

Managing Chronic Idiopathic Noninfectious Uveitis Affecting the Posterior Segment

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RETISERT READY™
RETISERT® PATIENT CASE STUDY SERIES

Noninfectious uveitis involving the posterior segment—which may include intermediate, posterior, or panuveitis—may result in vision-threatening ocular complications such as cataract, glaucoma, and vitreous debris.^{1,2} Among this group of uveitic conditions, macular edema stands as the most common structural complication to threaten central vision.^{2,3} The following case describes an elderly patient with chronic idiopathic noninfectious uveitis affecting the posterior segment, which was complicated by bilateral primary open-angle glaucoma. Inflammation was initially unilateral and was manifested by cystoid macular edema (CME) following cataract surgery in the same eye; rather than resolving as frequently happens after cataract surgery, the CME worsened, and later developed in the fellow eye secondary to posterior segment inflammation. Workup was unrevealing and over the course of 3 years, the patient underwent various topical, intravitreal, systemic, and surgical treatments for the intraocular inflammation, including corticosteroids, conventional immunomodulatory therapy (IMT), and cataract and glaucoma surgeries. Continued treatment of the patient's intraocular inflammation was complicated by hypotony and choroidal detachment. With inadequate response from first-line treatments and when escalation from antimetabolite-based immunosuppression to biologic therapy was denied by the patient's insurance, we discussed the risks and potential benefits of bilateral implantation with RETISERT (fluocinolone acetonide intravitreal implant) 0.59 mg. This case explores the need for long-term control of posterior segment inflammation amid a variety of ocular comorbidities and therapeutic complications.



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Case Report: Chronic Idiopathic Noninfectious Uveitis Affecting the Posterior Segment

BACKGROUND: A 75-year-old man with a history of bilateral primary open-angle glaucoma was referred for chronic uveitis and CME in the right eye. The uveitis and CME occurred subsequent to cataract extraction and IOL placement in the right eye, and inflammation persisted despite more than a year of antiinflammatory treatment with topical nonsteroidal antiinflammatory drugs (NSAIDs) and, later, topical corticosteroid therapy. Ocular history of the patient's left eye noted only cataract.

Indication

RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is a corticosteroid indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Important Safety Information

- Surgical placement of RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is contraindicated in active viral, bacterial, mycobacterial or fungal infections of the eye.

Please see additional Important Safety Information throughout and full Prescribing Information for RETISERT® on pages 5-7.

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Retisert®
(fluocinolone acetonide
intravitreal implant) 0.59 mg

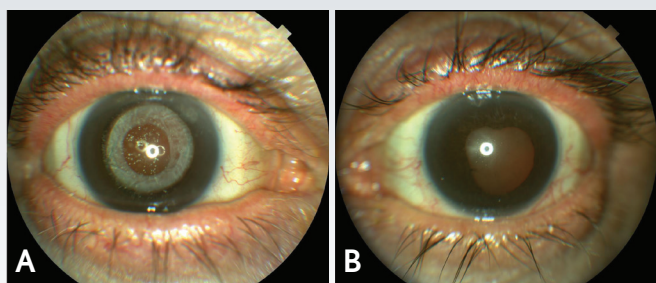


Figure 1. Slit-lamp photography. Right eye with posterior chamber IOL (A) exhibiting phimosis and asteroid hyalosis. Left eye (B) showed posterior synechiae and nuclear sclerosis.

DIAGNOSIS: At presentation, in June 2017, the patient's right eye had a BCVA of 20/70. A slit-lamp exam revealed grade 1+ anterior chamber cell as well as keratic precipitates and grade 1+ vitreous haze. A year before presentation, the patient had cataract surgery in the right eye. Phimosis now displayed with the posterior chamber IOL, and asteroid hyalosis was observable in the vitreous (Figure 1A). The patient's left eye initially presented with a BCVA of 20/25, and nuclear sclerosis of the lens and posterior synechiae were observed (Figure 1B). Both eyes initially had normal intraocular pressure. Fluorescein angiography of the right eye revealed disc leakage in a petaloid pattern (Figure 2A), indicative of CME,⁴ along with mild peripheral leakage, while the left eye was normal (Figure 2B). OCT of the right eye confirmed CME (Figure 3).

