PRODUCT MONOGRAPH

PrRETISERT™

Fluocinolone acetonide

0.59 mg

Intravitreal Implant

ATC Code: S01BA15

Bausch & Lomb Incorporated
1400 N Goodman Street
Rochester, NY 14609
USA

Imported by:
Bausch & Lomb Canada Inc.
520 Applewood Crescent
Vaughan, Ontario
L4K 4B4

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PrRETISERT™

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravitreal drug delivery system	0.59 mg implant	The non-medicinal ingredients are not considered clinically relevant *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

RETISERT™ (fluocinolone acetonide) is indicated for:

- Retisert is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye in patients for which conventional therapies are no longer appropriate.

RETISERT™ should not be used in patients with viral disease of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia and varicella.

RETISERT™ should not be used in patients with mycobacterial infections of the eye and fungal diseases of ocular structures.

Geriatrics (≥ 65 years of age):
Experience of RETISERT™ use in patients ≥ 65 years of age is limited. The safety and effectiveness has not been established.

Pediatrics (< 18 years of age):
Experience of RETISERT™ use in children and adolescents below the age of 18 is limited. The safety and effectiveness has not been established.

CONTRAINDICATIONS

- Patients with viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia and varicella.
- Patients with mycobacterial infection of the eye.
- Patients with fungal diseases of ocular structures.
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients sensitive to other corticosteroids including, but not limited to, a history or presence of uncontrolled IOP while on steroid therapy, resulting in loss of vision, or IOP > 25 mm Hg requiring 2 or more types of IOP lowering medications to lower to < 25 mm Hg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Patients should be warned that almost all phakic eyes will develop cataracts and require cataract surgery during the course of RETISERT™ treatment.
- Use of RETISERT™ may cause increased intraocular pressure which, if not controlled by IOP lowering medications, may require IOP lowering surgery.

Refer to the Ophthalmologic subsection for further details.

General

Care must be exercised in handling RETISERT™ in order to avoid damage to the implant, which could affect the release of fluocinolone acetonide inside the eye. RETISERT™ must be handled only by the suture tab. Care must be taken during implantation and explantation to avoid shear forces on the implant that could separate the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the suture tab. As with all intraocular surgery, sterility of the surgical field and RETISERT™ should be rigorously maintained. RETISERT™ should not be re-sterilized by any method.

A high level of surgical skill is required for implantation of the RETISERT™ Implant. Implantation should be performed by a qualified professional with prerequisite training and thorough knowledge of the procedure to be performed.

As with any surgical procedure there is a risk involved. Potential complications accompanying intraocular surgery to place RETISERT™ into the vitreous cavity may include, but are not limited to, the following: choroidal detachment, endophthalmitis, hypotony, retinal detachment, vitreous haemorrhage, vitreous loss, wound dehiscence, temporary decreased visual acuity, exacerbation of intraocular inflammation and increased intraocular pressure.

If an inadequate response to RETISERT™ therapy is seen during the first six months of treatment, consideration should be given to alternative treatment modalities since the patient's condition may not be responsive to treatment with intravitreal fluocinolone acetonide.

Retisert has not been evaluated in patients requiring chronic high dose systemic corticosteroid therapy (more than 15 mg prednisone or equivalent daily) to manage non-ocular diseases. When alternate treatment modalities are added to address an inadequate response to RETISERT™, follow-up care must consider the possibility that the steroid is contributing to the total clinical response and that the additive benefit of RETISERT™ could diminish as the drug is depleted after 30 to 36 months. Follow-up schedules should be similar to those used for RETISERT™ monotherapy.

After surgical implantation of RETISERT™, patients may experience a temporary decrease in visual acuity or blurred vision for up to one month. Patients should not drive or use machines until their vision has recovered.

Patients should be warned that cataract formation occurs in almost all phakic eyes during the course of RETISERT™ treatment and this may progress to a stage that, without surgical extraction of the cataract, could affect their ability to drive and use machines.

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. Physicians should monitor the integrity of the implant during ophthalmologic examinations.

Removal of RETISERT™

The safety of the depleted implant is unknown. Removal of RETISERT™ (before or at the end of drug delivery which may be suggested by the recurrence of clinical signs more than 24 months post-implantation) is at the discretion of the physician and must be based on the risk and benefit balance of implant removal against further surgery. It is important to note that implant separation (floating silicone cup) has been reported up to 5 years post-implantation which necessitated immediate surgery. These findings are based on the available data; therefore, the possibility of implant separation after 5 years is unknown.

Removal of the RETISERT™ implant in the presence of vitreous bands should be done carefully. There is a risk of retinal traction during removal of the implant in such patients. To avoid this complication, a vitrectomy might be considered before removal of the implant.

Removal of RETISERT™ from the eye may be performed by cutting the sutures over the insertion incision and carefully grasping the anchoring suture to effect removal. Care should be taken to avoid shear forces that might separate the drug-containing cup from the suture tab. The explantation incision may need to be larger than the implantation incision in order to avoid damage to the implant during the removal operation. An infusion line may be necessary to avoid globe collapse especially in vitrectomised eyes.

Ophthalmologic

Based on clinical trials with RETISERT™, within an average post-implantation period of approximately 2 years, nearly all phakic eyes are expected to develop cataracts and require cataract surgery. Cataracts were surgically extracted in 95.9% of implanted phakic study eyes versus 19.9% (37/186) in phakic fellow eyes and 19.3% (11/57) in phakic study eyes of patients treated with standard of care systemic therapies. At approximately 2.5 years post-implantation, glaucoma filtering surgeries were required to manage the pressure increase in 30.9% of the patients implanted with RETISERT™ 0.59 mg. IOP lowering surgeries were required for 1.8% (5/275) of fellow eyes and for 2.7% (2/74) of study eyes of patients treated with standard of care systemic therapies.

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. This decrease in visual acuity is probably a result of the surgical procedure.

Prolonged use of corticosteroids may result in elevated intraocular pressure with possible development of glaucoma with damage to the optic nerve, defects in visual acuity and visual fields, posterior subcapsular cataract formation, delayed wound healing and perforation of the globe where there is thinning of the sclera.

Steroids should be used with caution in the presence of glaucoma. Patients must be monitored for elevated intraocular pressure (IOP).

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used. In purulent conditions of the eye, steroids may mask infection or enhance existing infection. Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation is not recommended, in order to limit the potential for bilateral post-operative infection.

After exhausting all other surgical treatment options, if a patient experiences a sustained IOP of 25 mm Hg or more whilst using two or more types of antiglaucoma medication for at least two months or if the IOP is accompanied by progressive visual field deterioration, removal of RETISERT™ should be considered. If RETISERT™ appears damaged or is dislocated, the implant should be removed. If a patient develops late onset endophthalmitis, particularly in the absence of other risk factors, reassessment of the wound integrity or removal of RETISERT™ should be considered.

Carcinogenesis and Mutagenesis

Long term animal studies have not been performed on RETISERT™ to evaluate the carcinogenic potential.

Nonclinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

Dependence/Tolerance

There is no abuse potential with RETISERT™

Endocrine and Metabolism

Disturbances on the corticosteroids HPA axis in humans were not evaluated. However, effects are not expected due to the negligible systemic exposure to fluocinolone acetonide from RETISERT™

Neurologic

RETISERT™ is not expected to impair mental ability.

Peri-Operative Considerations

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

Special Populations

Pregnant Women: Adequate data from the use of fluocinolone acetonide in pregnant women are not available. Studies in animals have shown reproductive toxicity (SEE TOXICOLOGY). The potential risk for humans is unknown. RETISERT™ should not be used during pregnancy unless clearly necessary.

Adequate and well-controlled studies in pregnant women have not been conducted. RETISERT™ should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Women: It is not known whether intraocular administration of fluocinolone acetonide will result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. A decision on whether to continue breastfeeding should be made taking into account the benefit of breastfeeding to the child and the benefit of RETISERT™ therapy to the mother.

Pediatrics (<18 years of age): Experience of RETISERT™ use in children and adolescents below the age of 18 is limited. The safety and effectiveness have not been established.

Geriatrics (≥ 65 years of age): Experience of RETISERT™ use in patients > 65 years of age is limited. The safety and effectiveness has not been established.

