See What's Possible

BAUSCH + LOMB

Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

Please see additional Important Safety Information and accompanying full Prescribing Information.

Indication

RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is used to treat inflammation in the back of the eye that is not caused by an infection, called chronic non-infectious uveitis.

Important Safety Information

- RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg should not be used if you have an infection of the eye from viruses, bacteria, fungi or fungal diseases.
- After receiving the RETISERT® implant, you should periodically see an eye doctor for follow-up examinations of both eyes.
- As with any surgical procedure, there is risk involved. Complications can include injury to the eye; infection; mechanical complication, movement or ejection of the implant; and wound complications following the surgery.
- After receiving the RETISERT® implant, nearly all patients will experience an immediate and temporary decrease in vision in the implanted eye that lasts for approximately 1 to 4 weeks following the surgery.
- Based on clinical studies, within 3 years after receiving the RETISERT® implant, approximately 77% of patients require medications to lower pressure in the eye, and approximately 37% of patients will require a surgical procedure to control pressure in the eye.
- Long-term use of corticosteroids may result in an increased risk of glaucoma (high pressure in the eye).
- Based on clinical studies, within 3 years after receiving the RETISERT® implant, nearly all patients who have not already had cataracts will develop them and require surgery.
- The most common side effects, occurring in 50-90% of patients, were cataract, increased pressure in the eye, surgery complications and eye pain. Headache was also reported in 33% of patients.

You are encouraged to report negative side effects to the FDA at **www.fda.gov/medwatch** or **1-800-FDA-1088**.

Please see additional Important Safety Information and accompanying full Prescribing Information.

Retisert®
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Understanding Uveitis

Your doctor is talking to you about treatment options because you have been diagnosed with chronic noninfectious uveitis affecting the back of your eye.

What Is Uveitis?

Uveitis is inflammation inside the eye that affects the uvea (the middle layer of the eye). Uveitis can occur in several locations, such as the front (anterior uveitis) or the back (posterior uveitis) of the eye.[1]

The 2 types of uveitis[2]

Infectious uveitis is caused by a viral, bacterial, or other type of infection

Noninfectious uveitis is not caused by a virus or bacteria and the exact cause of the inflammation may be unknown

Common symptoms of uveitis[1,2]

- Eye pain
- Eye redness
- Sensitivity to light
- Dark, floating spots in your field of vision (floaters)
- Blurred vision
- Loss of vision that gets worse over time

Uveitis is often a chronic disease, meaning that the symptoms you experience may be persistent, lasting for months or years. You might also have "flare-ups" of inflammation that can last for short or long periods. Uveitis can cause serious damage, possibly leading to permanent vision loss.[3] Early diagnosis and treatment are important because of the complications caused by the chronic inflammation of uveitis.[3-5]

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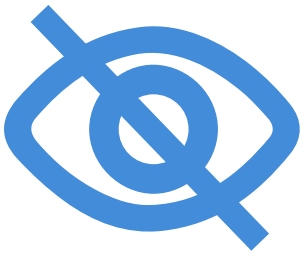
How Can Chronic Inflammation Lead to Vision Loss Over Time?

Uveitis in the back of the eye is a serious condition. Each time a flare-up of inflammation happens it can damage the ocular tissue. This damage can add up over time. After a period of months or years, the ocular tissue can be so badly damaged that it can lead to permanent vision loss, and sometimes blindness.[3,4]

In the United States, up to 20% of all blindness is caused by uveitis.[5] Some people with uveitis in the back of the eye develop vision loss or, in some cases, progress to legal blindness.[4] The definition of legal blindness is vision loss that cannot be corrected to the acuity of 20/200 or better in the better eye, or if your visual field is 20 degrees or less in your better eye.[6]



Up to 20%

of all blindness is caused by uveitis[5]

How Can You Reduce Your Risk of Recurrent Inflammation?

One way to decrease the risk of damage that adds up over time is to keep the inflammation in your eye under control.[3] Because noninfectious uveitis in the back of the eye is a chronic condition, you may require treatment for months to years and medical supervision to manage inflammation.[7,8]

By managing the number of times a flare-up happens, the damage from uveitis to the ocular tissue can remain stable. There are many different types of treatments that can help control inflammation. A treatment that may significantly reduce inflammation and then possibly keep it under control for a long period of time may be a good treatment option.[8]

However, it is still possible for you to have a flare-up while being treated for chronic noninfectious uveitis in the back of the eye. If this does happen, it's very important to talk to your doctor about other options to manage your risk of serious damage.

Please see additional Important Safety Information and accompanying full Prescribing Information.

Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

Treatment Options for Noninfectious Uveitis in the Back of the Eye

How Is this Condition Usually Treated?

