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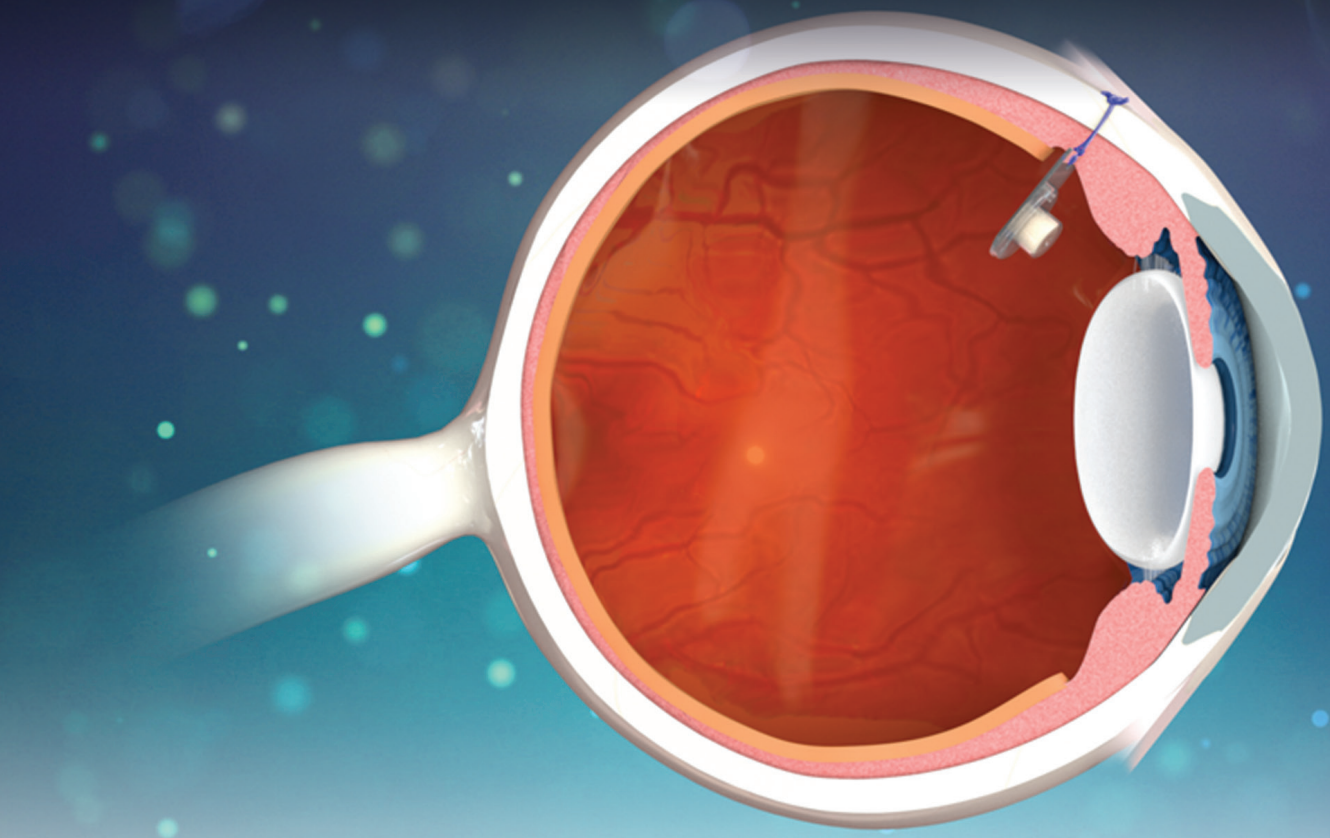

The Long-Term Management of Uveitis

Updated Information for Management of Chronic Non-Infectious Uveitis

Please see Important Safety Information on page 3 and throughout. Please see full Prescribing Information on pages 12-15.

The Long-Term Management of Uveitis

Updated Information for Management of Chronic Non-Infectious Uveitis

MODERATOR:

Thomas A. Albini, MD, is an associate professor of clinical ophthalmology at the Bascom Palmer Eye Institute in Miami. He specializes in uveitis, vitreoretinal diseases, and surgery. Dr. Albini may be reached at talbini@med.miami.edu.

FACULTY:

Quan Dong Nguyen, MD, MSc, holds the McGaw Memorial Endowed Chair in Ophthalmology and is a professor and chairman of the department of ophthalmology and the Inaugural Director of the Stanley M. Truhlsen Eye Institute at the University of Nebraska Medical Center. Dr. Nguyen is a retina surgeon and uveitis expert who specializes in the medical and surgical treatment of retinal diseases, as well as uveitis and ocular inflammatory diseases. He has served as study chair, principal investigator, and coinvestigator for numerous clinical trials in retina and uveitis. Dr. Nguyen may be reached at quan.nguyen@unmc.edu.

Sunil K. Srivastava, MD, is a vitreoretinal staff physician at the Cleveland Clinic Cole Eye Institute. Dr. Srivastava may be reached at srivass2@ccf.org.

