

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-737

PHARMACOLOGY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-737
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 5/28/04
PRODUCT: Retisert (Fluocinolone Acetonide Intravitreal Implant) 0.59 mg
INTENDED CLINICAL POPULATION: Patients with non-infectious posterior uveitis
SPONSOR: Bausch & Lomb, Inc.
DOCUMENTS REVIEWED: Vol. 1-13
REVIEW DIVISION: Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
PHARM/TOX REVIEWER: Conrad H. Chen, Ph.D.
PHARM/TOX SUPERVISOR: Josie Yang, Ph.D.
DIVISION DIRECTOR: Brian Harvey, M.D., Ph.D.
PROJECT MANAGER: Raphael Rodriguez

Date of review submission to Division File System (DFS): October 19, 2004

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability
This is a 505(b)(2) application. The pharmacology reviewer will not object the approval of this NDA if clinical benefits outweigh the possible risks.
- B. Recommendation for nonclinical studies
There is no further recommendation.
- C. Recommendations on labeling
Include the findings of mutagenicity studies in the labeling.
The findings of reproductive toxicity in rats and rabbits from the literature should be included in the labeling. See Suggested Labeling on page 16.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings
FA intravitreal implant was reasonably tolerated in the rabbit study but caused some ocular toxic effects in the dog study.
- B. Pharmacologic activity
The efficacy of FA in the intravitreal implant has been shown in rabbit model of tuberculin antigen induced uveitis. In addition, there are many published articles reporting the efficacy of corticosteroids in animal models of uveitis.
- C. Non-clinical safety issues relevant to clinical use
If the findings of corneal opacities are species specific only to dogs, it may not be relevant to clinical use. However, continuous monitoring of these findings in the clinical setting is recommended.

**Appears This Way
On Original**

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-737

Review number: No.1

Sequence number/date/type of submission: 000/May 28, 2004/CMA Original
Preclinical Reviewable Unit

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Bausch & Lomb, Inc.

Manufacturer for drug substance:

Reviewer name: Conrad H. Chen, Ph.D.

Division name: Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD #: 550

Review completion date: August 3, 2004

Drug:

Trade name: Retisert (Fluocinolone Acetonide Intravitreal Implant 0.59 mg)

Generic name: Fluocinolone Acetonide

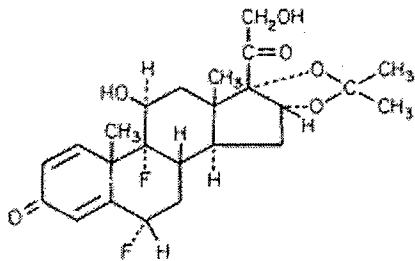
Code name:

Chemical name: 6 α ,9 α -difluoro-16 α -hydroxyprednisolone 16,17-acetonide

CAS registry number: 67-73-2

Molecular formula/molecular weight: C₂₄H₃₀F₂O₆/452.50

Structure:



Relevant INDs/NDAs/DMFs: IND 60,000 (Fluocinolone Acetonide Intravitreal Implant), NDA 20-569 (Intravitreal Sustained-release Ganciclovir)

Drug class: Corticosteroid

Intended clinical population: Patients with non-infectious posterior uveitis

Clinical formulation: 0.59 mg Fluocinolone Acetonide Intravitreal Implant

Route of administration: Intravitreal implant

Studies reviewed within this submission: Module 1 (Vol.C1.1), Module 2 (Vol.C1.2), and Module 4 (Vol.C1.3-C1.11), 13 Volumes Total

Studies not reviewed within this submission: CMC Section (Module 3) and Clinical section (Module 5) have not been submitted, therefore, no information from these modules is included in this review.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Fluocinolone acetonide (FA) is a synthetic corticosteroid with established clinical use to suppress inflammatory changes at various sites in the body. Topical formulations of fluocinolone acetonide are marketed in the US for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

The efficacy of FA in the intravitreal implant has been shown in rabbit model of tuberculin antigen induced uveitis. In addition, there are many published articles reporting the efficacy of corticosteroids in animal models of uveitis.

