RETISERT is surgically implanted into the posterior segment of the eye. Nearly all phakic patients are expected to develop cataracts and require cataract surgery. The most common non-ocular event reported was headache. Ocular adverse events included procedural complications, and eye pain (> 50%). Thirty-five to forty percent of patients reported ocular/conjunctival hyperemia, reduced visual acuity, and conjunctival hemorrhage. The most common non-ocular event was headache (33%). The most common serious ocular adverse event was cataract.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

**WARNINGS AND PRECAUTIONS**

- **Cataract Formation:** Nearly all phakic patients are expected to develop cataracts and require cataract surgery. (5.1)
- **Endophthalmitis:** Late onset endophthalmitis has been observed. (5.2)
- **Increased Intraocular Pressure:** Use of corticosteroids may result in elevated IOP and/or glaucoma. (5.3) IOP lowering medications were required in > 75% of patients; filtering surgeries were required in > 35% of patients. (6.1)
- **Separation of implant components:** Physicians should periodically monitor the integrity of the implant by visual inspection. (5.4)

- **ADVERSE REACTIONS**
  - Ocular adverse events included procedural complications, and eye pain (> 50%). Thirty-five to forty percent of patients reported ocular/conjunctival hyperemia, reduced visual acuity, and conjunctival hemorrhage. (6.1)
  - The most common non-ocular event was headache (33%). (6.2)

- **CONTRAINDICATIONS**
  - Surgical placement of RETISERT is contraindicated in active viral, bacterial, mycobacterial and fungal infections of ocular structures. (4.1)

- **DOSE AND ADMINISTRATION**
  - **Dosage Information:**
    - For the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. (4.1)

- **DOSAGE FORMS AND STRENGTHS**
  - 0.59 mg fluocinolone acetonide intravitreal implant. (3)

- **STORAGE AND HANDLING**
  - RETISERT should not be resterilized by any method.

- **HOW SUPPLIED/STORAGE AND HANDLING**
  - RETISERT (fluocinolone acetonide intravitreal implant) 0.59 mg for intravitreal use

- **INDICATIONS AND USAGE**
  - **INDICATIONS AND USAGE**
    - **RETISERT (fluocinolone acetonide intravitreal implant) 0.59 mg for intravitreal use**
      - **Initial U.S. Approval:** 1963
      - **RETISERT**
      - **Surgical Technique:**
        - Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure. (2.2)

- **WARNINGS AND PRECAUTIONS**
  - **OCULAR USE:**
    - **Cataract Formation:**
      - Nearly all phakic patients are expected to develop cataracts and require cataract surgery. (5.1)
    - **Endophthalmitis:**
      - Late onset endophthalmitis has been observed. (5.2)
    - **Increased Intraocular Pressure:**
      - Use of corticosteroids may result in elevated IOP and/or glaucoma. (5.3) IOP lowering medications were required in > 75% of patients; filtering surgeries were required in > 35% of patients. (6.1)

- **DOUBLE BLEB FORMATION**
  - **Cataract Formation:**
    - Nearly all phakic patients are expected to develop cataracts and require cataract surgery.
  - **Endophthalmitis:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **INFECTIONS**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **LATE ONSET ENDOPTHALMITIS**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **OCCULAR AND CONJUNCTIVAL HYPEREMIA**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **OVERALL SERIOUSNESS**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **PERIODIC MONITORING**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **PHYSICIAN MONITORING**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **POST-OPERATIVE INFECTION**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **PREVENTION OF POST-OPERATIVE INFECTION**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **PRODUCT INFORMATION**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **SAFETY INFORMATION**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **SIDE EFFECTS**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **STORAGE AND HANDLING**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **SUMMARY INFORMATION**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **WARNINGS AND PRECAUTIONS**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **WHAT IS MULTI FACTORIAL CAUSE**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **WHITE RING RACER**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.

- **YELLOWISH RING**
  - **Cataract Formation:**
    - Late onset endophthalmitis has been observed.
  - **Increased Intraocular Pressure:**
    - Use of corticosteroids may result in elevated IOP and/or glaucoma.
Ocular adverse events occurring in approximately 5-9% of patients in decreasing order of incidence were eye discharge, photophobia, blepharitis, corneal edema, iris adhesions, chondial detachment, diplopia, eye swelling, retinal detachment, photopsia, retinal hemorrhage and hyphema.

6.2 Clinical Trials Experience - Non-Ocular Events
The most frequently reported non-ocular adverse event was headache (33%). Other non-ocular adverse events occurring in approximately 5-29% of patients in decreasing order of incidence were nasopharyngitis, arthralgia, sinusitis, dizziness, pyresis, upper respiratory tract infection, influenza, vomiting, nausea, cough, back pain, limb pain, and rash.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
No adequate animal reproduction studies have been conducted with fluocinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Fluocinolone acetonide when administered subcutaneously at a dose of 0.13 mg/kg/day (approximately 10,000 times the daily clinical dose of RETISERT), during days 6 to 18 of pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week. When administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 mcg/kg/day (approximately 4,000 times the clinical dose of RETISERT), fluocinolone acetonide caused abortions and malformations in a few surviving fetuses.