Steven Yeh, MD, is the M. Louise Simpson Associate Professor of Ophthalmology, section of vitreoretinal surgery & diseases, at Emory Eye Center in Atlanta, Georgia. He is a consultant and advisory board member for Clearside Biomedical and a consultant to Bausch + Lomb and Santen. Dr. Yeh may be reached at steven.yeh@emory.edu.

INTRODUCTION

In some patients, uveitis is an acute condition requiring a short course of therapy. However, most of the patients with uveitis that retina and uveitis specialists see in their clinics are suffering from a chronic, long-term condition that will often require years of follow up and therapy. In uveitis, we rarely think of curative endpoints, but instead focus on helping patients control flare-ups of their disease and abating the disease process. This can sometimes require intensive therapy and complicated treatment regimens involving local and systemic agents of various classes to suppress the inflammatory response and keep it at bay.

For over 10 years, sustained-release corticosteroid implants have been available as a therapeutic option, although concerns over associated complications have limited their uptake by some physicians. However, long-term data may reinforce the utility of locally administered corticosteroids, in spite of known complications, because this treatment strategy may be able to achieve sustained, long-term control of disease. This approach may be prudent if patients can avoid the risk of systemic complications that may be associated with a course of systemic therapy.

This group of distinguished vitroretinal specialists were brought together at 2015 ARVO to discuss non-infectious posterior uveitis, review latest MUST trial data, which compare the long-term use of fluocinolone acetonide 0.59% intraocular implant (RETISERT, Bausch + Lomb) with systemic treatment.

—Thomas A. Albini, MD

Please see Indication and Important Safety Information on the following page. Please see full Prescribing Information on pages 12-15.

INDICATION AND USAGE

- 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.

- 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.

- 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 full Prescribing Information for RETISERT® on pages 12 – 15.

REVIEWING THE MUST DATA

Thomas A. Albini, MD: The 24-month follow up from the Multicenter Uveitis Steroid Treatment (MUST) Trial has been previously published.[1] The 54-month data have since been presented at a major scientific conference.[2] What have we learned from the MUST trial and why are its data relevant to our practices?

Sunil K. Srivastava, MD: There are a couple of unique features about MUST that make it particularly useful in practice. The design of MUST was unique in that it enrolled patients with recently active disease, which makes the findings applicable to practice—these are exactly the kinds of patients we are seeing in our clinics on a daily basis. In the study, patients were randomized to systemic therapy or the fluocinolone acetonide 0.59% intraocular implant (RETISERT, Bausch + Lomb), whereas many studies in uveitis tend to focus on only one active treatment arm. Moreover, multiple different therapies were used in the systemic arm, which, again, reflects how varied the approach is to uveitis in clinical practice. Another point about MUST is that we have long-term follow up out to 54 months, which is important because uveitis is not a 6 or 12 month disease.

Dr. Albini: I thought it was particularly interesting that the control arm reflected real-world utilization of systemic therapy, as opposed to some of the control arms that we see in other studies.

Dr. Srivastava: I agree. To be fair, this is also a limitation of the study, insofar as there was not a standardized comparator. In reviewing the data, it is not clear if patients may have failed multiple therapies and what particular agents were attempted. Although the data from the active arm are robust, it is a little difficult to know how adequately the control arm was treated.

Dr. Albini: That is certainly a good point, and yet, I believe there is value in comparing against how uveitis is treated in clinical practice every day. Can anyone comment on the 24- and 54-month data from this study and what we may glean from it?

Quan Dong Nguyen, MD, MSc: The results at 54 months are consistent with what was observed at 24 months: local therapy is effective for managing recently active uveitis. Both approaches to therapy were equally effective. The big takeaway at 54 months is that there were no surprises, and that the long-term data support what we learned about the importance of local therapy after the initial data read out at 24 months.

> "For specific patients, the fluocinolone acetonide 0.59% intraocular implant represents an excellent alternative to systemic medications."
>
> *—Steven Yeh, MD*

Dr. Albini: Have the results of MUST changed anyone's practice in terms of how you use the steroid implant, whether you are more confident in the implant because of the data?

Steven Yeh, MD: For specific patients, the fluocinolone acetonide 0.59% intraocular implant represents an excellent alternative to systemic medications. At 24 months of follow-up, there was a 3.2-letter gain with the implant and a 6-letter gain in the systemic therapy arm. Based on the statistical analysis, the authors correctly termed the improvements in metrics related to patient preference of the implant versus systemic therapy as "minimally important" in the 24-month analysis. And those outcomes leveled off between the two treatment arms at 54 months. In the real world clinical setting, however, patients may interpret these findings differently, and that is why I think it is important to present to patients that both options—implant and systemic therapy—are equally reasonable approaches to therapy. Before the MUST trial, we only had historically controlled clinical trial data and biologic plausibility that the implant was effective, and, as a result, some physicians may have felt reticent about using it. As well, there was legitimate concern that systemic therapy could lead to increased hospitalizations and risk of infection. In that regard, the MUST study was reassuring, both in affirming the efficacy of the

