Fluocinolone Acetonide 0.19mg Intravitreal Implant (ILUVIEN)

National Drug Monograph

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/ Mechanism of Action	Corticosteroids inhibit inflammatory responses to a variety of inciting agents. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation
Indication(s) Under Review	Diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure
Dosage Form(s) Under Review	Non-bioerodable intravitreal implant containing 0.19mg of fluocinolone acetonide (FA) designed to release FA at an initial rate of 0.25mcg/day and lasting 36 months
REMS	☐ REMS ☒ No REMS There are no Post Marketing Study requirements
Pregnancy Rating	Category C

Executive Summary	
Efficacy	FA 0.19mg insert was shown to significantly improve visual acuity relative to sham. Pseudophakic eyes and patients with chronic DME had greater improvement.
Safety	• Increase intraocular pressure and need for treatment interventions occurred more frequently with FA than sham. • Development of cataracts in phakic eyes and need for intervention occurred more frequently with FA than sham • Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber • Use of steroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses
Other Considerations	Potential for confusion with fluocinolone acetonide 0.59mg (Retisert) Less frequent administration compared to dexamethasone insert and triamcinolone intravitreal injection Patients were excluded from the FAME clinical trials if they had glaucoma, ocular hypertension, intraocular pressure (IOP) >2mmHg, or were using IOP-lowering drugs
Projected Place in Therapy	VEGF-inhibitors have become first-line drug treatment of DME. Intravitreal administration of steroids would be considered a second-line drug therapy option or as first-line for those unable to use VEGF-inhibitors. The use of FA 0.19mg insert is approved for patients with DME who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

Background

Purpose for Review	The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating fluocinolone acetonide (FA) for possible addition to the VA National Formulary.

Other Therapeutic Options

Formulary Alternatives	Other Considerations
Ranibizumab Aflibercept Bevacizumab (off-label)	VEGF inhibitors have become first-line treatment option for central DME. Patients may require administration of drug as often as once monthly.
Triamcinolone acetate preservative-free (off-label)	Steroids have a high risk for developing cataracts and elevated IOP. Frequency of administration is every 3-4 months
Non-formulary Alternatives	**Other Considerations**
Dexamethasone intravitreal implant	Steroids have a high risk for developing cataracts and elevated IOP. Frequency of administration every 6 months
See Appendix 1 for an indirect comparison of outcomes for 3-year trials for FA implant, dexamethasone implant and intravitreal triamcinolone	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2015) using the search terms fluocinolone acetonide, diabetic macular edema. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

The FDA approval of FA was based on 2 trials (FAME) that were conducted under a single protocol. These trials were randomized, double-blind, double-dummy, and placebo-controlled. Randomization took place according to baseline best-corrected visual acuity (BCVA) letter score ≤40 and >40.

Select Inclusion criteria for the trial were foveal thickness (FTH) at center point ≥250µm despite ≥1 prior focal/grid macular laser photocoagulation treatment, BCVA letter score 19-68 (20/50-20/400). Exclusions included glaucoma, ocular hypertension, intraocular pressure (IOP) >21mmHg, use of IOP-lowering drugs.

Demographic and mean baseline information was as follows: age 62.5 years, 59.4% males, time to diagnosis of DME 3.6 years, A1C 7.8%, pseudophakic 34.8%, BCVA 53.4 letters, center point thickness 469µm, IOP 15.2mmHg, cataract at baseline 47.1% (16.5% no cataract, 36.4% cannot grade or not applicable). In the 36-week study, 57.5% and 42.5% had chronic (≥3 years) and nonchronic (<3 years) DME respectively.

Patients were randomized to FA 0.2mg, 0.5mg, or sham. Rescue focal/grid laser for persistent edema was allowed after 6 weeks and could be repeated as frequently as every 3 months. Retreatment with originally assigned drug was allowed after month 12 if there was a loss of ≥5 letters in BCVA or increase in FTH ≥50µm compared to patient's best status during previous 12 months.

The primary outcome was the percentage of patients with improvement from baseline BCVA of 15 letters or more at month 24.