The first goal of treating uveitis is to decrease inflammation in the eye.[2,9] Treatment options for uveitis include corticosteroid and corticosteroid-sparing therapeutic agents. The choice of appropriate therapy is different depending on the cause, location, and severity of the uveitis. Most importantly, the goal of any uveitis treatment is to treat the condition in a way that may balance the potential risk of treatment.[10]

Corticosteroids

The main drug used to treat uveitis is called a corticosteroid.[2,9] Corticosteroids work by reducing the inflammation in the eye and come in different forms[2,9]:

- Eyedrops
- Oral tablets
- Injections into the eye
- Drug implants

Please see additional Important Safety Information and accompanying full Prescribing Information.

Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

Delivery Methods for Corticosteroids

The form, or delivery method, of the corticosteroid depends on the type of uveitis a person has. The main difference comes from how the drug is delivered to the specific area of inflammation.

Eyedrops[2,9]

Corticosteroid eyedrops are sometimes used to treat uveitis in the front of the eye. These drops have little or no effect on inflammation in the back of the eye because they are not designed to reach the affected area.

Injections[9]

Corticosteroids can also be delivered through an injection either right around the eye (periocular injection) or directly into the eye (intraocular injection). The effects of these injections typically last for 3 months, and some patients may require multiple injections.

Oral tablets[2]

An oral corticosteroid is a tablet taken by mouth. It reaches the eye by first entering the stomach, then the bloodstream and other parts of the body, and eventually the drug reaches the back of the eye. These tablets may affect the whole body and not just the inflammation in the eye. This means that they may cause side effects in other parts of the body.

Drug implants

Drug implants are drug-delivery systems placed in the eye by surgery or injection. They are designed to continuously deliver small amounts of corticosteroid to the inflamed area in the back of the eye. A variety of implants are currently available. Depending on the type of implant your doctor prescribes for you, the drug in the implant is delivered to your eye for anywhere from a few months to a few years.[9] While treatment with a drug implant is meant to reduce side effects in other parts of the body, the implant may cause some serious side effects to the eye because of its targeted delivery system, as well as some potential side effects to other parts of the body.[11,12] Talk to your eye doctor about side effects of any chosen course of therapy.

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Steroid-sparing Agents[10]

Steroid-sparing agents such as cyclosporine, methotrexate, and cyclophosphamide, may be used instead of corticosteroids or together with reduced amounts of corticosteroids. Biologic agents, such as infliximab and adalimumab, are a type of steroid-sparing therapy that is designed to target specific components of the immune system. These agents often act similarly to substances that occur naturally within the body. Like steroids, steroid-sparing and biologic agents work by reducing or preventing the inflammation that causes tissue damage during noninfectious uveitis. Typically, these medications are used to manage uveitis that is severe or that does not get better with other types of therapies.

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Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

What Is RETISERT®
(fluocinolone acetonide intravitreal implant) 0.59 mg?

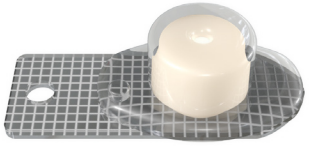
RETISERT® is very small, about the size of a grain of rice, and is surgically placed in the eye so it can deliver medicine directly to the back of the eye.

The RETISERT® implant slowly releases a corticosteroid called fluocinolone acetonide for approximately

RETISERT® actual size

RETISERT® is surgically implanted in the eye, in a hospital outpatient setting. In most cases, the procedure takes approximately 1 hour. After a short recovery period in the surgery center, you can usually go home the same day.

Two Views of RETISERT® and Its Delivery System



Top view

Side view

Important Safety Information

RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg should not be used if you have an infection of the eye from viruses, bacteria, fungi or fungal diseases.

After receiving the RETISERT® implant, you should periodically see an eye doctor for follow-up examinations of both eyes.

As with any surgical procedure, there is risk involved. Complications can include injury to the eye; infection; mechanical complication, movement or ejection of the implant; and wound complications following the surgery.

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Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

RETISERT® is an important choice to consider for the treatment of chronic noninfectious uveitis. It has been shown to provide consistent control of inflammation by delivering medication to the back of the eye, exactly where it is needed.[12]

Is RETISERT®

(fluocinolone acetonide intravitreal implant) 0.59 mg

an Effective Treatment?