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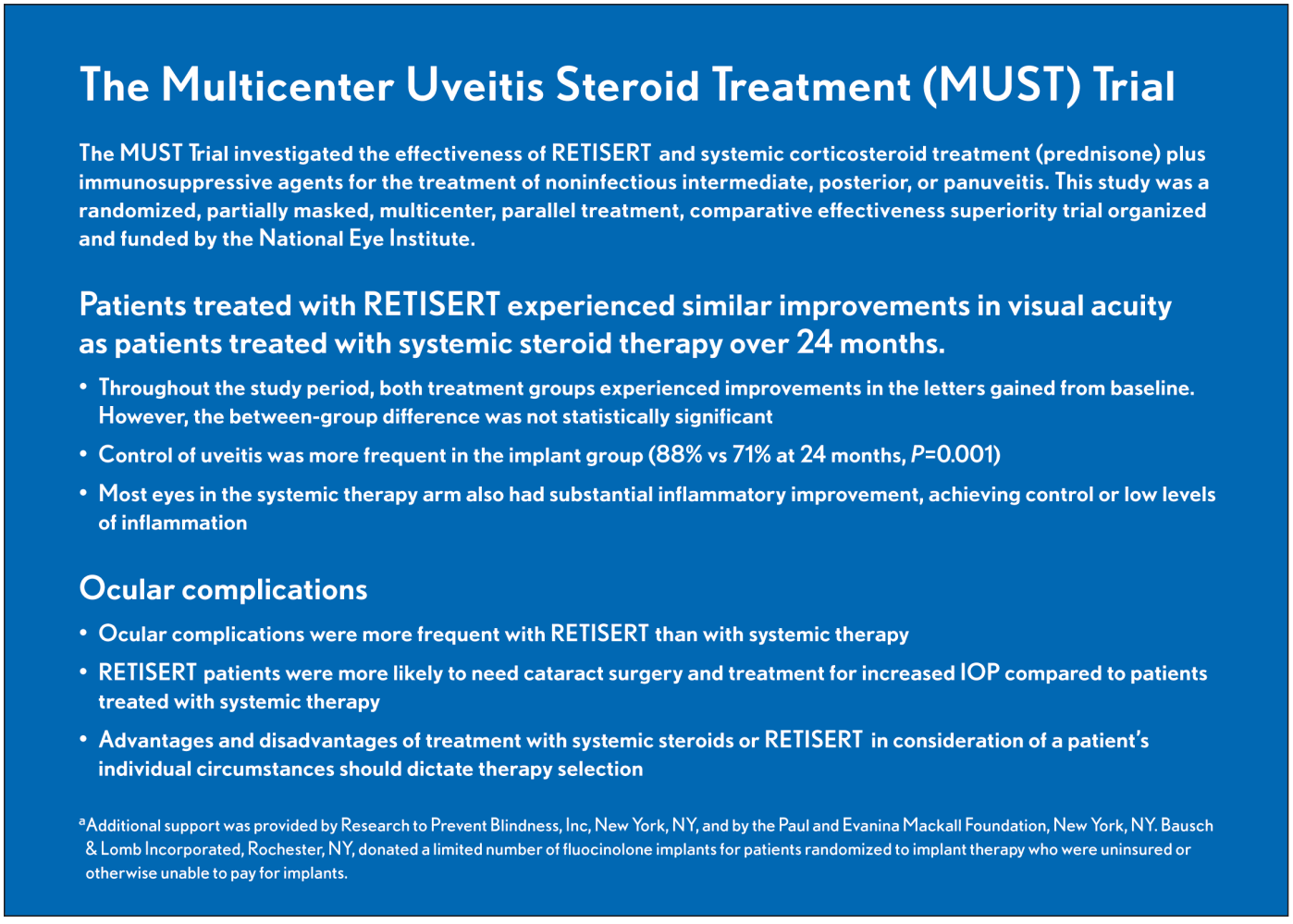

Figure 1. The fluocinolone acetonide intravitreal implant 0.59 mg outperformed systemic therapy with regard to control of inflammation.

implant, but also ensuring us that, perhaps, systemic therapy was not as risky a proposition as we thought.

Dr. Srivastava: I think you make a great point about the confidence we gain from more data. In the long-term, the treatments were about equal. If we extrapolate that to the clinical practice setting, it means that, as a result of MUST, we have reassuring clinical trial data that the implant was effective, as well as a more firm understanding that use of corticosteroids for uveitis according to expert panel recommendation is an equally reasonable choice (Figure 1).

I do, however, think there are some caveats to this line of thinking. For instance, MUST supplies us with aggregate results, and so, on average, patients with the implant or treated with systemic therapy have about the same chance of experiencing a beneficial outcome. But there is some nuance, in that patients in the systemic steroid arm required more immunosuppressive therapy through 54 months.[1] That additional medical requirement may not be a net benefit. Additionally, there will be certain circumstances where one or the other of these approaches will be more desirable to the patient. Use of the implant in MUST was associated with greater risk of cataracts and glaucoma,[3] and understandably, some patients may wish to avoid these potentialities. However, some patients may be accepting of certain risks if they perceive a benefit from treatment.

