ONSET

Diabetic macular edema (DME), the primary cause of vision loss associated with diabetic retinopathy, is a disease affecting the macula, the part of the retina responsible for central vision. Diabetic retinopathy is the ocular manifestation of the effect of diabetes on the cardiovascular system, where hyperglycemia causes damage to the small blood vessels of the retina, the light-sensitive tissue at the back of the eye. The affected blood vessel walls become weakened and leak fluid. This fluid causes the surrounding tissue to swell. When this swelling involves the macula, this is known as diabetic macular edema. Because the macula is a very small area of the retina where light is focused on the back of the eye, swelling of this tissue leads to distortion and loss of vision. The swelling or edema of this tissue can lead ultimately to irreversible damage to the photoreceptor system which is critical to vision.

STATISTICS

- Approximately 19 percent of patients with diabetes studied over a 10-year period were diagnosed with DME.1
- At least 382 million people worldwide have diabetes; this figure is likely to rise to 592 million by 2035.2
- More than 560,000 Americans have DME.3
- All people with type 1 or type 2 diabetes are at risk for DME.4

PREVENTION, SIGNS AND SYMPTOMS

- As a precaution, patients with diabetes should schedule a comprehensive dilated eye exam once a year. Early detection and timely treatment of diabetic retinopathy can potentially prevent the development of DME and potential vision loss.
- The macula in patients with DME swells due to excess fluid in the tissue from leaking vessels, which have been damaged because of the hyperglycemia associated with diabetes.
- This swelling of the macula blurs central vision, interfering with many daily tasks, such as reading, watching television and driving.
- If left untreated, DME can result in irreversible vision loss.

TREATMENT

- Treatment options in the U.S. include:
  - ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg – a tiny implant designed to release a continuous, low dose of the corticosteroid fluocinolone acetonide (FAc) into the back of the eye over 36 months. It is indicated in the U.S. for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. In phase 3 clinical trials in subjects with DME who had previously been treated with laser photocoagulation, the primary efficacy endpoint was met at 24 months.
Ozurdex®, a bioerodible intravitreal implant, delivers the corticosteroid dexamethasone. In the phase 3 clinical trials, subjects could receive treatment no more frequently than every six months. Efficacy was noted to peak three months after administration and diminish thereafter.

Retinal Laser photocoagulation is not approved for the treatment of DME, but was the standard of care prior to the approval of pharmacotherapies for DME. It continues to be used adjunctively and as monotherapy in some small, isolated focal areas of DME.

Ranibizumab and Aflibercept anti-VEGF injections target the cytokine vascular endothelial growth factor. These therapies are biological proteins. Ranibizumab is recommended to be administered by intravitreal injection once per month. Aflibercept is recommended to be administered every two months after five monthly loading doses.

**ILUVIEN IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

**WARNINGS AND PRECAUTIONS**

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

**ADVERSE REACTIONS**

- In controlled studies, the most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of >10 mmHg (ILUVIEN 34%; sham 10%).
- Patients are advised to have follow-up eye examinations at appropriate intervals following treatment with ILUVIEN. For full prescribing information, log onto www.ILUVIEN.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see Full Prescribing Information below.

1. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy
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DOSAGE AND ADMINISTRATION

1. Intravitreal injection procedure should be carried out under aseptic conditions, which include the use of sterile gloves, a sterile drape, a sterile caliper, and a sterile syringe (or equivalent). Adequate anesthesia and a broad-spectrum antibiotic should be given prior to the injection.

The intravitreal injection procedure for ILUVIEN® is as follows:

1. The outer portion of the tray should not be considered sterile. An assistant (non-
sterile) should remove the tray from the carton and examine the tray and lid for damage. If damaged, do not use unit.

If acceptable, the assistant should peel the lid from the tray without touching the interstitial button marks alongside the button track. At the first stop, release the button and it should move to the UP position. If the button does not rise to the UP position, do not proceed with this unit.

2. Visually check through the viewing window of the preloaded applicator to

3. Remove the applicator tip from within the opercular portion of the product and
inspect the tip to ensure it is not bent.

4. Gently displace the conjunctiva so that after withdrawing the needle, the conjunctival and scleral needle entry sites will not align. Care should be taken to avoid contact between the needle and the lid margin or lashes. Insert the needle through the conjunctiva and sclera. To release the implant, while the button is in the UP position, advance the button by sliding it forward to the end of the button track and remove the needle.

5. Remove the lid speculum and perform indirect ophthalmoscopy to verify placement of the implant, adequate central retinal artery perfusion and absence of any other complications.

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

6. Carefully remove the protective cap from the needle and inspect the tip to

7. Ensure that the button reaches the end of the track before removing the needle.

8. Remove the lid speculum and perform indirect ophthalmoscopy to verify placement of the implant, adequate central retinal artery perfusion and absence of any other complications.