The patient underwent a number of laboratory tests, including interferon gamma release assay and fluorescent treponemal antibody absorption, which yielded results negative for tuberculosis or syphilis, reducing the possibility for infectious uveitides.⁵ Results of an angiotensin converting enzyme assay were borderline high but, paired with a normal lysozyme assay and a normal chest x-ray, indicated a low probability of sarcoidosis.⁶ A test for human leukocyte antigen B27 was also negative. In addition, a complete blood count and a complete metabolic panel both returned normal results.

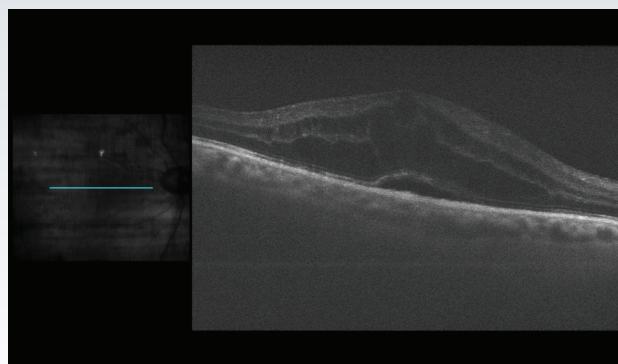


Figure 3. Spectral domain OCT B-scan of the right eye at presentation visit. Confirmed angiographic finding of CME, considered secondary to uveitis.

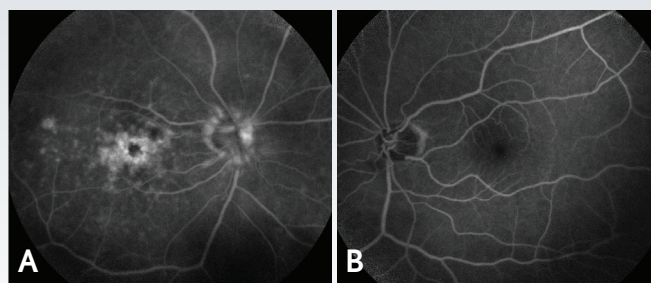


Figure 2. Fluorescein angiograms at presentation. Right eye (A) showed disc leakage indicative of CME secondary to uveitis, along with mild peripheral leakage (not pictured). Left eye (B) was normal.

Based on the ocular history, clinical findings, and laboratory tests, the patient was diagnosed with chronic idiopathic noninfectious anterior and intermediate uveitis of the right eye, with CME progression secondary to uveitis affecting the posterior segment.

TREATMENT: The patient elected to receive a periocular corticosteroid injection for his posterior segment uveitis. One month after the first injection, in July 2017, the patient's right eye BCVA was 20/32, and examination revealed no anterior chamber or vitreous inflammation. An OCT also showed improvement—but not complete resolution—of CME. IOP measured 19 mm Hg in the right eye and 18 mm Hg in the left eye. In follow-up 2 months later, the patient's CME had worsened (Figure 4). As this worsening indicated inadequate uveitic control, the patient underwent a second injection, in the right eye. By October 2017, the CME had improved (Figure 5) but was accompanied by an increase in IOP, and the patient was referred to a glaucoma specialist.

The patient was lost to follow-up until March 2018, at which time his chronic right-eye uveitis had become active again despite continued treatment with topical corticosteroid therapy, and the CME had returned. We began planning treatment with an intravitreal corticosteroid. In the meantime, more aggressive topical therapy was instituted, but this resulted in IOP increases, and the right-eye CME continued to worsen. In light of the risks of glaucomatous progression and the need to continue antiinflammatory therapy, the patient received a tube shunt in the right eye prior to treatment with intravitreal corticosteroids. Around the same time, the patient also underwent cataract surgery in the left eye. Subsequently, idiopathic uveitis involving the anterior and posterior segments developed in the left eye. Secondary CME also appeared then worsened in both eyes over the next four months, indicating inadequate control of bilateral uveitis on a chronic course. Systemic corticosteroid therapy began (limited to 40 mg/day due to systemic side effects)—but his ocular inflammation still did not improve.