I think what all this says is that on the aggregate, patients can choose between systemic and local therapy, but there will, of course, be situations where clinicians will determine that either systemic therapy or local therapy is a better therapeutic option.

Dr. Nguyen: Dr. Srivastava brings up an intriguing point, and it makes me wonder if anyone here is more or less concerned about adverse events based on the results MUST?

Dr. Srivastava: That is an interesting question. With the

implant, the complications are somewhat predictable: progression of cataracts and about 30% to 40% of patients are going to require an intervention for pressure elevation and/or glaucoma. With systemic therapy, the complications are more unpredictable, even if we do know that they are largely tolerable (Table).

Dr. Albini: The implant clearly outperformed systemic therapy with regard to control of inflammation, which was a secondary endpoint of MUST. What is the importance of this?

Dr. Srivastava: It is very important. The side effects of inflammation are unpredictable and can have severely negative consequences, and it is well known that prolonged inflammation is a dangerous situation for our patients in terms of their ocular health. If I have a patient who is experiencing consequences of continued inflammation that I cannot control on systemic therapy, I will try the fluocinolone acetonide 0.59% intraocular implant as an option. I have found that a large majority of my patients gain control of inflammation at 12 and 24 months, and that is important clinically.

Implant therapy is substantially more expensive for bilateral disease and has more risks, therefore, systemic therapy may be the preferred initial treatment for a number of patients. However, given the control of inflammation with implant therapy, it will continue to have a role for selected cases.[1]

PATIENT SELECTION

Dr. Albini: Where does the fluocinolone acetonide 0.59% intraocular implant fit in the approach to noninfectious uveitis patients? What do you try first and when will you go to the implant?

Dr. Nguyen: First line or second line is relative. I would be more likely to decide on first- and second-line therapy based on the needs of the patient rather than rigidly adhering to a predetermined sequence of interventions. For example, the fluocinolone acetonide 0.59% intraocular implant would be a good first-line approach for any patient who cannot tolerate or does not want to try systemic therapy; on the other hand, if the patient is reticent to try surgery, I know that systemic therapy is a good option. In some cases, the disease state will drive the treatment choice, for instance, in patients with birdshot choroidal retinopathy, where having a locally acting agent may be important. In other situations, the patient's preferences will be a significant factor.

Dr. Albini: Who are good candidates for the fluocinolone acetonide 0.59% intraocular implant?

Dr. Yeh: Generally speaking, patients who have tried systemic therapy but were unable to tolerate it, patients with

TABLE. POTENTIAL ADVERSE EFFECTS ASSOCIATED WITH SYSTEMIC CORTICOSTEROIDS

Cardiometabolic: Hypertension, sodium, fluid retention, centripetal obesity, hyperlipidemia, and fat redistrubtion

Dermatologic: Acne, striae, hirsutism and subcutaneous tissue atrophy

Endocrine: Above average A1C levels, adrenal insufficiency, Cushing's syndrome, growth failure in children, and menstrual disorders

Gastrointestinal: Gastric hemorrhage, intestinal perforation, pancreatitis, insulin resistance, and hyperglycemia

Immunologic: Impaired inflammatory response and delayed wound healing

Musculoskeletal: Osteoporosis, vertebral compression fractures and aseptic hip necrosis

Neuropsychiatric: Insomnia, mood swings, and psychosis

Adapted from Vitale AT, Foster CS. In: Foster CS, Vitale AT, eds. *Diagnosis and Treatment of Uveitis.* WB Saunders Company; 2002: 142-157.

"I would consider the level of risk associated with the surgical implant procedure similar to that of vitrectomy."

—Quan Dong Nguyen, MD, MSc

macular edema, pseudophakic patients, and those with specific disease entities such as birdshot chorioretinopathy and other conditions where local inflammation plays a major role are all good candidates. That said, the treating physician has to make a decision in the context of what systemic medications have been tried and consider the side effects of both systemic and local treatment options.

Dr. Srivastava: The ideal patient is the unilateral pseudophake who has a glaucoma tube, but that is rarely an entity we see in clinical practice. From my perspective, the ideal candidate for the fluocinolone acetonide 0.59% intraocular implant is the one in whom there is a need to minimize the risk of systemic issues from systemic therapy. The implant can be a good option when adequate inflammatory control cannot be achieved using steroid sparing systemic agents, for example, if there is chronic cystoid macular edema or retinal vascular leakage. I agree with others who have mentioned birdshot choroidopathy.

Dr. Albini: Another way to approach this question is in whom do you avoid using the fluocinolone acetonide 0.59% intraocular implant? To me, this category includes patients with pre-existing glaucoma and those who might have an issue with the cost, especially the cost of bilateral implantation—the implant may be viable in certain patients with bilateral disease, but in some circumstances, the associated cost may be prohibitive. I would add that patients in whom single agent steroid-sparing immunosuppression is effective may not need the implant; however, in patients in whom there is a need for more complicated two- and three-agent regimens, the fluocinolone acetonide 0.59% intraocular implant may be a way to streamline the therapeutic approach.