2.6.2.2 Primary pharmacodynamics

Corticosteroids are classified in one of two designations: mineralocorticoids and glucocorticoids; these designations reflect their relative potency in sodium retention (mineralocorticoid effects), modulatory effects on carbohydrate metabolism and anti-inflammatory activity (glucocorticoid effects).

2.6.2.3 Secondary pharmacodynamics

Corticosteroids preserve the normal function of the immune system, the cardiovascular system, the kidney, the skeletal muscle, the endocrine system, and the nervous system.

2.6.2.4 Safety pharmacology

The safety pharmacology studies were not performed. The systemic absorption of FA from the intravitreal implant is low.

2.6.2.5 Pharmacodynamic drug interactions

No studies were performed.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Tables summarizing several pharmacology studies for FA from the published literature are submitted. The Tables will not be reproduced here.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

As a product implanted directly into the vitreous body, at or near the intended site of action of FA, absorption is not an issue for the FA intravitreal implant. Absorption from

2.6.4.3 Absorption

With Retisert, FA is directly implanted into the vitreous body. Absorption of FA from inside the eye into the systemic circulation is low.

2.6.4.4 Distribution

In a one-year rabbit study with FA implants, the vitreous FA levels were 11 to 18 ng/g for the 0.5 mg implant and 75 to 146 ng/g for the 2 mg implant, respectively. Urine and plasma values were below LOQ (200 pg/mL). Concentrations of FA were higher in the vitreous and retina than in the aqueous humor.

2.6.4.5 Metabolism

FA in Retisert is very likely absorbed systemically and metabolized by liver through esterification. However, no study was conducted.

2.6.4.6 Excretion

FA, like other corticosteroids, is possibly excreted by the kidney. However, in the one-year rabbit implant study, the urinary excretion of FA was below the LOQ (200 pg/mL).

2.6.4.7 Pharmacokinetic drug interactions

No submission

2.6.4.8 Other Pharmacokinetic Studies

One-year ocular pharmacokinetic study in pigmented rabbits (Study No. 00-2686)

Intraocular disposition and release kinetics of 0.5 and 2 mg FA intravitreal implants were studied in pigmented rabbits for one year. The design of the study was to follow the animals for 1-year after a single implant in rabbit eye. Based on the calculation, the release rates of 0.5 mg and 2 mg implants were 0.76 $\mu\text{g/day}$ and 3.9 $\mu\text{g/day}$, respectively, over 1-year. **Therefore, the daily released amount of FA from the implant could be considered as the “daily repeat dose” in the 1-year study.**

A subset of this study examined the possible local toxicity of 0.5, 2, and 6 mg FA intravitreal implants (for results, see 2.6.6 Toxicology below).

Ocular tissues and plasma and urine were obtained for determination of FA concentrations at 2 hours, 2 weeks and 3, 6, 9, and 12 months after implantation.

Implants containing 0.5, 2, or 6 mg FA were successfully implanted intravitreally in rabbits and were well tolerated for up to one year after implantation.

Analysis of ocular tissues from animals receiving 0.5 or 2 mg inserts demonstrated presence of FA in all analyzed ocular tissues throughout the study period, beginning at 2 hours. There was little or no evidence of systemic exposure to FA in implanted animals based on analyses of plasma and urine samples.

2.6.4.9 Discussion and Conclusions

As a product implanted directly into the vitreous body, at or near the intended site of action of FA, local absorption is not an issue for the FA intravitreal implant. Absorption from inside the eye into the systemic circulation is very low, as plasma and urine levels were below the limit of quantitation (LOQ) of 100-200 pg/mL.