Renal/hepatic Impairment: Negligible quantities of fluocinolone acetonide from RETISERT™ are excreted via the systemic circulation. No specific precautions for treatment of patients with renal or hepatic impairment are necessary.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of the adverse events experienced by subjects implanted with RETISERT™ were related to the underlying disease process, the effect of corticosteroid, and the surgical implantation procedure.

Commonly reported ocular adverse events of the implanted eye included increased intraocular pressure, glaucoma, cataract, worsened cataract, conjunctival haemorrhage, conjunctival hyperaemia, reduced visual acuity, maculopathy, hypotony, post-operative wound complications, eye irritation, blurred vision, vitreous floaters, posterior capsular opacification, unusual sensation in the eye and pruritis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Two study designs were utilized in the pivotal clinical trials: 0.59 mg fluocinolone acetonide implant vs. standard of care (SOC) treatment (BLP 415-002); and 0.59 mg vs. 2.1 mg fluocinolone acetonide implant (BLP 415-001). Additional safety and efficacy data was obtained from two additional studies conducted in subjects with a clinical diagnosis of posterior uveitis: BLP 415-001J/JF and BLP 415-004. Two dosage strengths of the fluocinolone acetonide implant were evaluated in the clinical trials, 0.59 mg and 2.1 mg. Only safety data for the 0.59 mg strength is presented here.

The most common ocular adverse event observed in eyes treated with RETISERT™ 0.59 mg was increased intraocular pressure (57.3%).

Ocular adverse events reported at an incidence of ≥ 20% in implanted eyes included eye pain, cataract (worsened or de novo), conjunctival haemorrhage, conjunctival hyperaemia, reduced visual acuity, postoperative wound complications, hypotony, maculopathy, eye irritation, glaucoma, and postoperative complications. Some of these events were transient and associated with the implantation surgery.

The most common ocular adverse events observed in the non-study eye included increased intraocular pressure, eye pain, cataract (de novo and aggravated) and reduced visual acuity.

Based on clinical trials with RETISERT™, within an average post-implantation period of approximately 2 years, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

At approximately 2.5 years post-implantation, glaucoma filtering surgeries were required to manage the pressure increase in 30.9% of the patients implanted with RETISERT™ 0.59 mg.

Table #1 shows the occurrence of ocular adverse events for the study eye versus the non-study eye (≥1%).

Table #1: Ocular Adverse Event Occurring in ≥ 1% of Study Eyes

Preferred Term	Study Eye				Non-Study Eye			
	0.59 mg		SOC		0.59 mg		SOC	
	n = 307		n = 74		n = 307		n = 74	
Ocular	Eyes	%	Eyes	%	Eyes	%	Eyes	%
Intraocular Pressure Increased	176	57.3	6	8.1	47	15.3	5	6.8
Eye Pain	124	40.4	5	6.8	54	17.6	--	--
Cataract NOS	104	33.9	19	25.7	43	14.0	15	20.3
Cataract NOS Aggravated	102	33.2	21	28.4	48	15.6	12	16.2
Conjunctival Hyperaemia	91	29.6	3	4.1	35	11.4	2	2.7
Visual Acuity Reduced	83	27.0	2	2.7	45	14.7	2	2.7
Conjunctival Haemorrhage	82	26.7	2	2.7	21	6.8	2	2.7
Postoperative Wound Complication NOS	71	23.1	--	--	3	1.0	--	--
Maculopathy	65	21.2	4	5.4	26	8.5	1	1.4
Hypotony of Eye	64	20.9	1	1.4	15	4.9	--	--
Eye Irritation	63	20.5	1	1.4	21	6.8	1	1.4
Glaucoma NOS	61	19.9	5	6.8	8	2.6	3	4.1
Postoperative Complications NOS	61	19.9	--	--	5	1.6	--	--
Vision Blurred	59	19.2	1	1.4	38	12.4	1	1.4
Abnormal Sensation in Eye	58	18.9	--	--	13	4.2	--	--
Vitreous Floaters	51	16.6	1	1.4	40	13.0	--	--
Posterior Capsule Opacification	50	16.3	2	2.7	18	5.9	--	--
Eye Pruritus	44	14.3	--	--	12	3.9	--	--
Eyelid Oedema	40	13.0	3	4.1	5	1.6	1	1.4
Vitreous Haemorrhage	39	12.7	2	2.7	2	0.7	1	1.4
Macular Oedema	33	10.8	9	12.2	39	12.7	--	--
Eyelid Ptosis	32	10.4	--	--	4	1.3	--	--
Optic Nerve Cupping	31	10.1	1	1.4	5	1.6	1	1.4
Eye Inflammation NOS	30	9.8	6	8.1	22	7.2	4	5.4
Dry Eye NOS	29	9.5	4	5.4	18	5.9	2	2.7
Lacrimation Increased	27	8.8	1	1.4	7	2.3	--	--
Visual Disturbance NOS	24	7.8	--	--	14	4.6	--	--
Blepharitis	20	6.5	3	4.1	13	4.2	2	2.7
Corneal Oedema	20	6.5	1	1.4	4	1.3	--	--
Ocular Hypertension	19	6.2	6	8.1	4	1.3	2	2.7
Photophobia	18	5.9	--	--	12	3.9	1	1.4
Iris Adhesions	18	5.9	1	1.4	10	3.3	3	4.1
Hyphaema	18	5.9	--	--	2	0.7	--	--
Retinal Detachment	16	5.2	2	2.7	6	2.0	--	--
Wound Dehiscence	16	5.2	--	--	--	--	--	--
Eye Discharge	15	4.9	--	--	5	1.6	--	--
Choroidal Detachment	15	4.9	--	--	1	0.3	--	--
Eye Swelling	15	4.9	--	--	2	0.7	--	--
Eye Discharge	15	4.9	--	--	--	--	--	--
Conjunctivitis NOS	14	4.6	5	6.8	4	1.3	3	4.1

Preferred Term	Study Eye				Non-Study Eye			
	0.59 mg		SOC		0.59 mg		SOC	
	n = 307		n = 74		n = 307		n = 74	
Ocular	**Eyes**	**%**	**Eyes**	**%**	**Eyes**	**%**	**Eyes**	**%**
Retinal Haemorrhage	14	4.6	--	--	8	2.6	--	--
Conjunctivitis NOS	14	4.6	5	6.8	--	--	--	--
Conjunctival Cyst	14	4.6	--	--	--	--	--	--
Cataract Subcapsular	13	4.2	1	1.4	6	2.0	1	1.4
Punctate Keratitis	13	4.2	2	2.7	3	1.0	--	--
Diplopia	12	3.9	1	1.4	4	1.3	--	--
Iris Atrophy	12	3.9	--	--	6	2.0	--	--
Conjunctival Bleb	12	3.9	--	--	1	0.3	--	--
Intraocular Pressure Decreased	12	3.9	2	2.7	4	1.3	1	1.4
Conjunctival Oedema	11	3.6	1	1.4	4	1.3	--	--
Vitreous Opacities	10	3.3	4	5.4	15	4.9	--	--
Photopsia	10	3.3	--	--	12	3.9	--	--
Ocular Hyperaemia	10	3.3	2	2.7	2	0.7	1	1.4
Anterior Chamber Cell	10	3.3	2	2.7	12	3.9	1	1.4
Papilloedema	10	3.3	--	--	7	2.3	--	--
Visual Field Defect	10	3.3	--	--	6	2.0	--	--
Chemosis	9	2.9	1	1.4	4	1.3	1	1.4
Corneal Epithelium Defect	9	2.9	1	1.4	2	0.7	--	--
Ocular Discomfort	8	2.6	--	--	1	0.3	--	--
Endophthalmitis	8	2.6	--	--	--	--	--	--
Retinal Pigmentation	8	2.6	1	1.4	3	1.0	1	1.4
Corneal Abrasion	8	2.6	--	--	3	1.0	--	--
Postoperative Wound Site Erythema	8	2.6	--	--	--	--	--	--
Vitreous Detachment	7	2.3	--	--	10	3.3	1	1.4
Asthenopia	7	2.3	--	--	1	0.3	--	--
Meibomianitis	7	2.3	1	1.4	4	1.3	1	1.4
Glare	7	2.3	--	--	3	1.0	--	--
Iris Disorder NOS	7	2.3	--	--	3	1.0	--	--
Conjunctival Disorder NOS	7	2.3	--	--	3	1.0	--	--
Scotoma	7	2.3	--	--	5	1.6	--	--
Conjunctivitis Papillary	6	2.0	--	--	--	--	--	--
Corneal Ulcer	6	2.0	--	--	1	0.3	--	--
Dellen	6	2.0	--	--	--	--	--	--
Optic Atrophy	6	2.0	1	1.4	--	--	1	1.4
Optic Disc Disorder NOS	6	2.0	--	--	4	1.3	--	--
Anterior Chamber Disorder NOS	6	2.0	--	--	--	--	--	--
Device Expulsion	6	2.0	--	--	--	--	--	--
Eye Oedema	5	1.6	1	1.4	3	1.0	--	--
Corneal Deposits	5	1.6	1	1.4	8	2.6	1	1.4
Anterior Chamber Flare	5	1.6	--	--	5	1.6	--	--
Pupillary Disorder NOS	5	1.6	1	1.4	2	0.7	--	--
Therapeutic Procedural Complication	5	1.6	--	--	2	0.7	--	--
Retinal Disorder NOS	4	1.3	1	1.4	2	0.7	--	--
Chorioretinal Disorder NOS	4	1.3	1	1.4	1	0.3	1	1.4
Eye Allergy	4	1.3	--	--	4	1.3	--	--
Conjunctivitis Allergic	4	1.3	1	1.4	2	0.7	1	1.4
Meibomian Cyst	4	1.3	2	2.7	5	1.6	--	--
Erythema of Eyelid	4	1.3	--	--	3	1.0	--	--