Dr. Nguyen: The fluocinolone acetonide 0.59% intraocular implant is currently indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. In the past 10 years, the implant has been studied in Vogt-Koyanagi-Harada disease and birdshot choroidopathy, as well as in other disease states. Does any of this supply confidence in using the implant in bilateral cases?

Dr. Albini: There is good data supporting its use in birdshot and I think that we are more comfortable with the efficacy in bilateral disease than we used to be. However, cost is still an issue, and the efficacy of the device does not change those concerns.

Dr. Srivastava: I have fewer patients now on two-drug therapy because if I am not able to gain control of the uveitis after the first drug, I switch over to the fluocinolone acetonide 0.59% intraocular implant.

Dr. Albini: What do you tell patients about surgical complications and risks associated with the implant?

Dr. Nguyen: I would consider the level of risk associated with the surgical implant procedure similar to that of vitrectomy. It is not a very complicated procedure. However, I tell patients that we have to enter the eye and there is potential for hemorrhage and infection, as well as a small risk of retinal detachment.

As for risks associated with the implant itself, I echo the comments made earlier that the potential complications with the fluocinolone acetonide 0.59% intraocular implant are predictable in terms of cataract progression and intraocular pressure rise. Educating patients about these risks is mandatory before using the implant.

Dr. Albini: Do you mention that there is a 30% to 40% risk of needing incisional glaucoma surgery?

Dr. Nguyen: Yes, I do. I also tell patients that if they do require incisional glaucoma surgery in one eye and there is a need to use the implant in the fellow eye at a later date, that it is advisable to perform glaucoma surgery at the time that we perform the procedure for the fellow eye fluocinolone acetonide 0.59% intraocular implant.

Dr. Albini: Do you use a steroid challenge with these patients to see if there is a response?

Dr. Nguyen: I do not because I am not aware of any data suggesting that a steroid challenge would be helpful. It is pretty much a given that injecting something into the intravitreal space will cause an elevation in pressure, so I am always prepared to monitor the pressure in patients for whom I am considering the implant.

Dr. Albini: What do you tell patients about the outcomes of glaucoma surgery if it is needed in the future?

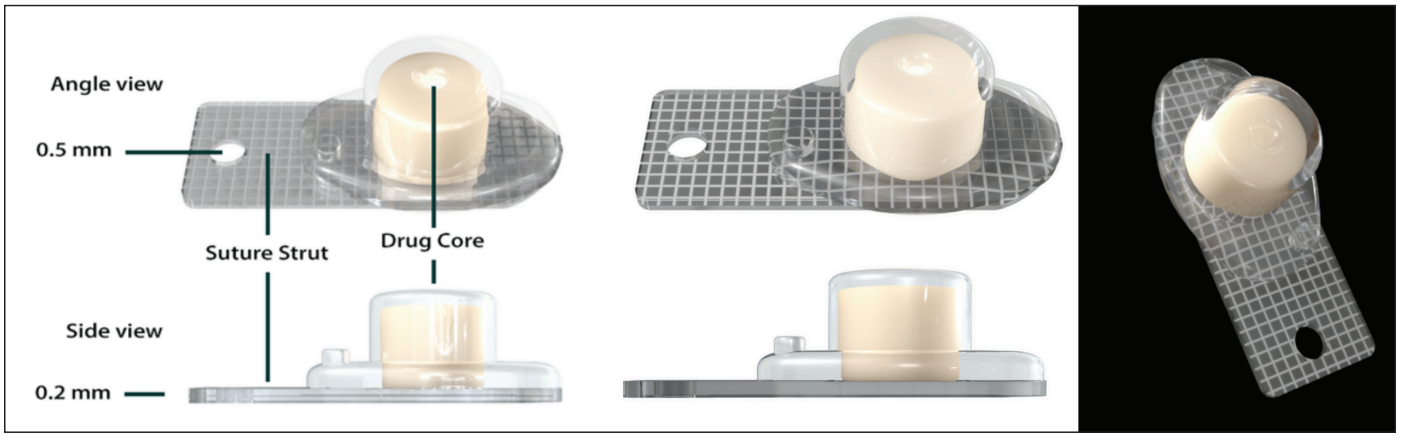

Figure 2. Two views of Retisert and its delivery system.[4]

Dr. Nguyen: We are very realistic about the outcomes of glaucoma surgery, that although it can be very effective, there is a risk of surgical failure or a need for surgical revision, regardless of whether we perform a trabeculectomy or place a drainage device. We are upfront about the potential need for additional surgery for every implant candidate, including glaucoma and/or cataract surgery.

Dr. Albini: How do you counsel patients about the need for cataract surgery with the fluocinolone acetonide 0.59% intraocular implant?

Dr. Yeh: I tell patients that cataract progression is inevitable within 24 months, which is why I tend to avoid the implant in young phakic patients if possible. It is important for patients to know that both distance and near vision are considerations from the long-term standpoint for complications.