In a one-year rabbit pharmacokinetic study with 0.5 and 2 mg FA intravitreal implants, the followings were observed:

In the vitreous, FA levels were relatively constant and dose-related over the 1-year study period. Concentrations of FA were higher in the vitreous and retina than in the aqueous humor. The vitreous levels were 11 to 18 ng/g for the 0.5 mg implants and 75 to 146 ng/g for the 2 mg implants during the study period.

2.6.4.10 Tables and figures to include comparative TK summary

Absorption from inside the eye into the systemic circulation is low, as plasma and urine levels were below the limit of quantitation (LOQ) of 100-200 pg/mL in dogs and rabbits. The FA concentration in ocular tissues and implants from 1-year rabbit study has been presented in a Table under 2.6.4.1 (Brief summary). No other comparative TK summary was provided in the submission.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No information is provided.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The route specific intravitreal toxicity studies were conducted for FA implants (0.5 mg, 2 mg, and 6 mg) in rabbits and dogs for up to one year. Significant FA implant-related systemic toxic effects were not observed in both species, except some histopathological changes to adrenals, liver, and thymus in dogs. However, these effects in dogs were probably caused by the long-term supplementary use of topical and systemic corticosteroids in controlling the inflammation by surgery during the study. The systemic effects of FA were ruled out because the total amounts of FA in the implant were small. The concentrations of FA in the plasma and urine from these animals were below the limit of quantitation (LOQ = _____) of analysis.

Cataracts and corneal opacities were also found in dogs treated with FA intravitreal implants. Sponsor explained that the cataracts were caused by mechanical contact between lens and vitreous implant. This is supported by the findings that cataracts were also found in the sham-operated (with empty implant) group. Corneal opacities were found only in the FA implanted eyes. The sponsors stated that these findings were species specific to dogs and have not been found in rabbits or humans.

Biocompatibility studies were conducted for the extracts of empty implant in accordance with ISO-10993 (International Organization for Standardization) and OECD Guidance (Organization for Economic Cooperation and Development) and the results were negative.

A battery of genotoxicity studies was conducted. FA was negative in the Ames test, mouse lymphoma TK assay, and mouse bone marrow micronucleus assay.

The waivers for carcinogenicity study and reproductive toxicity study have been granted by the Agency because the systemic absorption of FA intravitreal implant is small. The sponsor has submitted information from two articles regarding the reproductive toxicity for FA. It was reported that FA induced abortion in rabbits when administered at 0.13 mg/kg/day subcutaneously during Days 6-18 of gestation. When administered at 50

µg/kg/day subcutaneously during organogenesis in pregnant rats and rabbits, FA caused abortions and malformations in fetuses.

2.6.6.2 Single-dose toxicity

From the literature, the acute LD₅₀s for FA (drug substance) are as follows:

Species	Route	FA
Mouse	Oral	>4 g/kg (M/F)
	i.p.	103 mg/kg (F)
	s.c.	200 mg/kg (F)
	Oral	>4 g/kg (M/F)
Rat	i.p.	42 mg/kg (M)
	s.c.	108 mg/kg (M)
Guinea pig	s.c.	>3.17 g/kg (M/F)

For the drug product, toxicity studies (all are GLP studies) were conducted in rabbits (1-year) and dogs (4-week and 1-year).

One-year pharmacokinetic/toxicity study of FA intravitreal implants in pigmented rabbits (Study No. 00-2686)

This study is the same study reported in pharmacokinetic section above (section 2.6.4.8). FA implants (0.5, 2, and 6 mg FA) were surgically implanted in rabbit eyes and observed for 12-month. A sham implant was inserted in the opposite eye of animal. There was a mild post-operative reaction to implant in the eyes. However, no FA related reactions were observed during ophthalmoscopic examinations. Clinical pathology evaluations, evaluations of organ weights, macroscopic, and microscopic evaluations showed no effects related to FA implants. There was little or no evidence of systemic exposure to FA in implanted animals based on analyses of plasma and urine samples.

In conclusion, implants containing 0.5, 2, or 6 mg of FA were well tolerated in rabbits for up to one year after implantation.