Preferred Term	Study Eye				Non-Study Eye			
	0.59 mg		SOC		0.59 mg		SOC	
	n = 307		n = 74		n = 307		n = 74	
Ocular	**Eyes**	**%**	**Eyes**	**%**	**Eyes**	**%**	**Eyes**	**%**
Corneal Disorder NOS	4	1.3	1	1.4	2	0.7	--	--
Conjunctival Granuloma	4	1.3	--	--	--	--	--	--
Hypopyon	4	1.3	--	--	2	0.7	--	--
Flat Anterior Chamber of Eye	4	1.3	--	--	1	0.3	--	--
Eye Injury NOS	4	1.3	--	--	2	0.7	--	--
Iridectomy	4	1.3	--	--	--	--	--	--
Lenticular Opacities	3	1.0	3	1.0	2	0.7	--	--
Vision Abnormal NOS	3	1.0	--	--	--	--	--	--
Conjunctival Irritation	3	1.0	--	--	--	--	--	--
Vitreous Fibrin	3	1.0	--	--	1	0.3	--	--
Stye	3	1.0	--	--	2	0.7	--	--
Keratitis NOS	3	1.0	--	--	1	0.3	--	--
Corneal Striae	3	1.0	--	--	--	--	--	--
Orbital Oedema	3	1.0	--	--	--	--	--	--
Altered Visual Depth Perception	3	1.0	--	--	--	--	--	--
Scleritis NOS	3	1.0	--	--	--	--	--	--
Migration of Implant	3	1.0	--	--	--	--	--	--
Mechanical Complication of Implant	3	1.0	--	--	--	--	--	--
Implant Expulsion	3	1.0	--	--	--	--	--	--

Less Common Clinical Trial Ocular Adverse Events (< 1%, Study Eye)

Eye Disorders: cataract nuclear, eyelid disorder NOS, lens disorder NOS, scleral disorder NOS, retro-orbital pain, abnormal sensation in eye, painful red eyes, eye infection bacterial, NOS, eye infection NOS, Vogt-Koyanagi-Harada syndrome, staphyloma, herpes ophthalmic NOS, cellulitis orbital, conjunctivitis viral NOS, conjunctivitis bacterial NOS, open angle glaucoma NOS, glaucoma aggravated, chorioretinal atrophy, chorioretinal scar, photophobia aggravated, contact lens intolerance, retinal tear (excl detachment), retinal scar, macular degeneration, retinal oedema, retinal cyst, macular cyst, retinal deposits, dermatitis eyelid, eyelid margin crusting, meibomian gland discharge, optic nerve disorder NOS, halo vision, optic neuropathy NOS, retinal vasculitis, eyelid function disorder NOS, blepharospasm, keratoconjunctivitis sicca, corneal erosion, corneal perforation, sub epithelial opacities, choroidal haemorrhage, punctate keratitis, keratopathy band, corneal haze, corneal calcification, iris convex, Koeppe nodules, conjunctival follicles, conjunctival erosion, anterior chamber inflammation, retinal vascular disorder NOS, retinal neovascularisation, retinal infarction, corneal cyst NOS, iritis, uveitis NOS, iridocyclitis, eye injury NOS, retinal exudates retinopathy proliferative, astigmatism, anisometropia, myopia aggravated, refractive errors NOS, corneal defect, corneal infiltrates, episcleritis NOS, lens dislocation, eye haemorrhage, trichiasis, growth of eyelashes, blepharophimosis, blindness night, blindness NOS, strabismus, eyelid tumour, eye degenerative disorder NOS, retinitis pigmentosa, colour blindness, optic disc haemorrhage, xanthopsia

General Disorders and Administration Site Conditions: adverse drug reaction NOS, injection site oedema

Infections and Infestations: scleritis NOS, nasopharyngitis

Immune System Disorders: drug hypersensitivity, allergy to chemicals NOS, hypersensitivity NOS

Injury, Poisoning and Procedural Complications: procedural site reaction, post procedural pain, cataract fragments in eye postoperative, fibrin deposition on lens postoperative, drug toxicity NOS, abrasion NOS

Investigations: corneal staining, intraocular pressure abnormal

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps): skin papilloma,

Nervous System Disorders: headache NOS, hypoaesthesia, nystagmus NOS

Skin and Subcutaneous Tissue Disorders: rash NOS, pyogenic granuloma, skin ulcer NOS, photosensitivity reaction NOS, dermatitis contact

Surgical and Medical Procedures: eye operation NOS, intraocular lens dislocation, suture removal, conjunctival injection

Vascular Disorders: hypotension NOS, hyperaemia

Non-ocular adverse events (≥ 1%, implanted patients)

Most common non-ocular events reported included headache, nasopharyngitis, arthralgia, pyrexia, nausea, influenza, and vomiting.

Table #2 shows the occurrence of non-ocular adverse events (≥1%) in implanted patients.

Table #2: Non-ocular Adverse Events occurring in ≥ 1% of Implanted Patients

Preferred Term	0.59 mg (n = 307)		SOC (n = 74)	
	Subjects	%	Subjects	%
Nervous System Disorders				
Headache NOS	68	22.2	4	5.4
Dizziness	23	7.5	2	2.7
Paraesthesia	9	2.9	2	2.7
Migraine NOS	5	1.6	--	--
Sinus Headache	4	1.3	--	--
Hypoaesthesia	4	1.3	--	--
Loss of Consciousness	4	1.3	--	--

Preferred Term	0.59 mg (n = 307)		SOC (n = 74)	
	Subjects	%	Subjects	%
Infections and Infestations				
Nasopharyngitis	45	14.7	4	5.4
Sinusitis NOS	24	7.8	--	--
Influenza	25	8.1	5	6.8
Bronchitis NOS	11	3.6	--	--
Pneumonia NOS	10	3.3	1	1.4
Upper Respiratory Tract Infection NOS	11	3.3	2	2.7
Urinary Tract Infection NOS	8	2.6	--	--
Ear Infection NOS	5	1.6	1	1.4
Pharyngitis NOS	4	1.3	--	--
Gastroenteritis NOS	4	1.3	2	2.7
Bladder Infection NOS	4	1.3	--	--
Herpes Zoster	3	1.0	1	1.4
Staphylococcal Infection NOS	3	1.0	--	--
Infectious Mononucleosis	3	1.0	--	--
Skin and Subcutaneous Tissue Abscess NOS	3	1.0	--	--
Musculoskeletal and connective tissue disorders				
Arthralgia	40	13.0	3	4.1
Back Pain	19	6.2	4	5.4
Pain in Limb	19	6.2	--	--
Arthritis NOS	6	2.0	1	1.4
Arthritis NOS Aggravated	5	1.6	--	--
Bursitis	5	1.6	--	--
Joint Swelling	4	1.3	--	--
Myalgia	4	1.3	2	2.7
Neck pain	3	1.0	--	--
Peripheral Swelling	3	1.0	--	--
Muscle Cramps	3	1.0	--	--
Osteoporosis NOS	3	1.0	--	--
Muscle Weakness NOS	3	1.0	--	--
Gastrointestinal disorders				
Nausea	27	8.8	1	1.4
Vomiting NOS	24	7.8	3	4.1
Mouth Ulceration	9	2.9	--	--
Dyspepsia	9	2.9	1	1.4
Gastro-Oesophageal Reflux Disease	6	2.0	1	1.4
Toothache	6	2.0	--	--
Abdominal Pain NOS	6	2.0	1	1.4
Diarrhoea	7	2.3	1	1.4
Gastroenteritis Viral NOS	4	1.3	--	--
Dental Discomfort	4	1.3	--	--
Abdominal Pain Upper	3	1.0	--	--
Gastritis NOS	3	1.0	1	1.4
Tooth Caries NOS	3	1.0	--	--
Haemorrhoids	3	1.0	--	--
Constipation	4	1.3	1	1.4
General Disorders and Administration site				