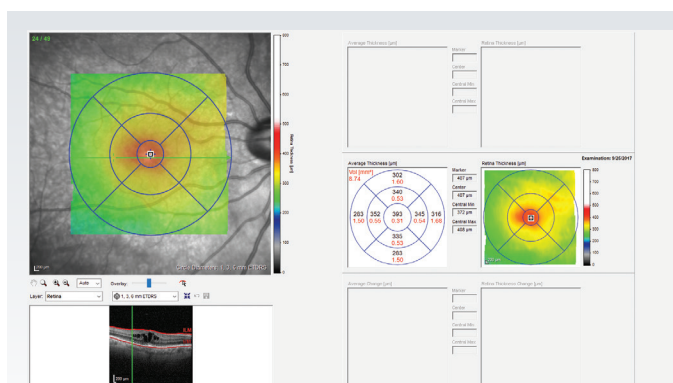


Figure 4. Retinal thickness map and spectral domain OCT B-scan 3 months following first injection of a periocular corticosteroid in the right eye. Although initial improvement was seen 1 month following injection, CME had worsened in second follow-up, indicating insufficient inflammatory control.

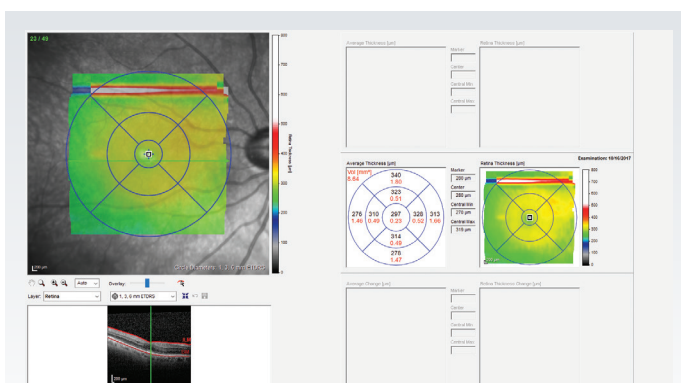


Figure 5. Retinal thickness map and spectral domain OCT B-scan 3 weeks following second injection of a periocular corticosteroid in the right eye. Inflammatory activity was decreased, and secondary CME showed improvement, although accompanied by IOP increases, posing the risk of glaucomatous progression.

After eventual intravitreal corticosteroid therapy in the right eye, hypotony (4 mm Hg) and choroidal detachment (which subsequently resolved) resulted. We now began steroid-sparing IMT with an antimetabolite-based immunosuppressant.

By March 2019, uveitis became worse in the left eye, which also showed IOP elevation. Due to the risk of IOP elevation, a sub-Tenon's corticosteroid injection was given to the left eye rather than an intravitreal corticosteroid. However, IOP in the left eye increased to 41 mm Hg; so in April 2019, the patient had a tube shunt implanted in the left eye to control glaucomatous progression.

The IMT regimen was escalated to full dose in May 2019, as the CME continued to progress in both eyes. In the continued absence of adequate inflammatory control, intravitreal corticosteroids were tried and retried in both eyes over the next 6 months with some limited duration of improvement. We discussed escalating the IMT but insurance denied the prescription.

The patient was lost to follow-up until the summer of 2020 due to the COVID-19 pandemic.

WHY RETISERT? The patient had chronic uveitis involving the posterior segment that was unresponsive to multiple treatments over a period of 3 years. It was critical to achieve long-term control of inflammation in order to spare the patient's sight. While already on full-dose IMT, the patient was unable to escalate to a biologic (adalimumab) because of insurance.