Four-week intravitreal implant toxicity study in dogs (Study No. ZVAW-104)

The purpose of this study was to evaluate the toxicity of 6 mg FA intravitreal implant during a follow up period of 1 month. A sham operation was conducted in the opposite eye of animal. Two groups of 3 dogs were used. One group was followed for 15 days and the other group was followed for 29 days.

By slit lamp examination and indirect ophthalmoscopy following surgery, the eyes of animals exhibited one or more of the following: discharge, swelling of the eyelids, hyperemia, conjunctivitis, keratitis, corneal edema, anterior uveitis, iritis, and inflammation of vitreous. Most of these findings decreased in severity with time. No increases in IOP were found. No marked differences in ophthalmic evaluation were found between treated eyes and sham-operated eyes. The sponsor thought that the conjunctivitis was likely related to surgical incision. Severe lesions in the eye such as vitreal hemorrhage, retinal detachment, corneal ulcers, and lateral canthotomy dehiscence were probably induced during placement of implant, rather than by the implant itself.

The sponsor stated that this canine model revealed additional limitations during the conduct of the study. As documented in the literature, the dog eye is prone to sterile inflammation following surgery (Taylor MM., et al. Intraocular bacterial contamination during cataract surgery in dogs. J. Am Vet Med Assoc. 1995; 206 [11]:1716-20). Also, the retinal detachment in this animal model may be associated with the surgical procedure. The sponsor concluded that there was no apparent evidence of adverse effect on the retina or lens or increase of IOP in response to FA intravitreal implants.

One-year intravitreal implant toxicity study in dogs (Study No. 153-001)

Twenty-seven dogs/sex were originally assigned to five groups. Three males and seven females were euthanized and replaced prior to the first scheduled necropsy at six months because of post-surgical complications. These dogs became sightless and/or suffered intractably pain in the eye following surgery. The sponsor claimed that this was unrelated to the ocular exposure to FA. The severe ocular inflammation in these animals precluded evaluation of intraocular structure.

Dogs were treated with 0.5, 2, or 6 mg FA implants and studied at 6 and 12 months post-implantation. There were untreated control and sham-operated control groups in the study. All dogs were treated with a topical mydriatic and antibiotic eye drop for 3 days and 7 days after surgery, respectively. In addition, dogs received systemic and topical corticosteroids as recommended by the study ophthalmologist and staff veterinarian, to treat post surgical complications (mostly in 2 mg and 6 mg implant groups).

No clear treatment related changes were noted in clinical observations, body weight, hematology or clinical chemistry parameters, IOP, ophthalmic examinations, ERGs, organ weights, or gross tissue examinations in ocular or non-ocular tissues. Adrenal microvacuolar changes (cortical, multifocal and bilateral) were present in some treated animals. The sponsor stated that these findings might be correlated to the systemic and topical corticosteroids given as a result of poor surgical outcomes. There were also findings of microvacuolar changes in the liver and thymus atrophy in some treated animals. The sponsor explained these results as the effects of post-surgically administered corticosteroids. The sponsor believes that these findings were not related to FA intravitreal implants because FA could not be detected in plasma of these dogs (below LOQ of 100 pg/mL). This explanation seems acceptable.

The following table shows the number of animals having histopathology changes in non-ocular tissues.

Histopathology changes	Control		Sham control		0.5 mg implant		2 mg implant		6 mg implant	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal, 6 mo	0/3	0/3					2/3	1/3	2/3	0/2
Adrenal 12 mo	0/3	0/3	0/3	0/3	0/4	0/4	0/4	0/4	1/4	0/4
Liver, 6 mo	0/3	0/3					0/3	1/3	1/3	1/2
Liver, 12 mo	0/3	0/3	0/3	1/3	0/4	0/4	0/4	0/4	1/4	1/4
Thymus, 6 mo	2/3	0/3					1/3	2/3	2/3	1/2
Thymus, 12 mo	0/3	0/3	0/3	0/3	0/4	0/4	3/4	3/4	2/4	3/4