Preferred Term	0.59 mg (n = 307)		SOC (n = 74)	
	Subjects	%	Subjects	%
Pyrexia	25	8.1	1	1.4
Fatigue	13	4.2	4	5.4
Pain NOS	12	3.9	--	--
Weakness	12	3.9	2	2.7
Chest Pain	10	3.3	2	2.7
Oedema Peripheral	7	2.3	1	1.4
Influenza Like Illness	5	1.6	1	1.4
Fall	3	1.0	--	--
Respiratory, Thoracic and Mediastinal Disorders				
Cough	22	7.2	1	1.4
Dyspnoea NOS	11	3.6	--	--
Upper respiratory tract infection NOS	11	3.6	2	2.7
Sinusitis NOS	10	3.3	--	--
Asthma NOS	6	2.0	--	--
Pharyngolaryngeal Pain	5	1.6	1	1.4
Sinus Disorder NOS	4	1.3	--	--
Lower Respiratory Tract Infection NOS	3	1.0	4	5.4
Pulmonary Congestion	3	1.0	2	2.7
Respiratory Tract Infection NOS	3	1.0	--	--
Nasopharyngitis	3	1.0	--	--
Pulmonary congestion	3	1.0	2	2.7
Bronchitis NOS	3	1.0	--	--
Skin and Subcutaneous Tissue Disorders				
Rash NOS	11	3.6	1	1.4
Pruritus NOS	9	2.9	--	--
Dermatitis Contact	4	1.3	--	--
Hypotrichosis	4	1.3	1	1.4
Face Oedema	3	1.0	2	2.7
Contusion	3	1.0	--	--
Abrasion NOS	3	1.0	--	--
Investigations				
Weight Decreased	9	2.9	1	1.4
C-Reactive Protein Increased	8	2.6	--	--
Blood Glucose Increase	7	2.3	2	2.7
White Blood Cell Count Increased	6	2.0	--	--
Blood Cholesterol Increased	5	1.6	1	1.4
Blood Pressure Increased	5	1.6	1	1.4
Liver Function Tests NOS Abnormal	4	1.3	3	4.1
Alanine Aminotransferase Increased	4	1.3	--	--
Hypoglycaemia NOS	4	1.3	--	--
Appetite Decreased NOS	4	1.3	--	--
Hyperlipidaemia NOS	4	1.3	--	--
Blood Bilirubin Increased	3	1.0	--	--
Weight Increased	3	1.0	1	1.4
Aspartate Aminotransferase Increased	3	1.0	--	--
Red Blood Cell Sedimentation Rate Increased	3	1.0	--	--

Preferred Term	0.59 mg (n = 307)		SOC (n = 74)	
	Subjects	%	Subjects	%
Psychiatric Disorders				
Insomnia	10	3.3	--	--
Depression	7	2.3	2	2.7
Anxiety NEC	6	2.0	--	--
Injury Poisoning and Procedural complications				
Laceration	5	1.6	--	--
Limb Injury NOS	5	1.6	--	--
Immune System Disorders				
Hypersensitivity NOS	11	3.6	--	--
Seasonal Allergy	8	2.6	--	--
Drug Hypersensitivity	9	2.9	--	--
Vascular Disorders				
Hypertension NOS	11	3.6	6	8.1
Hypotension NOS	3	1.0	--	--
Metabolism and Nutrition disorders				
Hyperglycaemia	4	1.3	-	-
Hypercholesterolaemia	6	2.0	3	4.1
Appetite decreased NOS	4	1.3	-	-
Hyperlipidaemia	4	1.3	-	-
Hypokalaemia	3	1.0	--	--
Reproductive System and Breast Disorders				
Genital Ulceration NOS	3	1.0	--	--
Renal and Urinary Disorders				
Urinary Tract Infection NOS	10	3.3	3	4.1
Urinary Incontinence	3	1.0	--	--
Blood and Lymphatic System Disorders				
Anaemia NOS	6	2.0	1	1.4
Cardiac Disorders				
Tachycardia NOS	4	1.3	--	--
Ear and Labyrinth Disorders				
Vertigo	5	1.6	--	--
Pregnancy , puerpereum and perinatal disorders				
Pregnancy NOS	4	1.3	--	--

Less Common Clinical Trial Non-Ocular Adverse Events (< 1%, implanted patients)

Blood and Lymphatic System Disorders: leucopenia NOS, leukocytes, lymphadenopathy, thrombocytopenia, neutropenia,

Cardiac Disorders: arrhythmia NOS, bradycardia NOS, left ventricular hypertrophy, cardiac sarcoidosis, palpitations, cyanosis NOS, coronary artery disease NOS, atrial fibrillation, acute coronary syndrome, endocarditis bacterial NOS

Congenital, Familial and Genetic Disorders: congenital atrial septal defect

Ear and Labyrinth Disorders: tinnitus, ear disorder NOS, deafness NOS, labyrinthitis NOS

Endocrine Disorders: cushingoid, Cushing's syndrome, thyroid nodule, hypothyroidism, goitre, thyroid disorder NOS, thyrotoxicosis, autoimmune thyroiditis, adrenal insufficiency NOS

Eye Disorders: photopsia, diplopia, glare, eyelid oedema, visual acuity reduced, orbital oedema, posterior capsule opacification

Gastrointestinal Disorders: retching, aphthous stomatitis, abdominal pain lower, tooth disorder NOS, periodontal disorder NOS, gastrointestinal discomfort, stomach discomfort, dysphagia, irritable bowel syndrome, irritable bowel syndrome aggravated, inflammatory bowel disease NOS, Crohn's disease aggravated, throat irritation, odynophagia, dry mouth, aptyalism, abdominal distension, hiatus hernia, oesophagitis NOS, lip ulceration, rectal haemorrhage, colonic polyp, tongue ulceration, diverticulitis NOS, intestinal obstruction NOS, gastrointestinal infection NOS, inguinal hernia NOS, duodenal ulcer, glossodynia, salivary gland enlargement NOS, gingival oedema, diverticulum intestinal, anal discomfort, rectocele

General Disorders and Administration Site Conditions: malaise, facial pain, axillary pain, general symptom NOS, ill-defined disorder NOS, ulcer NOS, chest tightness, energy increased, drug intolerance NOS, adverse drug reaction NOS, injection site swelling, injection site pain, injection site extravasation, discomfort NOS, feeling hot, chest mass NOS

Hepatobiliary Disorders: cholelithiasis, cholecystitis NOS, hyperbilirubinaemia, jaundice NOS, hepatic cyst NOS, bile duct stone,

Investigations: gastrointestinal obstruction NOS, enlarged prostate, glycosylated haemoglobin increased, protein urine present, blood urine present, urinary occult blood positive, urine oxalate quantitative, specific gravity urine increased, red blood cells urine, glucose urine present, neutrophil count increased, blood potassium decreased, blood potassium increased, blood viscosity increase, enzyme abnormality NOS, blood creatine increased, blood creatinine increased, red blood cell count decreased, mean cell haemoglobin increased, hematocrit decreased, blood in stool, laboratory test abnormal NOS, nuclear magnetic resonance imaging abnormal, heart rate irregular, activated partial thromboplastin time prolonged, csf abnormal NOS, platelet count increase, blood prolactin increased

Immune System Disorders: insect bite allergy, allergy to insect sting, Behcet's syndrome, sarcoidosis NOS, systemic lupus erythematosus,