Dr. Srivastava: I do not minimize the importance of cataract. However, I think it is important to relay that eyes implanted with a fluocinolone acetonide 0.59% intraocular implant that require cataract surgery may have a lower risk of complications due to the implant's ability to minimize the chance of a postoperative uveitis occurrence.[5] It has been my experience that the eye is pretty quiet following cataract surgery among patients with a fluocinolone acetonide 0.59% intraocular implant. Also, a lot of patients with uveitis are already at risk for developing cataract because of their uveitis and/or because they are receiving steroid therapy. I have found that patients who are motivated to get the implant understand the inevitability of cataract progression.

> "I have found that patients who are motivated to get the implant understand the inevitability of cataract progression."
>
> *—Sunil K. Srivastava, MD*

Dr. Albini: Dr. Yeh, you were one of the first to report on fluocinolone acetonide 0.59% intraocular implant disassociation. Could you explain a little about your case, what the problem was, how it was managed, and what kind of complications there were after the disassociation?

Dr. Yeh: The case involved a dissociation of the medication reservoir from the anchoring strut because of the PVA strut material and adhesive process used in the original design of the fluocinolone acetonide 0.59% intraocular implant. During an

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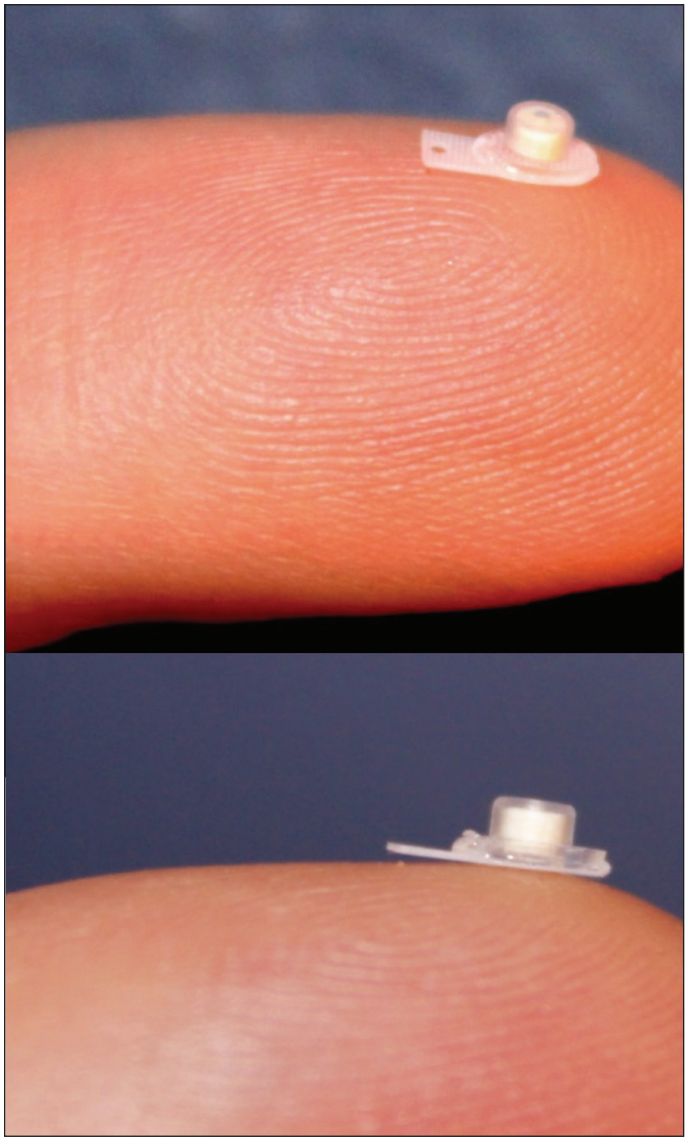

Figure 3. The redesigned implant may have a more flexible structure than the previous implant.

exchange of implants with these older devices, there is potential for the medication reservoir to dissociate from the anchoring strut, thus requiring a vitrectomy to engage the foreign body and to remove the medication reservoir that may fall posteriorly. The implant was subsequently redesigned, with a mesh that is embedded in a silicone-anchoring strut producing a silicone to silicone bond with the medication reservoir complex (Figure 2). I think dissociation may be an issue if older implants are being removed, but vitreoretinal surgeons are aware of this risk and can adjust their techniques accordingly. The company has also started hosting wet labs to provide forums for peer-to-peer education about surgical techniques.

> "The redesigned implant may have a more flexible structure than the previous implant."
>
> *—Quan Dong Nguyen, MD, MSc*

Dr. Albini: Two forms of dissociation have been reported. The first is a spontaneous disassociation within the eye, and the second is disassociation that occurs during the removal process when the surgeon is pulling on the strut through a tight wound. I would agree that greater awareness of the potential for dissociation during removal has spurred a lot of surgeons to alter their removal technique. However, it still remains a clinically relevant issue. Even though the fluocinolone acetonide 0.59% intraocular implant was redesigned a little more than a year ago, dissociation may occur during removal of some of the older implants.

