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Drug Use Research & Management Program

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Abbreviated Drug Evaluation: Fluocinolone acetonide intravitreal implant (Retisert®)

Month/Year of Review: January 2013

End date of literature search: September 2012

Generic Name: Fluocinolone acetonide intravitreal implant

Brand Name (Manufacturer): Retisert® (Bausch & Lomb)

FDA Approved Indication:

The Fluocinolone ocular implant is a corticosteroid surgically implanted; indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.¹

Research Questions:

- Is there evidence to support the use of fluocinolone acetonide intravitreal implant over another delivery device and/or standard of care for the treatment of uveitis or other macular edema indications?
- Is there any high quality evidence to support the use of fluocinolone acetonide intravitreal implant over other steroid implant devices?
- Are there certain subpopulations, where corticosteroid intravitreal implants are either more effective or safer than other treatments for uveitis and other macular edema indications?

Conclusions:

- There is low quality evidence that there is no difference in visual acuity outcomes between fluocinolone acetonide intravitreal implant and standard of care with systemic corticosteroids for the treatment of noninfectious uveitis. There is also low quality evidence that fluocinolone intravitreal implant may control inflammation in the eye faster and more frequently than standard of care, although both approaches decrease inflammation.
- There is moderate quality evidence that fluocinolone acetonide intravitreal implant is associated with more ocular adverse events than standard of care, including glaucoma (Hazard Ratio [HR] 4.2, 95% CI 1.82-9.63) and cataracts (HR 4.12, 95% CI 2.2-7.7).
- There is low quality evidence demonstrating potential benefit of fluocinolone acetonide intravitreal implant and dexamethasone implant for the treatment of diabetic macular edema, however significant complications have also been reported. There is insufficient evidence to support the use for diabetic macular edema or other off-label indications.
- There is insufficient evidence directly comparing fluocinolone acetonide intravitreal implant to dexamethasone intravitreal implant for any indications. There are significant differences in indications and administration techniques between the two agents.
- There is moderate quality evidence demonstrating efficacy of dexamethasone intravitreal implant following central retinal vein occlusion.

Recommendations:

- Recommend that the Health Evidence Review Commission evaluate the surgical procedure of the fluocinolone and dexamethasone ocular implants for line placement.

Background:

Uveitis is an ocular inflammatory condition that may be related to infection or are non-infective.^{2,3} The standard of care for noninfectious uveitis is local, topical, or oral corticosteroids in combination with immunosuppressive therapy, when indicated.³ The goal of treatment is to suppress inflammation and achieve remission and protection of visual acuity. Topical corticosteroids penetrate well only into the anterior segment of the eye and are useful in the management of anterior uveitis, but do not adequately penetrate the posterior segment of the eye. Periocular steroids are useful in intermediate uveitis and posterior uveitis. However, many patients need systemic steroids, primarily orally with or without immunosuppressive drug therapy. Treatment guidelines from 2000 and 2005 recommend topical, local, or systemic corticosteroids to control ocular inflammation rapidly. To decrease the risk of serious side effects associated with corticosteroid use, guidelines recommend the addition of immunomodulatory therapy as a steroid-sparing agent if inflammation is not controlled within three months with steroid use (≤ 10 mg/day of prednisone or equivalent).^{3,4} Intravitreal implants were developed to deliver a continuous concentration of drug over a prolonged period of time and are either biodegradable or nonbiodegradable. Although this continuous release may reduce the need for intravitreal injections or long-term systemic therapy, surgical implantation of the device carries its own risks, and the implant could potentially increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration.

In 2005, the FDA approved the intraocular fluocinolone implant (Retisert®) for chronic, noninfectious uveitis which is a non-biodegradable implant that delivers drug continuously for about 30 months. The fluocinolone implant is surgically implanted by a vitreoretinal surgeon. Approval for noninfectious uveitis was based on two phase III, randomized, double-masked, historically controlled clinical trials demonstrating a clinically and statistically significant difference in the proportion of patients with recurrence of uveitis within 34 weeks post-implantation compared to the proportion with recurrence in the 34 weeks preceding implantation.⁵ The fluocinolone implant reduced the rate of recurrence from 62% in the year preceding implantation to 20% in the 0.59-mg group and 41% in the 2.1-mg group post implantation. There was also a significant improvement in visual acuity when compared to the nonimplanted eyes ($p < 0.01$). There was no significant difference in the proportion of eyes with deteriorating visual acuity.⁵ There was a significant increase in the incidence of cataracts in the implant eyes compared to the nonimplanted eyes (67% vs. 18%, $p < 0.01$; RR 3.7, 95% CI 2.7 to 5.2) and 93% of implanted eyes underwent cataract surgery.⁵