Infections and Infestations: laryngitis NOS, peritonsillar abscess NOS, sinusitis chronic NOS, pyelonephritis NOS, herpes simplex, herpes viral infection, fungal infection NOS, vaginosis fungal NOS, respiratory tract infection NOS, infection NOS, abscess limb, parasitic infection NOS, localized infection, cellulitis, rash pustular, tooth abscess, tooth infection, dry socket NOS, pharyngitis streptococcal, streptococcal infection NOS, candidal infection NOS, haemophilus infection NOS, scabies infestation, leprosy NOS, hepatitis C, erythema infectiosum

Injury, Poisoning and Procedural Complications: road traffic accident, injury NOS, arthropod bite, wound NOS, accident NOS, wound haemorrhage, traumatic haematoma, animal bite, back injury NOS, tooth injury, muscle strain, tendon injury, ligament injury NOS, epicondylitis, joint sprain, foot fracture, fibula fracture, femur fracture, clavicle fracture, wrist fracture, postoperative wound site erythema, postoperative wound infection, post procedural pain, thermal burn, concussion

Metabolism and Nutrition Disorders: diabetes mellitus NOS, diabetes mellitus non insulin-dependent, anorexia, dehydration, hypoglycaemia NOS, obesity, gout

Musculoskeletal and Connective Tissue Disorders: polyarthralgia, joint effusion, musculoskeletal discomfort, muscle spasms, neck stiffness, limb discomfort NOS, contractures NOS, arthrosis NOS, joint stiffness, ankylosing spondylitis, fibromyalgia, myofascial pain syndrome, swelling NOS, neck swelling, bunion, bone spur, aseptic necrosis bone, bone lesion NOS, exostosis, myofascial spasm, muscle atrophy, myokymia, localized osteoarthritis, spinal osteoarthritis, tendonitis, ganglion, plantar fasciitis, fibula fracture, ankle fracture, coccydynia, pain in jaw, rotator cuff syndrome, upper limb fracture NOS

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps): cyst NOS, adenoma benign NOS, skin carcinoma NOS, basal cell carcinoma, squamous cell carcinoma of skin, benign breast neoplasm NOS, fibroadenoma of breast, brain neoplasm NOS, metastases NOS, thyroid adenoma NOS, oesophageal carcinoma NOS, small cell carcinoma, central nervous system lymphoma, uterine fibroids

Nervous System Disorders: frequent headaches, neurological disorder NOS, ageusia, burning sensation NOS, somnolence, depressed level of consciousness, vasovagal attack, syncope, peripheral nerve injury, gait abnormal NOS, balance impaired NOS, peripheral neuropathy NOS, neuropathy NOS, multiple sclerosis aggravated, brain herniation, spinal stenosis NOS, radiculitis brachial, cerebrovascular accident, vasculitis cerebral, memory impairment convulsions NOS, trigeminal neuralgia, mental impairment NOS, aphasia, cerebral oedema, demyelinating polyneropathy NOS, facial palsy, third nerve paralysis, hyperreflexia, facial bones fracture

Psychiatric Disorders: depression aggravated, stress symptoms, nervousness, panic attack, emotional distress

Renal and Urinary Disorders: dysuria, difficulty in micturition, calculus renal NOS, urine abnormal NOS, haematuria, glycosuria, cystitis NOS, calculus urinary, calculus ureteric, renal disorder NOS, kidney infection NOS, polyuria, cystocele

Reproductive System and Breast Disorders: menstruation irregular, uterine fibroids, endometriosis, breast cancer NOS, ovarian cyst, cervical carcinoma stage III, cervical polyp, vaginitis, menorrhagia, vulvovaginal dryness, vaginal pain, prostatitis, benign prostatic hyperplasia

Respiratory, Thoracic and Mediastinal Disorders: tonsillitis NOS, haemoptysis, throat irritation, sneezing, upper respiratory tract congestion, apnoeic attack, sinus congestion, asthma aggravated, chronic obstructive airways disease, rhinorrhoea, epistaxis, nasal turbinate hypertrophy, nasal septum deviation, rhinitis NOS, nasal congestion, rhinitis allergic NOS, respiratory tract infection viral NOS, pulmonary sarcoidosis, pulmonary granuloma NOS, laryngitis viral NOS, pleural effusion, hilar lymphadenopathy, metastases to lung

Social Circumstances: aborted pregnancy

Skin and Subcutaneous Tissue Disorders: skin eruption, exanthema, eczema NOS, dermatitis allergic, eczema seborrhoeic, skin lesion NOS, skin disorder NOS, dry skin, alopecia, acne NOS, urticaria NOS, uticaria NOS, sweating increased, rosacea, skin desquamation NOS, erythema nodosum, psoriasis, lichen planus, increase tendency to bruise, pigmentation disorder NOS, cutaneous sarcoidosis, granuloma annulare, erythema, photosensitivity reaction NOS, paronychia, epidermal cyst, rash papular, skin striae, scrotal ulcer, cellulitis

Surgical and Medical Procedures: tooth disorder NOS, tooth extraction NOS, hysterectomy NOS, nephrectomy, circumcision, nerve block

Vascular Disorders: hypertension aggravated, carotid artery stenosis, carotid artery occlusion, cerebral infarction, cerebellar infarction, vertebral artery occlusion, vertebro basilar insufficiency, haematoma NOS, thrombosis NOS, Raynaud's phenomenon, cerebrovascular accident, blood pressure inadequately controlled, pulmonary embolism, venous thrombosis deep limb, aortic aneurysm

Post-Market Adverse Drug Reactions

RETISERT™ has been marketed in the US since June of 2005. Since product approval to date (December 2007) in the U.S., twelve (12) spontaneous post-marketing cases have been reported with Restisert: 1 case of retinal detachment, 1 case of IOP decrease/ vitreous floaters/blurred vision/eye swelling/eye inflammation (reported by the patient), 1 case of scleral thinning, 1 case of menstrual disorder/tinnitus/headache/visual acuity reduced, 1 case of hypotony, 1 case of CMV retinitis, 1 case of endophthalmitis and 5 cases of lack of efficacy (one was determined to be for an unapproved indication of ocular lymphoma due to initial misdiagnosis of posterior uveitis). One case of lack of efficacy cataract, retinal tear, hyphaema and photophobia were also reported.

One published paper reported 4 cases of vitreous bands extending from the posterior pole of the eye to the implant. Three of the 4 cases developed vitreous bands more than 3 years after implantation (Lowder et al., 2007).

Implant separation (floating silicone cup) has been observed up to 5 years post implantation which necessitated immediate surgery. These findings are based on the available data; therefore, the possibility of implant separation after 5 years is unknown. Refer to Warnings and Precautions, General section.

Compared to the safety of the clinical trials up to December 2007, no unique emerging safety issues or signals have been detected in the post-marketing data.

DRUG INTERACTIONS

No interaction studies (i.e., drug-drug, drug- herb, drug-food and drug-laboratory tests) have been performed. Because of the negligible systemic levels of fluocinolone acetonide generated by the implant, interactions at the systemic level are not expected.

DOSAGE AND ADMINISTRATION

Dosing Considerations

RETISERT™ is for intravitreal implantation only.

The RETISERT™ is surgically implanted into the posterior segment of the affected eye through a pars plana incision and held in place with an anchoring suture. Clinical study data indicate that the therapeutic effect of RETISERT™ is maintained for approximately 3 years. The effective length of treatment time varies between patients and after 2 years post implantation patients should be closely monitored for clinical signs of uveitis recurrence. Following depletion of fluocinolone acetonide from RETISERT™, which may be suggested by recurrence of uveitis more than 24 months post-implantation, RETISERT™ may be removed at the physician's discretion based on the risk and benefit balance of implant removal. The safety and efficacy of re-implantation as well as the safety of the depleted implant have not been established (see Warnings and Precautions).

The average release rate of fluocinolone acetonide from the implant was estimated to be 0.4 µg/ day.

Recommended Dose and Dosage Adjustment

The recommended dosage is one intravitreal implant. The implant is inserted intravitreally and provides continuous release of fluocinolone acetonide for 30-36 months.

Missed Dose

Not applicable.

OVERDOSAGE

No information is available on overdosage in humans. Given the nature of the product (i.e., surgical implantation by physician), it is unlikely that overdose could occur. However, if signs and symptoms of overdose with RETISERT™ occur, treatment should be symptomatic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the oedema, 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.