EFFICACY (Table 1)

Visual Acuity Outcomes

The percentage of patients who gained ≥15 letters in BCVA and mean change from baseline in BCVA at 24 months was significantly greater with FA than sham. This effect was maintained at 36 months.

Subgroup analysis at 24 months showed that pseudophakic eyes had greater mean improvement in BCVA letter score than phakic eyes; however, there was no difference in the percentage of eyes that had a gain of ≥15 letters. Another subgroup analysis at 36 months found that those with chronic DME (≥3 years) had greater improvement in BCVA outcomes than those who had a shorter duration of DME (<3 years).

Anatomic Outcomes

More patients receiving FA had a CPT ≤250µm at 24 months. At 24 months, the mean central point thickness (CPT) was significantly lower with FA than sham; however, at 36 months only the subgroup with nonchronic DME receiving FA had a significantly greater reduction in in CPT than sham.

Number of study drug treatments

At months 24 and 36, the percentage of patients receiving 1, 2, or ≥3 doses of study drug was similar for FA and sham. Approximately 75% of patients required 1 FA implant over 36 months.

Need for additional therapies

After 6 weeks into the study, focal/grid laser treatment was allowed and may be performed as frequently as every 3 months for persistent DME. Approximately 40% of FA patients required ≥1 treatment compared to 60% of those in the sham group. The need for focal/grid laser treatments was similar for those with chronic and nonchronic DME.

Non protocol treatments (i.e., VEGF-inhibitors and intravitreal triamcinolone) could be administered when the investigator felt obligated to consider other treatments for those patients who have not shown improvement. Patients were not required to exit the study and the treatments were recorded as a protocol deviation. Significantly more patients receiving sham required additional non-protocol treatments.

Table 1: FAME Study Outcomes

	24 months		36 months	
	FA 0.2mcg/day	**Sham**	**FA 0.2mcg/day**	**Sham**
n	376	185	376	185
Completed 24 months (%)	80.1	77.3	-	-
Completed 36 months (%)	-	-	70.6	68.1
Gain of ≥15 letters in BCVA (%)	28*	16	28.7*¶	18.9¶
-Pseudophakic	28	13	-	-
-Phakic	29	18	-	-
-Chronic DME (≥3 yrs)	-	-	34.0*	13.4
-Nonchronic DME (<3 yrs)	-	-	22.3	27.8
Loss of ≥15 letters in BCVA (%)	12.8	7.6	-	-
-Pseudophakic	5	11	-	-
-Phakic	17	6	-	-
Mean change from baseline in BCVA	4.4*	1.7	5.3*¶	2.0¶
-Pseudophakic	7.1	1.5	-	-
-Phakic	2.8	1.8	-	-
-Chronic DME (≥3 yrs)	-	-	7.6*	1.8
-Nonchronic DME (<3 yrs)	-	-	2.4	2.3
CPT ≤250µm (%)	51	40	-	-
Mean CPT (µm)	293*	340	300	309
Change in CPT (µm)				
-Chronic DME (≥3 yrs)	-	-	-186.8	-160
-Nonchronic DME (<3 yrs)	-	-	-173.1*	-115.6
Received 1/2/≥3 study treatments (%)	76.5/21.3/2.2	76.2/19.5/4.3	74.4/21.6/4	71.7/23.4/4.9
-Chronic DME (≥3 yrs)	-	-	76.1/18.7/5.3	66.1/27.7/6.3
-Nonchronic DME (<3 yrs)	-	-	72.7/24.8/2.4	80.6/16.7/2.8
Need for focal/grid laser treatment (%)	36.7*	58.9	-	-
-Chronic DME (≥3 yrs)	-	-	40.7*	61.6
-Nonchronic DME (<3 yrs)	-	-	42.8	62.5
Received off-protocol treatment (%) ^	12.5	28.6	-	-
-Chronic DME (≥3 yrs)	-	-	13.4*	34.8
-Nonchronic DME (<3 yrs)	-	-	17.5*	30.6

*Significant vs. sham

¶Results for those who remained in the study for 36 months for FA and sham respectively: BCVA ≥15 letters 33% and 21.4% (p=0.03); those with chronic DME 38.9% and 16% (p<0.001); Mean change BCVA letter score 8.1 A and 3.1 (p=0.007)

^Off-protocol treatments included intravitreal triamcinolone and VEGF-inhibitors

Potential Off-Label Use

Age Related Macular Degeneration
Macular edema due to retinal vein occlusion

Safety (for more detailed information refer to the product package insert)

Boxed Warning

None

Contraindications

- Active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- Patients with glaucoma who have cup to disc ratios greater than 0.8
- Known hypersensitivity to any components of this product

Warnings/ Precautions

- Intravitreal injection-related effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Monitor patients following intravitreal injection.