At ARVO this year, Jennifer Thorne and colleagues detailed a 0.6% 5-year rate of implant spontaneous dissociation observed in the MUST trial and follow-up study.[6] However 31% of 36 eyes undergoing removal surgeries for the first implant had dissociated drug reservoirs, emphasizing how common implant dissociation was even in the hands of clinical trial surgeons. Hopefully the revised implant will address this complication.

This leads to a management question when patients require a second implant. Do you always replace the implant or add a second one instead of taking the old one out?

Dr. Srivastava: For a while, I was inserting a new implant in a different spot and not removing the older implant. However, I have changed my practice, and now I replace the old one when a patient needs a second implant because I am concerned about disassociation inside the eye.

Dr. Albini: I make my decision to add or replace the implant based on the health of the eye. I prefer not to remove a fluocinolone acetonide 0.59% intraocular implant from an eye that already suffers from many complication of chronic inflammation, such as hypotony, anterior membranes and ischemic retinopahty, because I feel there is greater risk for surgical complications, in these eyes than eyes without these complications.

Has anyone changed their surgical technique or approach since the redesign of the implant? Is there any thing about the redesigned fluocinolone acetonide 0.59% intraocular implant that is different from a technique point of view compared to the old one?

"The 5-year data from MUST show that the fluocinolone acetonide 0.59% intraocular implant provides at least equivalent efficacy and visual acuity outcomes as systemic therapy. The availability of corticosteroid implants affords an option to avoid systemic therapy."

—Thomas A. Albini, MD

Dr. Nguyen: There is really nothing fundamentally different with the redesigned implant (Figure 3). I still perform the incision the same way: 4.0 mm from the limbus and 4 mm in width. The redesigned model has a stronger bond, which gives me more confidence, and I think the pellets are better situated than previously. I am still using 8-0 prolene for the center suture and 9-0 prolene on each side to close the wound.

Dr. Yeh: I think the redesigned implant may have a more flexibile structure compared with the original, and so I tend to use larger incisions with this model than when I first started using the implant. However, my surgical time has not changed, and my approach is otherwise similar, except that I take extra care to ensure that the medication reservoir is successfully negotiated past the choroid to make sure that there is not any implant flexing. There are some very subtle differences in the flexibility of this model and locating it accurately is slightly more challenging.

Dr. Albini: Is there any difference in efficacy in terms of disease control between the original implant and the redesigned version?

Dr. Yeh: I think it is too early to say but it will be important to evaluate these patients in several years to determine their long-term efficacy as well as any comparative safety concerns.

THE IMPACT OF LONG-TERM DATA

Dr. Albini: We have 5 years of follow up from MUST. What does the cumulative data mean for clinical practice?

Dr. Srivastava: The 5-year data are intriguing, and they show me that patients can benefit greatly from the device even after the implant is replaced. It is important to note that the fluocinolone acetonide 0.59% intraocular implant was approved in 2005, and so we actually have 10 years of use with this device in the clinic. There is a lot of data demonstrating how effective it is in patients with progressive disease.

Dr. Albini: One of the primary objectives in uveitis treatment is to find strategies that avoid long-term reliance on systemic steroids so as to minimize the associated complications. The availability of corticosteroid implants affords an option to avoid systemic therapy and systemic safety risks. In terms of alternatives for long-term steroid-sparing therapy, however, there do not seem to be a lot of options that work as consistently as steroids.

If all we had in our arsenal were immunosuppressants, and a steroid were introduced, we would likely readily accept it as a viable alternative, because steroids function on the immune cascade at multiple locations, achieving therapeutic success in 90% of patients in the short term. The side effects would, appropriately, give us pause, but in terms of reliability in controlling inflammation, I do not really see anything out there that is superior to steroids.

Dr. Srivastava: I would agree with that.

Dr. Yeh: Just as we need to consider RETISERT side effects in the context of the patient's ocular health before making a decision to implant RETISERT, all of the various side effects of systemic treatments need to be considered in the context of the patient's overall health. For instance, in patients with hepatitis or liver insufficiency, the antimetabolites would be less desirable. With alkylating agents, there is the long-term risk of malignancy with cyclophosphamide and chlorambucil; for these reasons, the potency of the agent (ie, both efficacy and safety) needs to be weighed against known side effects and risks. Corticosteroids have been associated with hypertension, diabetes, and osteoporosis.

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- 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.

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Dr. Albini: Is there anything else we have learned about the device over the past 10 years?

Dr. Yeh: I think we have learned about the reimplantation rate. Based on data from the Cleveland Clinic, the rate of reimplantation is about 20%.

Dr. Srivastava: I think we have also learned that for most patients, the need for reimplantation is around year 4, not year 3 as we previously believed—and I have had a number of patients who have remained under control well beyond that time point with a single implant. The implant's ability to control inflammation in an eye has a profound effect on a lot of patients. We have also learned that patients who do require a reimplantation tend to do very well after the second procedure, which reinforces that this device is a long-term solution for select patients.