Pharmacodynamics

Directly applied to the inflamed eye, corticosteroids exert an anti-inflammatory effect. In the case of RETISERT™, subjects in the clinical studies were implanted during a period of relative remission of their ocular inflammatory disease. Thus, it was not possible to observe an immediate anti-inflammatory effect. As well, the implantation surgery, like any ocular surgery, elicits a relatively brief period of inflammation. The intent of the product is not to have a rapid onset, but to have an extended duration of effect.

The sustained release of fluocinolone acetonide from RETISERT™ results in a reduction of uveitic inflammatory recurrences and in the area of cystoid macular oedema over approximately three years. Overall, the sustained anti-inflammatory effect preserves visual acuity, except when affected by cataract development.

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 humour samples were assayed for fluocinolone acetonide in a further subset of patients. Whilst 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.

Special Populations and Conditions

Pediatrics: RETISERT™ has only been used in a limited number of paediatric patients. The safety and effectiveness has not been established.

Geriatrics: Experience of RETISERT™ use in patients ≥ 65 years of age is limited. The safety and effectiveness has not been established.

STORAGE AND STABILITY

Store at 15-25°C in the original container. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Care must be exercised in handling of the RETISERT™ in order to avoid damage to the implant, which could affect the release of fluocinolone acetonide inside the eye. RETISERT™ must be handled only by the suture tab. Care must be taken during implantation and explantation to avoid sheer forces on the implant that could separate the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the suture tab. As with all intraocular surgery, sterility of the surgical field and RETISERT™ should be rigorously maintained. RETISERT™ should not be resterilized by any method.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RETISERT™ is an intravitreal implant containing a 0.59 mg fluocinolone acetonide tablet with the following inactive ingredients: microcrystalline cellulose, polyvinyl alcohol and magnesium stearate. The tablet is encased in a silicone elastomer cup containing a release orifice and a polyvinyl alcohol membrane positioned between the tablet and the orifice. The cup assembly is attached to a silicone suture tab with silicone adhesive. RETISERT™ is approximately 3 mm wide, 2 mm thick and 5 mm long.

Each RETISERT™ implant is packed in a clear polycarbonate case with a twist off cap. The case and cap are overwrapped with a foil pouch and placed in a polyethylene peelable overwrap. Each implant is placed in a carton. The pack contains one RETISERT™ implant.

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PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Fluocinolone acetonide

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

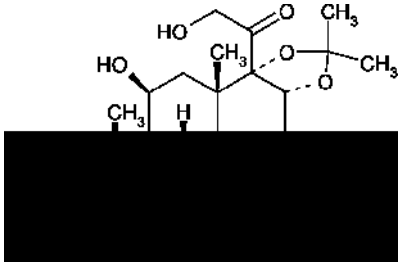
6α,9α-Difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione

6α,9α-Difluoro-16α-hydroxyprednisolone 16,17-acetonide

Molecular formula and molecular mass: $C_{24}H_{30}F_2O_6$(anhydrous), 452.50

Structural formula:



Physicochemical properties:

Appearance/Description:	White or almost white, odourless, crystalline powder
Purity:	98.0 – 102.0%, calculated on the dried basis
Melting Point:	265- 266°C (crystals from acetone + hexane)
Optical Rotation:	+95° (chloroform)
Hydrate:	Anhydrous form is used; also occurs as dihydrate
Solubility:	Practically insoluble in water 1 in 10 acetone 1 in 45 alcohol 1 in 26 dehydrated alcohol 1 in 15 to 25 chloroform 1 in 350 ether

	Soluble in methyl alcohol
Absorbance:	238 nm (log $\in$ 4.21)
Partition Coefficient:	2.5 (octanol/water)
Polymorphs:	Multiple polymorphic forms exist
Isomers:	None

CLINICAL TRIALS

Given the unique nature of the product and patient population for RETISERT™, a typical Phase I, Phase II and Phase III development path was not appropriate. In particular, it was considered inappropriate to test this product in healthy volunteers for Phase I safety evaluation.

Evaluation of a wide range of doses from 0.59 mg (the lowest manufacturable dose) to 15 mg showed that the higher doses tended to have greater effects on elevating intraocular pressure. Thus, as the investigations progressed, lower doses were used. Based upon the safety profile on intraocular pressure, and the perception from the Investigators that the treatments were effective, for subsequent studies, the 0.59 mg and 2.1 mg intravitreal implants were used.

Two study designs were utilized in the pivotal clinical trials: 0.59 mg fluocinolone acetonide implant vs. standard of care (SOC) treatment (BLP 415-002); and 0.59 mg vs. 2.1 mg fluocinolone acetonide implant (BLP 415-001). Two dosage strengths of the fluocinolone acetonide implant were evaluated in the clinical trials, 0.59 mg and 2.1 mg.

In both designs, subjects with either unilateral or bilateral non-infectious uveitis affecting the posterior segment of the eye were enrolled. For subjects with bilateral disease, the more severely affected eye was chosen to be the study eye. It was expected that for bilateral subjects, the less severely affected eye had to be controlled with only periocular injections for 1 year. The control for the 415-002 study design was the group of subjects enrolled in the standard of care (SOC) arm, which required administration of systemic corticosteroids and if necessary, administration of systemic non-steroidal immunosuppressive agents for a minimum period of 6 months.

For the study design employed in the BLP 415-001 study, two types of controls were employed: 1) a historical control; and 2) a dose-comparison (0.59 mg vs. 2.1 mg) for both safety and efficacy evaluations.

Study demographics and trial design

Table #3- Summary of patient demographics for clinical trials in specific indication

Study # and design	Dosage, route of administration and duration	Study subjects (n=number)	Age Range (years)	Gender	Race	Duration of Treatment
BLP 415-002 Open-label, parallel	0.59 mg implant Standard of Care	140	12 to 75	Male – 58 Female – 82	Caucasians – 124 Black – 1 Hispanics – 8 Other - 7	3 years
BLP 415-001 Double (dose) masked parallel	0.59 mg implant 2.1 mg implant	278	7 to 84	Male – 77 Female – 201	Caucasians – 184 Blacks – 49 Asians – 21 Hispanics – 17 Other - 7	3 years

Study results

RETISERT™ was shown to be efficacious for the treatment of uveitis affecting the posterior segment of the eye as demonstrated by the results of the clinical trials. In the assessment of efficacy, the primary efficacy variable for the BLP 415-002 study design was the time to first protocol defined recurrence of uveitis in the study eye occurring in the 24 months after randomization for the SOC group and the 24 months after Visit 7 for the implant group. The first 12 weeks to Visit 7 were excluded for the implant group to allow post-operative inflammation therapy to be discontinued to prevent post-operative inflammation from being recorded as a recurrence, and to allow the tapering of previous anti-inflammatory systemic therapy. For the BLP 415-001 uveitis study the primary efficacy analyses involved a comparison of the rates of protocol-defined recurrences of uveitis before and after implantation.

<u>BLP 415-002</u>

The time to recurrence of uveitis for implant vs. SOC study eyes was evaluated by Kaplan Meier methods (freedom from recurrence). A clinically significant impact of RETISERT™ was observed as evidenced by the freedom from uveitis recurrence through two years of study, but the Kaplan Meier analysis did not demonstrate a statistically significant difference between the implant and SOC study eyes when both observed and inferred recurrences were considered (p=0.065). It was noted that many of the failures were not due to clinical signs of inflammation but instead, due to inferred failures because of excess exposure to systemic immunosuppression resulting from incorrect tapering. These observations were recorded as uveitis recurrence.

To better understand the impact of failures inferred for reasons not associated with ocular inflammation, a supplementary analysis considering these cases, censored instead of failed, was conducted. For the supplementary analysis, each subject with an inferred failure was re-assessed to determine if they failed for reasons associated with ocular inflammation. A failure was reported in a total of 67 subjects (in the implant and SOC treatment groups); of those failures, 26 were inferred (18 in the implant group and 8 in the SOC group). Only 3 of the 11 implant failures reported for Time 0 were due to clinical signs, accounting for the biggest difference between the primary and supplemental Kaplan-Meier plots. The slope of the supplemental survival curve for the study eyes clearly demonstrated the benefits of the implant treatment. The time-to-recurrence of uveitis in the implant study eyes was considerably longer than the SOC study eyes (p=0.0008).

When the efficacy of the implant was stratified according to the SOC type at baseline (prior to study initiation), greater efficacy of the implant (prevention of recurrence) was shown for patients that took corticosteroids alone at baseline. Evidence of efficacy of the implant was also shown for patients that took corticosteroids and one immunosuppressant at baseline, but the difference was not statistically significant. Because of the limited number of patients taking corticosteroids and two immunosuppressants at baseline, no conclusions could be reached for that sub-group.