Nearly all phakic eyes are expected to develop cataracts and require cataract surgery during the 3-year postimplantation period.⁷ However, this patient already had bilateral cataract surgery: in the right eye 3 years prior to RETISERT implantation, and in the left eye over a year prior. RETISERT can also cause IOP elevation, but the patient had already had tube-shunt surgery to lower the risk of IOP elevation. In addition, many patients experience immediate and temporary loss of visual acuity lasting from one to four weeks after implantation with RETISERT.⁷ In the pursuit of long-term inflammatory control of noninfectious uveitis of the posterior segment, he appeared to be a good candidate for RETISERT, which is designed to deliver fluocinolone acetonide over a period of 30 months. The risks and benefits of RETISERT were reviewed with the patient, and he elected to receive a RETISERT implant in his right eye, which was placed in July 2020.

Important Safety Information (cont'd)

- 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.
- As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place RETISERT® into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, 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.

Please see additional Important Safety Information throughout and full Prescribing Information for RETISERT® on pages 5-7.

Retisert®
(fluocinolone acetonide
intravitreal implant) 0.59 mg

The patient's health insurance delayed approval of RETISERT for the left eye, and so in August 2020 a fourth corticosteroid intravitreal implant was placed in the left eye. In December 2020 the patient's left eye was also implanted with RETISERT.

PATIENT FOLLOW-UP: In February of 2021 the patient's follow-up visit revealed a BCVA in the right eye of 20/150 with an IOP of 8 mm Hg. In the left eye BCVA was 20/80 with an IOP of 9 mm Hg. The right eye demonstrated trace pseudophakic capsule opacification (PCO) and asteroid hyalosis. The PCO in the left eye was more serious, with a grade of 3+. No signs of posterior segment inflammation were observed in either eye. The secondary CME had improved in both eyes (Figure 6).

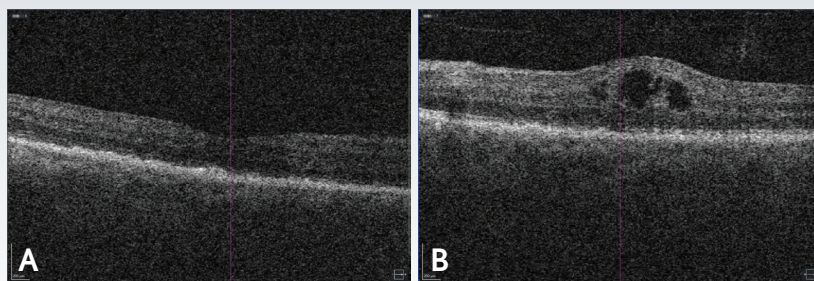


Figure 6. Latest (February 2021) spectral domain OCT B-scans following time-offset RETISERT implantation in each eye. On last follow-up, 7 months after implantation in the right eye and 2.5 months after implantation in the left eye, the posterior segment was quiet bilaterally. There was also resolution of secondary CME in the right eye (A) and dramatic improvement in the left eye (B).

In the early follow-up period, the patient is continuing with IMT until prolonged quiescence and stability is observed. To address the PCO in the left eye, a Nd:YAG laser capsulotomy is planned.

Conclusions

This case study describes an elderly pseudophakic patient who presented with chronic idiopathic noninfectious anterior and intermediate uveitis, with progressive CME secondary to uveitis affecting the posterior segment. Because systemic corticosteroid therapy and IMT failed to control his uveitis, the patient was deemed a good candidate for RETISERT for control of posterior segment inflammation.⁷ This patient was pseudophakic and status post tube shunt surgery bilaterally. Given inadequate response following first-line therapy, IMT, and multiple routes of corticosteroid administration, RETISERT was considered this patient's best option for long-term inflammatory control.⁷

Important Safety Information (cont'd)

- Use of corticosteroids may result in elevated IOP and/or glaucoma. 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.
- Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of RETISERT®. Physicians should periodically monitor the integrity of the implant by visual inspection.
- Ocular administration of corticosteroids has been associated with delayed wound healing and perforation of the globe where there is thinning of the sclera.
- The most frequently reported ocular adverse events in clinical trials with RETISERT® occurring in 50-90% of patients included: cataract, increased intraocular pressure, procedural complications and eye pain. The most common non-ocular event reported was headache (33%).