In 2009 the dexamethasone ocular implant (Ozurdex®) was approved for macular edema following retinal vein occlusion (RVO), and in 2010 also for the treatment of non-infectious uveitis, affecting the posterior segment of the eye. This implant is biodegradable and releases dexamethasone over about 6 months. The dexamethasone ocular implant can be given as an outpatient procedure, while fluocinolone has to be surgically inserted. The safety and efficacy of the dexamethasone intravitreal implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye was studied in a single, multicenter, masked, randomized 26 week trial.⁶ Two hundred and twenty nine subjects were randomized to dexamethasone implant 0.35mg, 0.7mg, or a sham procedure. The primary outcome was the percentage of eyes with a vitreous haze score of 0, which represents no inflammation, at week eight of the trial. Outcome investigators and patients were masked, while treatment investigators were unmasked in order to perform the implant placement. The percentage of eyes with a vitreous haze score of 0 at week eight was significantly greater in both the 0.7-mg (47%; $p < 0.001$) and the 0.35 mg group (36%; $p < 0.001$) than the sham group (12%).⁶ There were also significantly more eyes with improved visual acuity in the dexamethasone implant groups than the sham group. The authors concluded that in this study a single dose of the dexamethasone implant was well tolerated and produced significant improvements in intraocular inflammation and visual acuity that persisted for six months. In addition, it was noted that the 0.7 mg implant demonstrated greater efficacy than the 0.35

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implant, with similar safety.⁶

Research is also being conducted on evaluating the safety and efficacy of fluocinolone acetonide intravitreal implant as off-label use for the treatment of diabetic macular edema (DME). Previous treatment approaches for DME include laser photocoagulation, intravitreal steroid injections, vitrectomy, and vascular endothelial growth factor (VEGF) inhibitors. Laser photocoagulation has historically been the gold standard but has not been successful in improving vision, only preserving it. Intravitreal steroids are not commonly used due to the risk of elevated intraocular pressure and cataracts.⁷ There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with DME relative to laser treatment and sham injection, with similar improvements across agents.⁸ An additional fluocinolone intravitreal implant (Iluvien[®]) has been submitted to the FDA for the indication of DME but has not yet been approved.

Systematic Reviews

National Institute for Health and Clinical Excellence

A 2011 technology appraisal was published in 2011 by the National Institute for Health and Clinical Excellence (NICE) on dexamethasone implant for macular edema secondary to retinal vein occlusion.⁹ Dexamethasone intravitreal implant is recommended as an option for macular edema following central retinal vein occlusion (CRVO). It is recommended as an option for macular edema following branch retinal vein occlusion (BRVO) when treatment with laser photocoagulation has not been beneficial or is not considered suitable because of macular hemorrhage.⁹

O'Doherty, et al.

A 2008 review of the literature for diabetic macular edema treatment reported on a single study of fluocinolone implant in 97 patients with DME randomized to receive either the implant or standard of care with laser treatment or observation.¹⁰ Studies were evaluated on a standardized data extraction form; however a specific quality assessment was not defined and risk of bias for the fluocinolone study was not evaluated. At 3 years, 58% of patients had resolution of DME and associated improvement in visual acuity, compared to 30% of patients in the control group ($p < 0.001$). The most common adverse effects included a higher risk of cataract formation and glaucoma in the treatment group compared to control. A total of 5% of patients required removal of the implant to control the glaucoma. Overall, there was little evidence to support the use of the implant and at the time no available studies were available to make conclusions on superiority or noninferiority of fluocinolone acetate implant to other intravitreal injection.

Cochrane Collaboration

A Cochrane review evaluated the effectiveness and safety of intraocular steroids in treatment DME.¹¹ Three of the total seven trials examined intravitreal steroids implantation (fluocinolone or dexamethasone). The authors concluded that evidence suggests that steroids administered either by intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DME.

Two trials evaluated fluocinolone implant versus standard of care or observation. At 12 months, there was no evidence of effect on three or more lines improvement in visual acuity (RR 2.73, 95% CI 0.63 to 11.93). The other trial demonstrated a marginal statistically significant effect on three or more lines in visual acuity at 36 months (RR 1.93, 95% CI 1.02 to 3.66). Data was insufficient to combine for a meta-analysis and both trials had a high risk of bias. The dexamethasone implant trial included participants with various underlying causes of macular edema. In a subgroup analysis of DME patients, 58% in the dexamethasone group showed a two-line improvement in vision compared to 21% in the observation group (RR 2.75, 95% CI 1.59 to 4.76) at 3 months. This suggests a beneficial effect from dexamethasone and possible evidence of benefit with the use of fluocinolone. There were many methodology limitations in the fluocinolone data, making it difficult to draw strong conclusions on the magnitude of effect.