When the number of recurrences in the 52-week pre-treatment period was compared to the 2-year post-treatment period, there was a statistically significant difference in favour of the implant study eye (p=0.0 140) compared to the SOC study eye. Visual acuity was maintained in both the SOC and the implanted eyes during the course of the study. Differences were not statistically significant (p=0.655).

BLP 415-001

The primary efficacy measure for the BLP 415-001 study was a comparison of rates of recurrence between the pre-implantation and the 34 week, 1 year, 2 year, and 3 year postimplantation time points, recurrences were imputed (assumed) for these time points when a subject was not seen within 10 weeks of their scheduled visits.

For both dose groups combined, uveitis recurrence rates in study eyes were reduced from 59.7% (166/278) during the one year pre-implantation period to 32.7% (9 1/278) at 3 years post-implantation, using observed data only (p<0.0001), (40.7% [113/278] using imputed data [p<0.0001]). In the 0.59 mg dose group, 1 year pre- and 3 years post-implantation uveitis recurrence rates for study eyes were 61.8% and 20.0%, respectively, using observed data only (30.0% using imputed data at 3 years). The differences for both observed and imputed data were statistically significant (p< 0.0001). In the 2.1 mg dose group, uveitis recurrence rates for study eyes for the 1 year period prior to implantation and 3 years post-implantation were 58.3% and 41.1%, respectively, using observed data (p = 0.0006), (47.6% using imputed data at 3 years [p = 0.0314]). For both dose groups combined, uveitis recurrence rates in fellow eyes increased from 25.5% (70/275) during the one year pre-implantation period to 57.1% (157/275) at 3 years post-implantation, using observed data only (p<0.0001), (63.3% [174/275] using

imputed data [p<0.0001]). A reduced need for systemic therapy and for periocular injections (in study eyes) to control uveitis was observed by the 3-year post-implantation visit, compared with the enrollment visit (p<0.0001 for each dose group and both dose groups combined). The mean change from baseline in visual acuity of implanted eyes was statistically insignificant in both dose groups. On average, reductions in visual field were small, less than 2dB, but were statistically significant for both implanted and fellow eyes, p<0.005.

For study eyes in both dose groups combined, 56.8% (54/95) of eyes showed a reduction in the area of CME between baseline and 3 years post-implantation, compared with 24.2% (23/95) of fellow eyes (p<0.0001). An analysis of the change in mean area of CME from baseline to each post-implantation visit showed that in the 0.59 mg dose group, mean CME area decreased up to 34 weeks post-implantation and remained relatively constant thereafter.

Conclusion

The two pivotal studies, BLP 415-002 and BLP 415-001 were confirmatory of each other in demonstrating that RETISERT™ is highly efficacious in controlling inflammation secondary to non-infectious uveitis affecting the posterior segment of the eye.

DETAILED PHARMACOLOGY

Animal Pharmacology

Sixteen 0.5 µg/day implants and sixteen 0.1 µg/day implants were implanted into the vitreous of the right eye of NZW rabbits fourteen days after subcutaneous injection of tuberculin antigen. Control animals (n=14) received empty implants. A masked observer graded corneal neovascularization, anterior chamber (AC) flare cell, iris congestion, and vitreous opacity on days 1-7, 9, 16 and 21 after uveitis induction. Animals were sacrificed on days 6 and 9 for aqueous WBC count, and protein measurement. Retinal function was evaluated by ERG. Histological sections of enucleated eyes were studied under light microscopy.

By clinical criteria, treated eyes were significantly less inflamed than untreated eyes. Anterior chamber cell flare and vitreous opacity were significantly reduced (p≤0.02) in both drug implant groups compared with control animals. Overall, inflammation was suppressed to a greater degree with the 0.5-µg/day implant compared to the 0.1-µg/day implant but there was no significant difference between 0.1- and 0.5-ȝg/d implants. As compared to the control eyes, treated eyes had a reduction in aqueous WBC count and protein concentration, and had lower inflammatory grade at histopathologic examination; however, these differences were not statistically significant. It is concluded that the fluocinolone acetonide intravitreal implant suppresses ocular inflammation in a rabbit model of severe uveitis. (Mruthyunjaya, 2006).

Safety Pharmacology
No specific safety pharmacology experiments with the intravitreal implant have been done. Although some local ocular secondary pharmaceutical effects were observed, systemic secondary pharmacological actions are not expected to occur as systemic levels of fluocinolone acetonide resulting from the implant are negligible.

Pharmacokinetics-Distribution
In a one-year study, 24 rabbits received a 0.59 mg intravitreal implant. Based on the amount of fluocinolone acetonide remaining in the intravitreal implants after removal, the in-vivo release rate was indirectly estimated to be 0.76 μg/ day.

TOXICOLOGY

Toxicology studies investigated primarily 0.59, 2.1 and 6 mg fluocinolone acetonide intravitreal implants.

Rabbit and dog studies were conducted using intravitreal implants to assess ocular and systemic uptake, as well as the safety of the fluocinolone acetonide released from the implant. These studies investigated primarily 0.59, 2.1 and 6 mg fluocinolone acetonide intravitreal implants. In summary, fluocinolone acetonide intravitreal implants were well tolerated in rabbits, while in dogs significant abnormal findings were made.

Overall, results of rabbit studies suggested that the implant was well tolerated. However, in a one-year study in NZ black/satin cross rabbits, the electroretinography tests showed low b-wave amplitude without change in latencies. These changes were however not consistent and it is not clear whether or not these changes were related the fluocinolone acetonide implants.

A one-year study was conducted in 54 beagle dogs, 36 received fluocinolone acetonide intravitreal implants (0.59 mg, or 2.1 mg, or 6.0 mg) in one eye and 18 received a sham implant or no implant at all. Findings included the following:

- Eleven dogs had severe ocular lesions associated with ocular inflammation. It is not clear whether the ocular inflammation was a post-surgical complication per se or was due to fluocinolone acetonide implants
- Corneal opacities that were interpreted as species-specific to dogs with no relevance to humans
- Increased incidence of cataracts might have been due to fluocinolone acetonide, or to the mechanical contact between the implant and posterior surface of the lens.
- Findings in the adrenal glands (microvacuolar change and/or cortical atrophy). It is not clear whether these findings were related to fluocinolone acetonide or to corticosteroids received from other routes (eye ointment/drops, or systemic).

Significant, fluocinolone acetonide implant related, systemic toxic effects were not observed in both species. Some, generally minimal to mild, histopathological changes to liver, adrenals and thymus were observed in the dogs. However, the surgical procedures involved in inserting the implants into the dog's eye necessitated the administration of topical and systemic corticosteroids to control inflammation. The exact cause of the histopathological effects cannot be established, but it appears likely that they were caused by the long-term supplementary use of therapeutic corticosteroids. Similar findings were not observed in rabbits, which did not require additional corticosteroid therapy.

Single Dose Toxicity
After implantation, the implant is intended to stay in the vitreous for a prolonged period of time. Therefore the toxicity studies performed with the implants involved long-term exposure. These studies showed that the implanted fluocinolone acetonide implants did not cause any acute toxic effects.

Acute toxicity of the empty intravitreal implant was assessed from a medical device standpoint after intraperitoneal/intravenous injection of implant extracts in mice and after intravenous injection of implant extracts in rabbits. These studies showed that extracts of the implant do not induce any systemic toxicity.

Reproduction Toxicity
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. When fluocinolone acetonide was administered subcutaneously at a dose of 0.13 mg/kg/day (approximately 10,000 times the daily clinical dose from RETISERT^{TM}), during days 6 to 18 of pregnancy in the rabbit, abortions were induced at the end of the third and at the beginning of the fourth gestational week (Kilhström and Lundberg, 1987). When fluocinolone acetonide was administered subcutaneously to rats and rabbits during gestation at a maternally toxic dose of 50 µg/kg/day (approximately 4,000 times the clinical dose from RETISERT^{TM}), abortions and malformation were seen in a few surviving foetuses (Casilli et al, 1977).

At doses exceeding the intended clinical dose by many orders of magnitude considering the release rate from the implant and the negligible, if any, systemic uptake of fluocinolone acetonide from the implant, fluocinolone acetonide could potentially be teratogenic. This is considered a class effect of glucocorticosteroids. No evidence of toxic effects on the reproductive organs was observed in the 1-year studies in dogs and rabbits

Long-term animal studies have not been performed on RETISERT^{TM} to evaluate the effect of fluocinolone acetonide on fertility.