Please see additional Important Safety Information throughout and full Prescribing Information for RETISERT® on pages 5-7.

References: 1. Luo L, Yang J, Oh Y, et al. Controlled release of corticosteroid with biodegradable nanoparticles for treating autoimmune uveitis. *J Control Release*. 2019;296:68-80. 2. Dick AD, Tundia N, Sorg R, et al. Risk of ocular complications in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology*. 2016;123(3):655-662. 3. Grzybowski A, Sikorski BL, Ascaso FJ, Huerva V. Pseudophakic cystoid macular edema: update 2016. *Clin Interv Aging*. 2016;11:1221-1229. 4. American Academy of Ophthalmology. Cystoid macular edema. https://eyewiki.aao.org/Cystoid_Macular_Edema. Published August 8, 2019. Accessed March 3, 2021. 5. Lin P. Infectious uveitis. *Curr Ophthalmol Rep*. 2015;3(3):170-183. 6. American Academy of Ophthalmology. Sarcoid uveitis. http://eyewiki.aao.org/Sarcoid_Uveitis. Updated February 11, 2021. Accessed March 3, 2021. 7. RETISERT Prescribing Information. Bausch & Lomb Incorporated.

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Retisert®
(fluocinolone acetonide
intravitreal implant) 0.59 mg

Retisert®

(fluocinolone acetonide
intraocular implant) 0.59 mg
STERILE

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RETISERT safely and effectively. See full prescribing information for RETISERT.

RETISERT (fluocinolone acetonide intraocular implant) 0.59 mg for intraocular use
Initial U.S. Approval: 1963

INDICATIONS AND USAGE

RETISERT is a corticosteroid indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. (1)

DOSAGE AND ADMINISTRATION

- RETISERT is surgically implanted into the posterior segment of the affected eye through a pars plana incision. (2.1)
- RETISERT is designed to release fluocinolone acetonide 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. (2.1)
- Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure. (2.2)

DOSAGE FORMS AND STRENGTHS

- 0.59 mg fluocinolone acetonide intraocular implant. (3)

CONTRAINDICATIONS

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

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)
- Increase in 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 reported was headache (33%). (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RETISERT is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

RETISERT (fluocinolone acetonide intraocular implant) 0.59 mg is implanted into the posterior segment of the affected eye through a pars plana incision.

The implant contains one tablet of 0.59 mg of fluocinolone acetonide. RETISERT is designed to release fluocinolone acetonide 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. Following depletion of fluocinolone acetonide as evidenced by recurrence of uveitis, RETISERT may be replaced.

2.2 Handling of Implant

Caution should be exercised in handling RETISERT in order to avoid damage to the implant, which may result in an increased rate of drug release from the implant. Thus, RETISERT should be handled only by the suture tab. Care should be taken during implantation and explantation to avoid shear forces on the implant that could disengage the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the suture tab. Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure.

RETISERT should not be resterilized by any method.

3 DOSAGE FORMS AND STRENGTHS

0.59 mg fluocinolone acetonide intraocular implant.

4 CONTRAINDICATIONS

4.1 Viral, Bacterial, Mycobacterial and Fungal Infections of Ocular Structures
Surgical placement of RETISERT is contraindicated in active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in active bacterial, mycobacterial or fungal infections of the eye.

5 WARNINGS AND PRECAUTIONS

5.1 Cataract Formation

Use of corticosteroids may result in posterior subcapsular cataract formation.

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.

5.2 Endophthalmitis and Surgical Complications

Late onset endophthalmitis has been observed. These events are often related to the integrity of the surgical wound site. Careful attention to assure tight closure of the scleral wound and the integrity of the overlying conjunctiva at the wound site is important.

Potential complications accompanying intraocular surgery to place RETISERT into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, 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.

5.3 Increase in Intraocular Pressure

Prolonged use of corticosteroids may result in elevated IOP and/or glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Patients must be monitored for elevated IOP.

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)].