Dr. Yeh: I would be interested in the reimplantation rate over longer-term follow-up. The 20% figure comes from a retrospective series with limited follow up. As the MUST study follows patients over time, it will be interesting to see if in fact one in five patients will need another implant. Whatever the case, though, I think the majority of patients will not need an additional surgery.

Dr. Albini: The 5-year data from MUST show that the fluocinolone acetonide 0.59% intraocular implant provides at least equivalent efficacy and visual acuity outcomes as systemic therapy. It is interesting that in spite of the complications that seem to be associated with the implant—glaucoma and cataract surgery—patients are doing remarkably well after 5 years.

CONCLUSION

Dr. Albini: Let us try and put this all in context by returning to the first question we addressed but asked in a slightly different way: What does it mean to have access to 5-years of prospective follow-up on patients from the MUST trial?

Dr. Nguyen: I think that is an important point to emphasize, that even though there may be a need for an additional surgery—which is no small proposition to some patients—overall, patients are accepting of this treatment approach. We did not know that 10 years ago and I do not think any of us thought that would be the case.

Something that is emerging and that will be interesting to follow is how the MUST data informs how we educate patients about the short- and long-term risks. Perhaps we, as treating physicians, should consider the context of the case and the patient's needs.

Dr. Albini: Context is important, because in MUST, we saw at least equivalent efficacy between the treatment arms. I think the data allows us to comfortably say that either is a reasonable and viable option for select patients, and that you can expect about the same outcome with either approach. It is encouraging to have the confidence to say that to patients in an era where they are more knowledgeable and want greater involvement in their treatment choices.

Dr. Srivastava: It is also interesting to look at the worst-case scenarios in the MUST treatment groups. In some cases, patients required multiple surgical procedures or daily systemic therapy for 5 years. As well, about 20% of patients in the systemic therapy group required an implant due to failure of their treatment.[3] These should be presented to patients as tangible facts to help them process the decision between surgery and medical therapy.

We are in the process of looking back at some of the patients we have been following for 10 years using the fluocinolone acetonide 0.59% intraocular implant. It will be interesting to see what the efficacy data looks like over such an extended follow up and whether that will give us additional confidence that the implant is a long-term solution.

Dr. Albini: I think we all agree here that that the fluocinolone acetonide 0.59% intraocular implant is a potent and effective corticosteroid. RETISERT is a good choice to treat chronic noninfectious uveitis affecting the posterior segment of the eye. ■

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2. Kempen JH, Altaweel MM, Drye LT, et al. Benefits of systemic anti-inflammatory therapy versus fuocinolone acetonide intraocular implant for intermediate, posterior and panuveitis: 54 month results of The Multicenter Uveitis Steroid Treatment Trial and Follow-up Study. Presented at Association for Research in Vision and Ophthalmology Annual Meeting. Program Number 3209. May 5, 2015; Denver, Colorado.
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4. Bausch + Lomb. Fluocinolone acetonideintravitreal implant 0.59 mg (Retisert). Package Insert. 2012. www.bausch.com/Portals/107/-/m/BL/United%20States/USFiles/Package%20Inserts/Pharma/retisert-prescribing-information.pdf. Last Updated May 2012. Accessed Jan. 15, 2016.
5. Sheppard JD Jr, Nguyen QD, Usner DW, et al. Post-cataract outcomes in patients with noninfectious posterior uveitis treated with the fluocinolone acetonide intravitreal implant. *Clin Ophthalmol*. 2012;6:79-85. doi: 10.2147/OPTH.S24397. Epub 2012 Jan 11.
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BAUSCH + LOMB

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 µg/day, decreasing over the first month to a steady state between 0.3-0.4 µg/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 at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised 05/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 µg/day, decreasing over the first month to a steady state between 0.3-0.4 µg/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 6.1 Clinical Trials Experience - Ocular Events section).

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.

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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, macula 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

Pregnancy Category C
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 µg/kg/day (approximately 4,000 times the clinical dose of RETISERT), fluocinolone acetonide caused abortions and malformations in a few surviving fetuses.

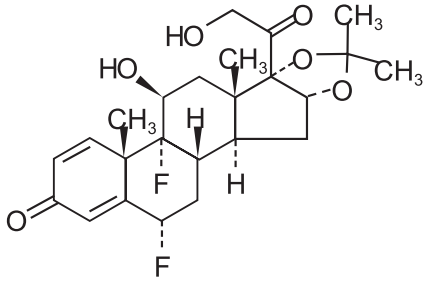
There are no adequate and well-controlled studies in pregnant women. RETISERT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 µg/day, decreasing over the first month to a steady state between 0.3-0.4 µg/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 265-266°C.

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

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 preimplantation 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

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 6.1 Clinical Trials Experience - Ocular Events section).

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.

MANUFACTURER INFORMATION
Revised May 2012
Marketed by:
Bausch & Lomb Incorporated
Rochester, NY 14609
Manufactured by:
Bausch & Lomb Incorporated
Waterford, Ireland
U.S. Patent # 6,217,895
U.S. Patent # 6,548,078

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