RETISERT® has been tested in clinical studies and is approved by the FDA for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye[12]:

In 2 clinical studies of 224 patients, additional episodes of inflammation

decreased by more than 50%

at 3 years after treatment with RETISERT®[12]

- During the course of treatment with RETISERT® in clinical trials, patients had less of a need for additional medications to control inflammation in the eye, such as oral corticosteroids or corticosteroid injections around or in the eye[3,13]

The effect of RETISERT® on patient vision was an additional measure in the same 2 clinical trials of 224 patients[3]:

8/10

patients had improved or stabilized vision

- Individual results may vary

The Multicenter Uveitis Steroid Treatment (MUST) Trial[14]

An independent study conducted by the National Eye Institute showed that noninfectious uveitis patients treated with RETISERT® had a similar improvement in vision compared to patients who were treated with systemic anti-inflammatory medications.

- RETISERT® patients were more likely to need cataract surgery and treatment for increased intraocular pressure (IOP) compared to patients treated with systemic therapy

Please see additional Important Safety Information and accompanying full Prescribing Information.

Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

Possible Side Effects

Corticosteroid treatments, such as implantation of the RETISERT® intravitreal implant, can cause side effects like cataract formation or high intraocular pressure. Other side effects may also occur.[12]

Nearly all patients who have not already had cataracts develop them and require surgery within 2 to 3 years after implantation of the RETISERT® intravitreal implant.[12]

You should be sure to talk to your eye doctor about all possible side effects and risks related to the use of RETISERT® intravitreal implant.

What Is a Cataract?

The lens of the eye focuses the light that passes through to the retina at the back of the eye and allows us to see clearly—it is supposed to be clear. A cataract is a clouding of the lens that can cause problems with your vision.[15]

The many causes of cataracts

- Aging[15]
- Treatment with corticosteroids[12]
- Uveitis in the back of the eye can also cause cataracts as inflammation gets worse[16]

Cataracts can be corrected by the removal of the natural lens in your eye that is clouded. It is replaced with an artificial lens, called an intraocular lens. An intraocular lens is a clear plastic lens that requires no care and becomes a permanent part of your eye. You won't be able to feel or see the new lens.[15] Once a natural lens is replaced, cataracts will not return.[17]

Important Safety Information

After receiving the RETISERT® implant, nearly all patients will experience an immediate and temporary decrease in vision in the implanted eye that lasts for approximately 1 to 4 weeks following the surgery.

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Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

What Is Elevated Intraocular Pressure?

Intraocular pressure, or IOP for short, is the measurement of the pressure of the fluid inside the eyes. This fluid provides nourishment to the cornea, iris, and lens, and allows the eyes to maintain their round shape. The amount of fluid that is produced in the eye, the way it travels through the eye, and how it is removed from the eye all affect IOP.[18]

Chronic inflammation from uveitis can cause an increase in IOP above what is considered healthy. Some medications, such as corticosteroids, can also cause elevated IOP. When the IOP is elevated, there is too much pressure inside the eye, which can cause problems.[18]

This increase in IOP can cause a serious condition called glaucoma. This condition can cause damage to the nerve in the eye, leading to vision loss or even blindness.[18]

A person with uveitis, or someone with a RETISERT® implant, should have their IOP checked regularly and treated as needed. Glaucoma can be managed with medication or with surgery.

Important Safety Information

Based on clinical studies, within 3 years after receiving the RETISERT® implant, approximately 77% of patients require medications to lower pressure in the eye, and approximately 37% of patients will require a surgical procedure to control pressure in the eye.

Long-term use of corticosteroids may result in an increased risk of glaucoma (high pressure in the eye).

Please see additional Important Safety Information and accompanying full Prescribing Information.

Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

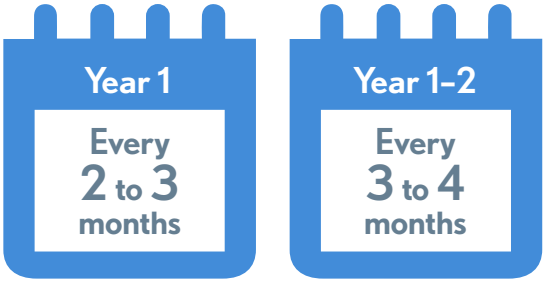
What Can I Expect During and After RETISERT® Surgery?

The procedure used to implant RETISERT® is performed in an outpatient setting. This means that you will usually be able to go home the same day and you will not have to be hospitalized. Only local anesthesia may be used to numb your eye, sparing you the risks associated with general anesthesia.

After surgery

A decrease in vision should be expected for approximately 1 to 4 weeks after surgery before there is improvement. Your doctor will want to monitor your progress, examine your eyes, and look for improvements or any changes in the condition of the implanted eye.[12]

Follow-up visits:



During these follow-up visits, your doctor will check your eyes for[12]:

- Inflammation
- Cataract formation
- Elevated IOP
- Gains or losses in your vision

These follow-up visits are very important. Your doctor needs to check for any changes in the condition of the implanted eye. Even if you are feeling fine or your vision has improved a lot, you still need to see your doctor for follow-up care.