There are no adequate and well-controlled studies in pregnant women. RETISERT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could result in sufficient systemic absorption to produce detectable quantities in human milk.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 mcg/day, decreasing over the first month to a steady state between 0.3-0.4 mcg/day over approximately 30 months. The drug substance is the synthetic corticosteroid.

Fluocinolone acetonide is a white crystalline powder, insoluble in water, and soluble in methanol. It has a melting point of 265-266°C.

Each RETISERT consists of a tablet containing 0.59 mg of the active ingredient, Fluocinolone Acetonide, USP, and the following inactives: magnesium stearate, microcrystalline cellulose, and polyvinyl alcohol.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibrinolysis, deposition of collagen, and scar formation associated with inflammation.

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A, inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A. Corticosteroids are capable of producing a rise in intraocular pressure.

12.3 Pharmacokinetics
In a subset of patients who received the intravitreal implant, and had blood samples taken at various times (weeks 1, 4 and 34) after implantation, plasma levels of fluocinolone acetonide were below the limit of detection (0.2 ng/mL) at all times. Aqueous and vitreous humor samples were assayed for fluocinolone acetonide in a further subset of patients. While detectable concentrations of fluocinolone acetonide were seen throughout the observation interval (up to 34 months), the concentrations were highly variable, ranging from below the limit of detection (0.2 ng/mL) to 589 ng/mL.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed on RETISERT. Carcinogenic potential of the effect on fertility of fluocinolone acetonide.

Fluocinolone acetonide was not genotoxic in vitro in the Ames test, the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.

14 CLINICAL STUDIES
In a phase I, double-masked, multicenter controlled clinical trials, 224 patients with chronic (a one year or greater history) non-infectious uveitis affecting the posterior segment of one or both eyes were randomized to receive a 0.59 mg RETISERT. The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the study eye in the 34 week pre-implantation period compared to the rate of recurrence in the 34 week post-implantation period. Uveitis recurrence rates at 1, 2, and 3 year post-implantation period were also compared to the 34 week pre-implantation period.

Detailed results are shown in table 1 below:

<table>
<thead>
<tr>
<th>TIME POINT</th>
<th>STUDY 1</th>
<th>STUDY 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=108</td>
<td>N=116</td>
<td></td>
</tr>
<tr>
<td>Uveitis Recurrence Rates¹²</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>34 Weeks Pre-implantation</td>
<td>58 (53.7)</td>
<td>46 (39.7)</td>
</tr>
<tr>
<td>34 Weeks Post-implantation</td>
<td>2 (1.8)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>1 Year Post-implantation</td>
<td>4 (3.7)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>2 Years Post-implantation</td>
<td>11 (10.2)</td>
<td>16 (13.8)</td>
</tr>
<tr>
<td>3 Years Post-implantation</td>
<td>22 (20.4)</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td>3 Years* Post-implantation</td>
<td>33 (30.6)</td>
<td>28 (24.1)</td>
</tr>
</tbody>
</table>

¹ Recurrence of uveitis for all post-implantation time points was compared to the 34 weeks pre-implantation time point.
² p-value <0.01 from McNemar’s χ² test.

The results presented include imputed recurrences. Recurrences were imputed when a subject was not seen within 10 weeks of their final scheduled visit.

16 HOW SUPPLIED/STORAGE AND HANDLING
The implant consists of a tablet encased in a silicone elastomer cup containing a release orifice and a polyvinyl alcohol membrane positioned between the tablet and the orifice. The silicone elastomer cup assembly is attached to a silicone elastomer suture tab with silicone adhesive. Each RETISERT is approximately 3 mm x 2 mm x 5 mm. Each implant is stored in a clear polycarbonate case within a foil pouch within a Tyvek peelable overwrap. Each packaged implant is provided in a carton which includes the package insert.

NDC 24208-416-01 0.59 mg 1 count

Storage: Store in the original container at 15°-25°C (59°-77°F). Protect from freezing.

17 PATIENT COUNSELING INFORMATION
Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of RETISERT.

As with any surgical procedure, there is risk involved. Potential complications accompanying intravitreal surgery to place RETISERT into the vitreous cavity may include, but are not limited to, the following: two or three years post-implantation period, temporary decreased visual acuity, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.

Following implantation of RETISERT, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately one to four weeks post-operatively.

Based on clinical trials with RETISERT, within 3 years post-implantation, approximately 77% of patients will require IOP lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure [see Adverse Reactions (6.1)].

Based on clinical trials with RETISERT, during the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

Manufactured for:
Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Valeant Pharmaceuticals Ireland Limited
U/B a/ Bausch & Lomb Ireland
Waterford, Ireland

U.S. Patent Numbers: 6,217,895 and 6,548,078

Retisert is a trademark of Bausch & Lomb Incorporated or its affiliates. © Bausch & Lomb Incorporated