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Systemic therapy vs. Implant therapy:

The Multicenter Uveitis Steroid Treatment Trial Research Group

A recent fair quality randomized, partially masked, controlled trial reported 24-month results of an evaluation of fluocinolone acetonide implant compared to systemic therapy with oral corticosteroids and immunosuppressive drugs when indicated (standard of care) for noninfectious intermediate uveitis, posterior, or panuveitis.¹² The Multicenter Uveitis Steroid Treatment (MUST) Trial compared 129 participants in the implant group to 126 participants in the systemic therapy group. Appropriate randomization methods were used. Patients, clinicians, and coordinators were unable to be masked; however visual acuity outcome examiners were masked. Most baseline demographics and characteristics were similar between groups; however eyes with uveitis in the implant group had poorer visual field sensitivity than those in the systemic group.

Both groups experienced improvement of best-corrected visual acuity (BCVA; a measure of visual acuity) during follow-up at all time points. There was no statistically significant difference between the treatment groups in improvement in visual acuity at 24 months, with a mean improvement from baseline of 6.0 letters in the implant group compared to 3.2 letters in the systemic group (estimated treatment effect 2.70, 95% CI -1.16 to 6.68; $p=0.16$). At 24 months, 21% and 13% of eyes assigned to implant or systemic therapy, respectively, had gained at least 15 letters ($p=0.065$). Both groups experienced control of active uveitis, however more frequent in the implant group (88% vs. 71%, $p=0.001$). Authors concluded that both groups were successful in controlling inflammation in the majority of cases, without clear evidence indicating superiority of effectiveness for either group. The implant has the potential to achieve inflammatory control faster and more often and ocular complications of uveitis or treatment were more common in the implant group.

The implant group had a more than 4-fold higher rate of incidence of intraocular pressure (IOP) elevation ≥ 10 mmHg, absolute IOP of ≥ 30 mmHg, and of needing medical and surgical treatments for elevated IOP. Glaucoma developed in 17% and 4.0% in the implant and systemic groups, respectively (HR=4.2, 95% CI 1.82-9.63; $p=0.0008$). Those in the implant group also experienced higher cumulative 24-month risk of both cataract (91% vs. 45%, HR 4.12 95% CI 2.2-7.7; $p<0.0001$) and cataract surgery (80% vs. 31%, HR 3.3 95% CI 2.2-5.0; $p<0.0001$). Adverse systemic events were infrequent in both groups and there was no significant difference in risk of hospitalizations.

Pavesio, et al.

A previous poor-fair quality 3-year, open label, randomized, phase 2b/3 superiority study compared fluocinolone implant with standard of care in subjects with unilateral or bilateral noninfectious posterior uveitis.¹³ The study was conducted from April 2002 through August 2005 at 37 centers across 10 countries. Subjects were randomized to a 0.59-mg fluocinolone implant ($n=66$) or SOC ($n=74$) with either systemic prednisolone or equivalent corticosteroid monotherapy or, if deemed necessary, combination therapy with an immunosuppressive agent plus a lower dose of prednisolone or equivalent corticosteroid. Approved immunosuppressants included cyclosporine A, methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, and tacrolimus. Subjects were allocated to receive either an implant or SOC as determined by a centrally administered randomization procedure. It was not possible to mask study treatments; however efforts were made to avoid selection bias. Treatment allocation was masked until the confirmation of inclusion of the subject and some outcome assessments

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were masked. There was a statistically significant difference between the treatment groups in gender ($p=0.02$); other baseline characteristics were similar between the two groups.

The primary outcome was time to first recurrence of uveitis, and 2-year results are included in the study. Using uveitis activity as a primary outcome may bias the results against systemic therapy because systemic regimens rely on tapering medications until uveitis activity returns and then increasing the medication to control inflammation.¹⁴ Subjects that received fluocinolone had delayed onset of observed recurrence of uveitis and statistically significant lower rate or percentage of subjects who had at least 1 recurrence compared with SOC (34.8% vs. 64.9%; $p<0.01$). The mean time to first recurrence was 6.4 ± 7.0 months and 7.1 ± 7.2 months for implanted eyes and the SOC eyes, respectively. There was no statistically significant difference in visual acuity between the two groups, as measured by improvement in at least 3 lines in BCVA (17.2% of implanted eyes vs. 14.3% of SOC; $p=0.66$). There were no treatment related nonocular adverse events in the fluocinolone group compared to 25.6% of subjects receiving SOC.