In addition to having your vision checked, it is very important that you be monitored for increases in eye pressure. If your eye pressure is high, your doctor can prescribe eye drops to bring the pressure down. Some people may require a surgical procedure to relieve the pressure in the eye.[12]

Please see additional Important Safety Information and accompanying full Prescribing Information.

Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

Prior to surgery, talk to your eye doctor about benefits and risks related to the use of RETISERT® intravitreal implant. Be sure to have all of your questions answered before undergoing any treatment.

Important Safety Information

As with any surgical procedure, there is risk involved. Complications can include injury to the eye; infection; mechanical complication, movement or ejection of the implant; and wound complications following the surgery.

The most common side effects, occurring in 50-90% of patients, were cataract, increased pressure in the eye, surgery complications and eye pain. Headache was also reported in 33% of patients.

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Where Can I Find Out More about Uveitis?

Suggested Websites for more information*:

American Uveitis Society

www.uveitissociety.org

Prevent Blindness America

www.preventblindness.org

National Eye Institute

www.nei.nih.gov/health

See What's Possible

Please see additional Important Safety Information and accompanying full Prescribing Information.

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1. National Eye Institute. Facts about uveitis. August 2011. https://www.nei.nih.gov/health/uveitis/uveitis. Accessed April 20, 2021. **2.** Gupta R, Murray PI. *Drugs Aging*. 2006;23:535-558. **3.** Callanan DG et al. *Arch Ophthalmol*. 2008;126:1191-1201. **4.** The Ocular Immunology and Uveitis Foundation. Glossary of terms. Uveitis. http://www.uveitis.org/patients/education/glossary/t-z#Uveitis. Accessed April 20, 2021. **5.** American Uveitis Society. Home page. 2021. https://uveitissociety.org/. Accessed April 20, 2021. **6.** US Social Security Administration. If you are blind or have low vision—how we can help. January 2014. http://www.ssa.gov/pubs/EN-05-10052.pdf. Accessed April 20, 2021. **7.** de Smet MD et al. *Prog Retin Eye Res*. 2011;30:452-470. **8.** Biscette OM et al. Uveitis diagnosis, management and treatment. *Retinal Physician*. May 2007. http://www.retinalphysician.com/printarticle.aspx?articleID=100300. Accessed April 20, 2021. **9.** Arcinue C et al. *Retina Today*. July/August 2012:72-74. **10.** Barry RJ et al. *Clin Ophthalmol*. 2014;8:1891-1911. **11.** Callanan DG. *Exp Rev Ophthalmol*. 2007;2:33-44. **12.** RETISERT Prescribing Information. Bausch & Lomb Incorporated. **13.** Sangwan VS et al. *Ophthalmol Ther*. 2014. Epub ahead of print. **14.** Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group. *Ophthalmology*. 2011;118:1916-1926. **15.** National Eye Institute. Facts about cataract. https://www.nei.nih.gov/health/cataract/. Accessed April 20, 2021. **16.** Multicenter Uveitis Steroid Treatment Trial Research Group. *Am J Ophthalmol*. 2010;149:550-561.e10. **17.** Turner TD. VisionAware™. Can a cataract come back? http://www.visionaware.org/info/your-eye-condition/cataracts/can-a-cataract-come-back/125. Accessed April 20, 2021. **18.** EyeSmart. What is ocular hypertension? American Academy of Ophthalmology. http://www.geteyesmart.org/eyesmart/diseases/ocular-hypertension.cfm. Accessed April 20, 2021.

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(fluocinolone acetonide intravitreal implant) 0.59 mg

Retisert®
(fluocinolone acetonide intravitreal 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 intravitreal implant) 0.59 mg, for intravitreal 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 intravitreal 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: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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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 intravitreal 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 sheer 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 intravitreal 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 dehiscense.

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.

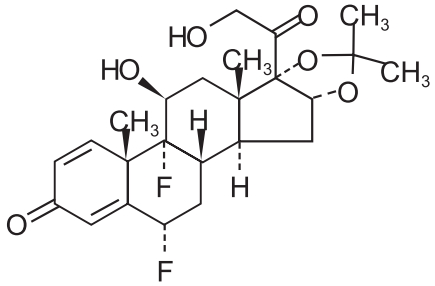
8.3 Nursing Mothers
It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or 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:



$C_{24}H_{30}F_2O_6$ 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)],(6α,11β ,16α)-.

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

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, 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 A_2 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_2. 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° to 25°C (59° to 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.

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