Genotoxicity
The standard battery of *in vitro* and *in vivo* genotoxicity studies were conducted with fluocinolone acetonide in accordance with the ICH guidances.

Fluocinolone acetonide demonstrated no mutagenic potential in *in vitro* (Ames test and Mouse Lymphoma test) and *in vivo* (Micronucleus test) tests. Most of the published data report that fluocinolone acetonide is both non-carcinogenic as well as an inhibitor of DNA synthesis and an inhibitor of tumour promotion. Based on the absence of suspicious toxic effects in the long term implant studies, the negative mutagenic potential and the negligible systemic exposure resulting from the intravitreal implant, further investigation into the carcinogenic potential of fluocinolone acetonide did not seem warranted. Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

The genotoxic potential of the empty RETISERT™ was assessed in specific biocompatibility studies. These studies were part of the biocompatibility testing package. The three studies (*in vitro* and *in vivo)* studies showed that the RETISERT™ implant extracts did not present any mutagenicity risk.

Carcinogenicity
Long-term animal studies have not been performed on RETISERT™ to evaluate the carcinogenic potential.

No evidence of preneoplastic or hyperplastic lesions was observed in the 1-year toxicity studies in implanted dogs and rabbits. There was no relevant local ocular reaction or other pathophysiological response to fluocinolone acetonide following long-term implantation either.

The majority of studies dealing with fluocinolone acetonide's carcinogenic potential show that it is an inhibitor of chemically-induced tumours as well as an inhibitor of tumour promoter-induced formation of adducts when co-administered. Two published studies however found some tumour enhancement effect of fluocinolone (Fukao et al., 1988; Woodworth et al., 1986).

Topical Toxicity
The two long-term intravitreal implant studies have shown good local tolerance of the complete, drug-containing implant.

Corticosteroids in sufficient dosage are known to diminish tissue repair processes (Schimmer and Parker, 2001; Martindale's Extra Pharmacopoeia, 1996b), but there has been no evidence of harm due to that activity in the toxicity tests.

Immunotoxicity
No immunotoxicity studies have been conducted on RETISERT™.

It is anticipated that fluocinolone acetonide will exhibit the same effects as other corticosteroids on the immune system (Martindale's Extra Pharmacopoeia, 1996b; Schimmer and Parker, 2001).

The potential risk for immunotoxic effect (suppression of host response) cannot be excluded, especially in the implanted eye, and should be considered when prescribing RETISERT™ (see Warnings and Precautions).

Biocompatibiity
A comprehensive set of conventional experiments has been done to explore local tolerance, cytotoxicity, sensitizing potential, and genotoxicity of blank RETISERT™ implants not containing fluocinolone acetonide.

The device was tested for haemolytic potential and cytotoxicity of saline, oil or DMSO extracts and of the solid plastics in contact with cell cultures, extensive genotoxicity testing was done *in vitro* and *in vivo*, and sensitizing potential, pyrogenicity of extracts, muscle irritancy and effect on tissue repair after *in vivo* implantation were investigated.

In general the extracts and the device itself showed no harmful action in any of the tests. The blank device and aqueous and sometimes oil extracts did produce slight cytotoxic/cytostatic effects in certain but not all studies, but usually within the limit of acceptability of USP 26/NF 21 (2003). There was no evidence of any potential for an unacceptable level of tissue damage or irritancy, sensitization, pyrogenicity, haemolysis or genotoxicity.

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PART III: CONSUMER INFORMATION

PrRETISERT™
flucocinolone acetonide

This leaflet is part III of a three-part "Product Monograph" published when RETISERT™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RETISERT™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RETISERT™ is used to treat a rare inflammatory disease called non-infectious posterior uveitis that affects the back section of the eye.

What it does:
RETISERT™ is a brand name for a drug that belongs to a group of medicines called corticosteroids which are used to reduce inflammation. It is believed that RETISERT™ reduces inflammation in your eye by blocking the production of substances that cause inflammation.

When it should not be used:
RETISERT™ should not be used if you:

- Have a bacterial infection in your eye
- Have a viral infection in your eye
- Have a fungal disease in your eye
- Are allergic or have a known or suspected hypersensitivity to any of the ingredients in RETISERT™ or other corticosteroids (see what the nonmedicinal ingredients are).

What the medicinal ingredient is:
RETISERT™ is a small, sterile implant that contains the active ingredient fluocinolone acetonide. Fluocinolone acetonide belongs to a group of medicines called corticosteroids. Corticosteroids are known to reduce inflammation.

What the important nonmedicinal ingredients are:

- Magnesium Stearate
- Microcrystalline Cellulose
- Polyvinyl Alcohol
- Silicone Elastomer
- Silicone Adhesive

What dosage forms it comes in:
0.59 mg intravitreal implant

WARNINGS AND PRECAUTIONS

BEFORE you are implanted with RETISERT™ talk to your doctor or pharmacist if:

- You have a mycobacterial infectious disease
- You have a fungal disease of the eye
- You are pregnant or intend to become pregnant. If you become pregnant after RETISERT™ has been put into your eye, tell your doctor so that he can decide if your RETISERT™ must be removed.
- You are breast feeding or intend to breast feed. Your doctor will tell you whether to stop or continue breast feeding once RETISERT™ has been put into your eye.
- You have known or suspected hypersensitivity to any of the ingredients in RETISERT™ or other corticosteroids.
- You have had recent eye surgery or further eye surgery is planned.

Tell your doctor if you are taking or have recently taken any other medicines, especially other corticosteroids, including medicines obtained without a prescription. These medicines may affect how you feel during surgery. Your doctor will prescribe eye drops for you to use after the operation. All eye care products must be discussed with your doctor before use.

Your doctor will tell you about eating and drinking at the time of the operation to implant RETISERT™. Once the operation is over, you will be able to eat and drink as normal.

After the operation you are likely to have blurred vision for up to four weeks. Do not drive or operate machinery until you can see clearly again. If you have any concerns about how well you can see, talk to your doctor to have your eyes tested. Always tell your doctor that you have RETISERT™ in your eye because it will be visible during the examination.

Contact your doctor if an eye infection develops or your eye condition worsens.

INTERACTIONS WITH THIS MEDICATION

Drug interactions were not studied with this product and are not expected.

PROPER USE OF THIS MEDICATION

Usual dose:
A doctor in a hospital will implant RETISERT™ into the eye by making a small incision (cut) in the sclera (white part of the eye).

Each RETISERT™ implant contains 0.59 mg of fluocinolone acetonide. You will not be able to feel RETISERT™ after it has been implanted in your eye. The active substance is slowly released from the implant into your eye over approximately 3 years. Your doctor will decide if you need another RETISERT™ implanted after approximately 3 years. It will take about one month before you get the benefits from RETISERT™

Overdose:
Given the nature of the product (i.e., surgical implantation by physician), it is unlikely that overdose could occur.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, RETISERT™ can cause side effects, although not everybody gets them. As with any surgical procedure there is risk involved. If any side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

If you get any of the following side effects you must contact your doctor. More than 1 in 10 patients may experience the following side effects from RETISERT™ treatment:

- A rise in the pressure inside your eye with or without glaucoma – you will not be able to tell if this is happening and it is therefore important that you have your eyes checked regularly by your doctor
- Blurred vision from the operation.
- Cataract (clouding of the lens of your eye). Your doctor must check your eyes regularly to see if a cataract is forming. Cataract requires surgery.
- Blurred vision due to cataract formation
- Eye pain from the operation.
- Appearance of Floaters in the eye.

Other side effects that may affect more than 1 in 10 patients include:

- Bleeding in the eye – if this happens see your doctor immediately.
- Swelling of the eye lids
- Increased tear production
- Irritation of the eye (itching, feeling there is 'something' in the eye)
- Photophobia (pain in the eye in strong light)
- Runny nose or cough
- Feeling of, or being sick
- Headache or dizziness

This is not a complete list of side effects. For any unexpected effects, contact your doctor or pharmacist.

HOW TO STORE IT

RETISERT™ is stored at the hospital until it is implanted in your eye. It is kept in its original package at a temperature of 15-25°C until surgery takes place.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345 By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Bausch & Lomb, at:
1-800-686-7720 (English)
1-800-686-0002 (French)

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