Treatment emergent ocular adverse events occurred in 98.5% of implanted eyes versus 79.7% of SOC eyes with a greater number of serious ocular events in implant eyes. Adverse events commonly observed significantly more in eyes with the implant compared to placebo included cataracts requiring extraction (87.8% vs. 19.3%, $p<0.01$), and increased IOP requiring surgery (21.2% vs. 2.7%, $p<0.01$). Other serious ocular events included 3 cases of endophthalmitis (4.5%) in the implant group compared to none in the SOC eyes. None of the subjects in the implant group experienced a nonocular adverse event related to treatment, whereas 19 (25.7%) subjects in the SOC group did. The authors concluded that based on the results of the study, the fluocinolone acetonide intravitreal implant seemed to be more effective than SOC therapy in controlling the intraocular inflammation in those with posterior uveitis. It was also associated with increased rates of cataract development and elevated IOP which were managed by surgical or medical treatment.

Diabetic macular edema:

Pearson, et al.

A prospective, fair quality, randomized, 4 year clinical trial studied reported the 3-year efficacy and safety results evaluating fluocinolone implant compared to standard of care in 196 patients with diabetic macular edema (DME).¹⁵ This was evaluator-masked only (patients and investigators were not masked) trial comparing 0.59 mg fluocinolone implant ($n=127$) to standard of care ($n=69$) with focal/grid laser photocoagulation or observation at the investigators' discretion. The primary efficacy outcome was ≥ 15 letter increase in visual acuity at 6 months, measured by masked, certified examiners using a standardized Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Demographic characteristics were similar between the two groups. Improvements in visual acuity were seen in both treatment groups. Though 31.1% of patients reached the primary endpoint, the results were not statistically different from standard of care ($p=0.015$). At both 6 and 9 months, visual acuity was significantly higher with the implant than with standard of care ($p<0.0012$ and $p<0.002$, respectively), but the difference was not significant at 1 year ($p=0.119$) or 3 years ($p=0.1566$). There was also a significant difference in change from baseline in macular edema at 6 months and 1 year, but no difference was seen at 3 years ($p=0.861$).

There was a higher rate of ocular adverse events in eyes treated with the implant than in eyes receiving standard of care (100% vs. 88.4%). The most common adverse effects in implanted eyes were elevated intraocular pressure (69.3%), worsening cataract (55.9%), vitreous hemorrhage (40.2%), and pruritus (38.6%). The most frequent adverse events in SOC eyes were macular edema (36.2%), reduced visual acuity (23.2%), worsening cataract (21.7%), and pruritus (21.7%). Rates of nonocular adverse events were similar in both groups.

Campochiaro et al.

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Two identical fair-quality randomized, double blind, sham injection-controlled studies were conducted comparing low (0.2 mcg/day) and high dose (0.5 mcg/day) fluocinolone acetonide intravitreal inserts in 956 patients with DME over a 36-month period. The primary outcome measure was the percentage of subjects with improvement in baseline BCVA of 15 letters or more at month 24. In the modified intention to treat analysis, both of the fluocinolone insert groups had more subjects showing an improvement in BCVA letter score of 15 or more at 24 month (26.1% in the low-dose group, 26.7% in the high-dose group, 13.0% in the sham group/ $p < 0.001$).

The most common serious adverse event was cataract surgery, which occurred in 50.9% of patients in the high-dose implant group, 41.1% in the low-dose group, and 7.0% in the sham group. Increased IOP and glaucoma also occurred more frequently in the implant groups than in the sham group. Overall attrition was 19% in the high-dose group, 19.9% in the low-dose group, and 22.7% in the sham group. Withdrawals due to adverse events were higher in the high-dose group than both the low-dose group and the sham group (5.1%, 1.1%, and 1.6%, respectively). The incidence of serious cardiovascular events was similar in the 3 groups (sham 10.3%, low-dose 12.0%, and high-dose 13.2%). However, myocardial infarction occurred in 4.0% of patients in the low dose implant group compared to 1.1% in the sham group ($p = 0.0347$). The authors suggested this is highly likely a result of chance because the release of fluocinolone within the eye is so low that levels are not measurable in the systemic circulation.

Dexamethasone: Haller, et al.

A prospective, poor quality, randomized, single-masked controlled trial evaluated the safety and efficacy of two doses of the dexamethasone implant compared to observation in patients with DME.¹⁶ The primary outcome was the proportion of eyes that achieved an improvement in BCVA of 10 letters or more at day 90. A statistically significant difference in the primary outcome was shown at day 90 (33% vs. 12%, $p = 0.07$, 95% CI for difference, 6.14% to 35.96%). The differences between the low and high dose dexamethasone groups (300 mcg and 700 mcg) were not statistically significant. There was no significant difference in the number of cataract between the groups. There was a significant difference in the number of subjects experiencing increased IOP in the dexamethasone groups compared to observation (14.5% vs. 9.4% vs. 0%; $p = 0.006$).¹⁶ This was a sub-analysis of a larger study including patients with macular edema from additional causes including retinal vein occlusion, uveitis, and Irvine-Gass syndrome, and therefore should be interpreted with caution.

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