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure (6.1). To report SUSPECTED ADVERSE REACTIONS, contact Alimera Sciences, Inc. at 1-844-645-8443 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

ILUVIEN® contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection.

2.2 Administration

2.2.1 Initial U.S. Approval: 1963

Full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

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Fluocinolone acetonide is a white or almost white, microcrystalline powder, practically insoluble in water, soluble in methanol, ethanol, and sparingly soluble in ether.

Each ILUVIEN consists of a light brown 3.5mm x 0.37mm implant containing 0.19 mg of the active ingredient fluocinolone acetonide and the following inactive ingredients: polyethylene terephthalate, polyvinyl alcohol, silicone adhesive and water for injection.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Cor tcosteroids inhibit inflammatory responses to a variety of inciting agents. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibrinolytic proliferation, deposition of collagen, and scar formation associated with inflammation. Cor ticosteroids are thought to act by inhibition of phospholipase A₂ via induction of inhibitory proteins collectively called lipocortins. It is postulated that these proteins control biosynthesis of potential mediators of inflammation such as prostaglandins and leukotrienes by inhibiting release of the common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

12.2 Pharmacokinetics

In a human pharmacokinetic study of ILUVIEN, fluocinolone acetonide concentrations in plasma were below the lower limit of quantification of the assay (100 pg/mL) at all post-administration time points from Day 7 through Month 36 following intravitreal administration of a 0.2 mcg/day or 0.5 mcg/day fluocinolone acetonide insert.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to determine the carcinogenic potential of the effect of fertility of ILUVIEN. Fluocinolone acetonide was not genotoxic in vitro in the Ames test (E. coli and S. typhimurium) and the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.

14 CLINICAL STUDIES

The efficacy of ILUVIEN was assessed in two three-year, randomized (2:1: active: sham), multicenter, double-masked, parallel-groups studies that enrolled participants with diabetic macular edema that had previously been treated with laser photocoagulation.

The primary efficacy endpoint in both trials was the proportion of subjects in whom vision had improved by 15 letters or more from baseline after 24 months of follow-up.

### Table 3: Baseline BCVA (Letters)

<table>
<thead>
<tr>
<th>Study 1: Phakic Subjects</th>
<th>Study 2: Pseudophakic Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ILUVIEN</strong> (N=124)</td>
<td><strong>ILUVIEN</strong> (N=66)</td>
</tr>
<tr>
<td><strong>Sham</strong> (N=61)</td>
<td><strong>Sham</strong> (N=34)</td>
</tr>
<tr>
<td><strong>Mean change from baseline in BCVA (n (%))</strong></td>
<td><strong>Mean change from baseline in BCVA (n (%))</strong></td>
</tr>
<tr>
<td>7.1 (14.5)</td>
<td>5.6 (0.7, 10.6)</td>
</tr>
<tr>
<td>1 (-2.5, 4.4)</td>
<td>2.5% (95% CI)</td>
</tr>
<tr>
<td>12.1% (2.4%, 21.6%)</td>
<td>3.5% (1.5%, 5.5%)</td>
</tr>
<tr>
<td>10% (1.8%, 15.1%)</td>
<td>3.2 (2.8, 6.3)</td>
</tr>
<tr>
<td>16.8% (15.2, 18.4)</td>
<td>13.0% (2.7%, 23.4%)</td>
</tr>
<tr>
<td>6.1 (14.1, 10.8)</td>
<td>6.1 (14.1, 10.8)</td>
</tr>
</tbody>
</table>

*Study 1: ILUVIEN, N=190; Sham, N=95
*Study 2: ILUVIEN, N=186; Sham, N=90

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 2 and Figure 3. The occurrence of cataracts impacted visual acuity during the study. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the Month 24 study visit.

### Table 4: Visual Acuity outcomes at Month 24 (All randomized subjects with LOCF)

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>ILUVIEN</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Gain of ≥15 letters in BCVA (n (%))</td>
<td>53 (27%)</td>
<td>14 (15%)</td>
<td>12.1% (2.6%, 21.6%)</td>
</tr>
<tr>
<td>2nd</td>
<td>Loss of ≥15 letters in BCVA (n (%))</td>
<td>26 (14%)</td>
<td>5 (5%)</td>
<td>8.6% (1.3%, 15.1%)</td>
</tr>
<tr>
<td>Mean change from baseline in BCVA (SD)</td>
<td>3.7 (18.7)</td>
<td>3.2 (23.1)</td>
<td>1.8 (2.8, 6.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Study 1: ILUVIEN, N=130; Sham, N=95
*Study 2: ILUVIEN, N=126; Sham, N=90

The BCVA outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 24 are presented in Table 5.