points comparing LUCENTIS 0.3 mg to sham from Month 3 through Month 24

At Month 24, DR improvement by ≥3-steps in ETDRS-DRSS 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.

The difference in the proportion of patients treated with LUCENTIS 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-DRSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.
Study D-3 enrolled DR patients with and without DME; 88 (22%) eyes with baseline DME and 306 (78%) eyes without baseline DME and balanced across treatment groups. Study D-3 was a randomized, active-controlled study where patient age ranged from 20 to 83 with a mean age of 51 years. A total of 394 study eyes from 305 patients, including 89 who had both eyes randomized, were enrolled (LUCENTIS, 191 study eyes; pan-retinal photocoagulation; 203 study eyes). All eyes in the LUCENTIS group received a baseline 0.5 mg intravitreal injection followed by 3 monthly intravitreal injections, after which treatment was guided by pre-specified retreatment criteria. Patients had baseline ETDRS-DRSS ranging from 20 to 85. At baseline, 11% of eyes had NPDR (ETDRS-DRSS less than 60), 50% had mild-to-moderate PDR (ETDRS-DRSS equal to 60, 61, or 65), and 37% had high-risk PDR (ETDRS-DRSS greater than or equal to 71).

An analysis of data from Study D-3 demonstrated that at Year 2 in the LUCENTIS group, 31.7% and 28.4% of eyes in the subgroups with baseline DME and without baseline DME, respectively, had ≥ 3-step improvement from baseline in ETDRS-DRSS.

Table 8
Proportion of Eyes with ≥ 3-Step and ≥ 2-Step Improvement from Baseline in ETDRS-DRSS at Year 2 in Study D-3

<table>
<thead>
<tr>
<th>Outcome Measure (in ETDRS-DRSS)</th>
<th>LUCENTIS group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eyes with</td>
</tr>
<tr>
<td></td>
<td>Baseline DME</td>
</tr>
<tr>
<td></td>
<td>n = 41 (31.7%)</td>
</tr>
<tr>
<td>≥ 3-step improvement from baseline</td>
<td>13 (17.5%, 46.0%)</td>
</tr>
<tr>
<td>95% CI for percentage</td>
<td></td>
</tr>
<tr>
<td>≥ 2-step improvement from baseline</td>
<td>24 (43.5%, 73.6%)</td>
</tr>
<tr>
<td>95% CI for percentage</td>
<td></td>
</tr>
</tbody>
</table>
14.5 **Myopic Choroidal Neovascularization (mCNV)**

The efficacy and safety data of LUCENTIS were assessed in a randomized, double-masked, active-controlled 3-month study in patients with mCNV. 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 PDT 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 Best Corrected Visual Acuity (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.

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 PDT group. (Figure 9; Table 9). Efficacy was comparable between Group I and Group II.

### Table 9

<table>
<thead>
<tr>
<th>Study Arms</th>
<th>Mean change in BCVA from baseline (Letters)</th>
<th>Proportion of patients who gained ≥15 letters from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Estimated Difference (95% CI)²</td>
</tr>
<tr>
<td>Group I</td>
<td>12.1 (10.2)</td>
<td>10.9 (7.6, 14.3)</td>
</tr>
<tr>
<td>Group II</td>
<td>12.5 (8.8)</td>
<td>11.4 (8.3, 14.5)</td>
</tr>
<tr>
<td>Control (PDT)</td>
<td>1.4 (12.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted estimates based on stratified models; p < 0.01
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 PDT group. The mean number of injections between baseline and Month 3 was 2.5 and 1.8 for Groups I and II, respectively. 41% of patients received 1, 2 or 3 injections between baseline and Month 3 with no injections afterwards.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and a CLEAR finger grip. Each prefilled syringe is sterile and is packed in a sealed tray.

- Each LUCENTIS 0.3 mg carton (NDC 50242-082-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 6 mg/mL ranibizumab solution. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and an ORANGE finger grip. Each prefilled syringe is sterile and is packed in a sealed tray.

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-02) contains a single-use, 2-mL glass vial with a BLUE CAP designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution.

- Each LUCENTIS 0.3 mg carton (NDC 50242-082-02) contains a single-use, 2-mL glass vial with a WHITE CAP designed to deliver 0.05 mL of 6 mg/mL ranibizumab solution.

EACH CARTON IS FOR SINGLE-EYE USE ONLY.

LUCENTIS should be refrigerated at 2º-8ºC (36º-46ºF). DO NOT FREEZE. Do not use beyond the date stamped on the label. Protect LUCENTIS prefilled syringes and vials from light and store in the original carton until time of use. Do not open LUCENTIS prefilled syringe sealed tray until time of use.

17 PATIENT COUNSELING INFORMATION

Advise patients that 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, advise the patient to seek immediate care from an ophthalmologist [see Warnings and Precautions (5.1)].
| LUCENTIS® (ranibizumab injection) | LUCENTIS® is a registered trademark of Genentech, Inc. ©2018 Genentech, Inc. |
|----------------------------------|-----------------------------------------------------------------
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| Genentech, Inc.                 |                                                                  |
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| 1 DNA Way                       |                                                                  |
| South San Francisco, CA         |                                                                  |
| 94080-4990                      |                                                                  |