5.4 Separation of Implant Components

In vitro stability studies show that the strength of the adhesive bond between the silicone cup reservoir and the suture tab is reduced with prolonged hydration, indicating a potential for the separation of these components. The suture tab composition is a silicone elastomer reinforced with a polyester mesh. Physicians should periodically monitor the integrity of the implant by visual inspection.

5.5 Other Corticosteroid Induced Adverse Reactions

RETISERT should be used with caution in patients with a history of a viral, bacterial, mycobacterial or fungal infection of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia and varicella. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections (bacterial, fungal, and viral). In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term application of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used.

Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation should not be carried out, in order to limit the potential for bilateral post-operative infection.

Ocular administration of corticosteroids has also been associated with delayed wound healing and perforation of the globe where there is thinning of the sclera.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience - Ocular Events

The available safety data includes exposure to RETISERT in patients with chronic non-infectious uveitis affecting the posterior segment in two multicenter controlled clinical trials. Patients were randomized to dosage regimens of 0.59 mg or 2.1 mg implants.

The most frequently reported ocular adverse events were cataract, increased intraocular pressure, procedural complication, and eye pain. These events occurred in approximately 50 - 90% of patients. Cataract includes aggravated cataract, and posterior capsular opacification. Procedural complications includes post-op complication, post-op wound complication, post-op wound site erythema, and wound dehiscence.

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. IOP lowering medications to lower intraocular pressure were required in approximately 77% of patients; filtering surgeries were required to control intraocular pressure in 37% of patients. Ocular adverse events occurring in approximately 10 - 40% of patients in decreasing order of incidence were ocular/conjunctival hyperemia, reduced visual acuity, glaucoma, conjunctival hemorrhage, blurred vision, abnormal sensation in the eye, eye irritation, maculopathy, vitreous floaters, hypotony, pruritus, ptosis, increased tearing, vitreous hemorrhage, dry eye, eyelid edema, macular edema and visual disturbance.

Ocular adverse events occurring in approximately 5 - 9% of patients in decreasing order of incidence were eye discharge, photophobia, blepharitis, corneal edema, iris adhesions, choroidal 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 5-20% of patients in decreasing order of incidence were nasopharyngitis, arthralgia, sinusitis, dizziness, pyrexia, 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 suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when RETISERT is implanted in a nursing woman.

8.4 Pediatric Use

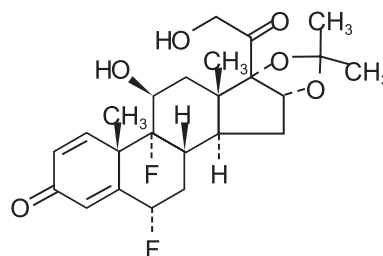
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

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, represented by the following structural formula:



C₂₄H₃₀F₂O₆ Mol. Wt. 452.50

Chemical Name: Pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy-16,17-[(1-methyl-ethylidene)bis(oxy)],(6 α ,11 β ,16 α)-.

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 inactive: 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, fibroblast proliferation, 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 A₂ 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 A₂. 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 to evaluate the carcinogenic potential or 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 two randomized, 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 were also compared to the 34 week pre-implantation period.

Detailed results are shown in Table 1 below:

Table 1: Uveitis Recurrence Rates

TIME POINT	STUDY 1	STUDY 2
	N=108	N=116
	Uveitis Recurrence Rates ^{1,2} N (%)	
34 Weeks Pre-implantation	58 (53.7)	46 (39.7)
34 Weeks Post-implantation	2 (1.8)	15 (12.9)
1 Year Post-implantation	4 (3.7)	15 (12.9)
2 Years Post-implantation	11 (10.2)	16 (13.8)
3 Years Post-implantation	22 (20.4)	20 (17.2)
3 Years ³ Post-implantation	33 (30.6)	28 (24.1)

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 χ^2 test.

³ 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 intraocular surgery to place RETISERT into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, 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 Incorporated
Bridgewater, NJ 08807 USA

Manufactured by:

Bausch Health Ireland Limited
d/b/a Bausch & Lomb Ireland
Waterford, Ireland

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Retisert®
(fluocinolone acetonide
intravitreal implant) 0.59 mg