- Steroid-related effects: Use of steroids may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of steroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

  Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection

- Risk of implant migration: patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber

Safety Considerations

There is an ongoing 5-year open-label prospective observational study (patient registry) to evaluate safety of FA. Expected enrollment is 800 patients and anticipated primary completion date is December 2018.

Increased intraocular pressure

Increase in IOP and need for treatment interventions occurred more frequently with FA than sham.

Table 2: Intraocular Pressure-Related Adverse Events (36 weeks)

	FA (n=375)	Sham (n=185)
Any IOP increase (%)	37	12
IOP increase ≥ 10 mmHg from baseline (%)	34	10
IOP increase ≥30mmHg (%)	20	4
Any IOP-lowering medication (%)	38	14
Any surgical intervention for elevated IOP (%)	5	1

Cataracts and cataracts surgery in phakic patients

Cataracts developed in 82% and 50% of FA and sham patients respectively. The median time to cataract being reported was 12 months and 9 months respectively. Among these patients 80% of FA patients and 27% of sham patients underwent cataract surgery, generally within the first 18 months (median 15 months for both groups).

Table 3: Cataracts and Cataracts Surgery in Phakic Patients (36 weeks)

	FA (n=235)	Sham (n=121)
Cataract considered an AE (%)	81.7	50.4
Cataract surgery (%)	80.0	27.3

Cardiovascular

At 24 months, serious cardiovascular events were reported in 12% (FA 0.2), 13.2% (FA 0.5) and 10.3% (sham) of randomized patients. Types of events were evenly distributed except for MI which occurred in 4% of the (FA 0.2), 2.8% (FA 0.5), and 1.1% of the sham groups.

Other serious CV AEs reported numerically more often with FA (incidence ≤ 1.1%) than sham were unstable angina, cardiac arrest, cardiac disorder, and cardiac failure.

Adverse Reactions

			FA (n=375) (%)	Sham (n=185) (%)
Common adverse reactions	Ocular adverse reactions reported by ≥1% of patients	Cataract in phakic patients	192/235 (82)	61/121 (50)
		Myodesopsia	21	9
		Eye pain	15	14
		Conjunctival hemorrhage	13	11
		Posterior capsular opacification	9	3
		Eye irritation	8	6
		Vitreous detachment	7	7
		Conjunctivitis	4	3
		Corneal edema	4	2
		Foreign body sensation in eye	3	2
		Eye pruritus	3	2
		Ocular hyperemia	3	2
		Optic atrophy	2	1
		Photophobia	2	1
		Retinal exudates	2	0
		Anterior chamber cell	2	1
		Eye discharge	2	1
	Non-ocular adverse reactions reported by ≥5% of patient	Anemia	11	5
		Headache	9	6
		Renal failure	9	5
		Pneumonia	7	4

Death/Serious adverse reactions	**Deaths** Results for FA 0.2, FA 0.5, and sham respectively. Cause of death not provided in publication. Month 24: 6.4%; 5.8%, 3.8% Month 36: 7.2%; 7.8%; 5.9% **SAEs include** glaucoma, increased IOP, cataract surgery, glaucoma surgery, cardiovascular events, and are discussed in the Safety Considerations section.
Discontinuations due to adverse reactions	Results for FA 0.2, FA 0.5, and sham respectively Month 24: 1.1%; 5.1%, 1.6% Month 36: 1.1%; 3.8%; 2.7%

Drug Interactions

Drug-drug interactions	None
Drug-food interactions	None
Drug-lab interactions	None

Risk Evaluation

As of June 2015

Sentinel event advisories: None
Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Fluocinolone acetonide 0.19mg	Fluocinonide	None	None	Fluocinolone acetonide 0.59mg (Retisert) Flunisolide Fludrocortisone Fluoromethalone
Iluvien				Ilevro Iletin Levulan

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Needle size 25G needle
Storage: 15°-30°C (59°-86°F)
Pharmacokinetics: Plasma FA concentrations were below the lower limit of quantitation (100pg/mL) of the assay at all post-administration time points from day 7 though month 36.

Dosing and Administration

Iluvien contains 0.19 mg of fluocinolone acetonide. The intravitreal implant is designed to initially release 0.25 µg of fluocinolone acetonide/day and lasting 36 months.

The intravitreal injection procedure for FA should be carried out under aseptic conditions. Adequate anesthesia and broad-spectrum antibiotic should be given prior to injection. Please refer to product package insert for detailed information on the injection procedure.

Following the injection, monitor patients for elevation in IOP and for endophthalmitis. This may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between 2 and 7 days following the injection.

Patients should be instructed to immediately report symptoms suggestive of endophthalmitis.

Special Populations (Adults)

	Comments
Elderly	No overall difference in safety and efficacy between elderly and younger patients.
Pregnancy	• No adequate well-controlled studies in pregnant women. Use during pregnancy if potential benefits outweigh potential risks to the fetus. • Animal reproduction studies have not been conducted with FA. Corticosteroids have been shown to be teratogenic in lab animals when administered systemically at relatively low dosage levels.
Lactation	Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroids production. The systemic concentration of FA following intravitreal treatment with ILUVIEN is low. It is not known if intravitreal ILUVIEN could result in sufficient systemic absorption to produce detectable quantities in human milk. Use with caution in nursing women.
Renal Impairment	No data identified

Hepatic Impairment	No data identified
Pharmacogenetics/ genomics	No data identified

Projected Place in Therapy

VEGF-inhibitors have become first-line drug treatment of DME. Intravitreal administration of steroids would be considered a second-line drug therapy option or as first-line for those unable to be administered VEGF-inhibitors. The use of FA 0.19mg insert is restricted to patients with DME who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. FA has a longer duration of action to 36 months with one injection, as compared to other available agents with shorter durations of effect.

Studies directly comparing FA, dexamethasone, and triamcinolone (TCA) are needed. Indirect comparison of 3 year outcome data indicates slightly better visual outcomes for FA than dexamethasone implant or intravitreal TCA. Development of cataracts and increased IOP was greater with FA than dexamethasone, and similar to the higher dose of TCA. Selection of drug should take into account convenience, risk of adverse events, and cost.

References

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Prepared by Deb Khachikian, PharmD
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Appendix 1: Indirect Comparison of Steroids 3-year Outcomes for Treatment of DME

	Fluocinolone implant- 3yr		Dexamethasone Implant- 3yr		Intravitreal triamcinolone- 3yr	
	Study 1 (n=190)	**Study 2 (n=186)**	**Study 1 (n=163)**	**Study 2 (n=165)**	**1mg (n=93)****	**4mg (n=98)****
Mean Baseline BCVA	53	53	56	55		
Gain of ≥15 letters in BCVA	27	31	21	18	20	21
Loss of ≥15 letters in BCVA	14	12	9	18	17	16
Mean change in BCVA	3.7	5.2	4.1	0.4	0	0
Mean # treatments	1.3^		4		4.2	4.1
Laser photocoagulation (%)	40.7		Allowed; data not shown		23	20
Cataract (%)	82		68		-	-
Cataract surgery (%)	80		59.2		46	83
IOP increase ≥ 10 mmHg from baseline (%)	34		28		18	33
IOP increase ≥30mmHg (%)	20		15		15*	10*
Any IOP-lowering medication (%)	38		42		2	12
Any surgical intervention for elevated IOP (%)	5		1.2		0	N=4

*IOP increase >21mmHg
**data shown for completer group
^number calculated from % of patients receiving 1, 2, ≥3 injections
Not intended to be directly comparative as study design, patient population, etc. for each drug varied