Cataract formations secondary to contact between the implant and lens were found in FA implanted dogs. Cataracts started in the posterior, superior, and temporal quadrant of the lens. The majority of the cataracts occurred where the implant was in contact with the lens capsule, as the implant often could be seen in contact with the posterior lens. *In vivo* ophthalmic examinations showed that cataracts were present in 2/3 of the 6 mg implant animals at 6-month. However, cataracts were present in 3/4 of the 0.5 mg implant and in 1/4 of 6 mg implant animals at 12-month. Since the dose-effect relationship could not be established and occurrence of cataracts was also found in the sham-operated (with empty implant) control eyes, the sponsor attributed the formations of cataracts to mechanical contact between the implant and the lens.

The number of animals having cataracts and corneal opacities is shown below.

Ocular findings	Control		Sham control		0.5 mg implant		2 mg implant		6 mg implant	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Catar, ophthal. exam. 6 mo	0/3	0/3	0/3	0/3	0/4	0/4	0/4	0/4	1/3	1/2
Catar, ophthal. exam. 12 mo	0/3	0/3	1/3	1/3	3/4	0/4	0/4	1/4	0/4	0/4
Catar, histopa. exam. 6 mo	0/3	0/3					0/3	0/3	2/3	0/2
Catar, histopa. exam. 12 mo	0/3	0/3	0/3	0/3	3/4	0/4	0/4	0/4	1/4	0/4
Corneal opacity, 6 mo	0/3	0/3	0/3	0/3	0/4	0/4	0/3	0/3	0/3	1/2
Corneal opacity, 12 mo	0/3	0/3	0/3	0/3	3/4	3/4	3/4	4/4	2/4	3/4
Intraocular inflammation	0/6	0/6	0/3	0/3	0/4	2/4	1/7	3/7	2/7	3/7

Corneal opacities developed at 6-7 months post surgery in test article implanted eyes only. *In vivo* ophthalmic examinations showed that corneal opacities were present in one 6 mg group animal at 6-month and in 6, 7, and 5 animals in 0.5 mg, 2 mg, and 6 mg group, respectively, at 12-month. Corneal opacities noted in ophthalmic examinations were not detected histopathologically. The sponsor stated that it is possible that opacities may have been removed by fixation during the tissue preparation.

The sponsor speculated that corneal opacities were attributed to species specificities in dogs to prolonged exposure to FA implant. Despite extensive investigation, the composition of these opacities could not be determined. Corneal opacities have not been observed in humans or the rabbits following long term exposure.

2.6.6.3 Repeat-dose toxicity

The one-year FA implant studies in rabbits and in dogs and the 4-week FA implant study in dogs listed under the Single-dose toxicity study (2.6.6.2) are, in essence, also the repeat-dose studies. They are, by definition, single-dose studies because only single implant was conducted during the study period. However, they are also the repeat-dose studies because FA is released at a constant rate of 0.76 µg/day (0.5 mg implant) or 3.9 µg/day (2 mg implant) during the entire study period.

2.6.6.4 Genetic toxicology

In vitro study (All are GLP studies, conducted by _____)

Study title: Ames test

FA in DMSO vehicle ranging from 33.3 to 5,000 µg/plate was tested in the presence or absence of mammalian microsomal enzymes (S9) in bacterial tester strains for its ability to induce reverse mutations. *S. typhimurium* TA98, TA100, TA 1535 and TA1537 and *E. coli* strain WP2uvrA were used. Under the condition of this study, FA did not cause a positive increase in the mean number of revertants per plate in any tester strain in the presence or absence of Aroclor-induced rat liver S9.

Study title: Mouse lymphoma forward mutation assay

The objective of this test was to evaluate the ability of FA to induce forward mutations at the thymidine kinase (TK) locus in the mouse lymphoma L5178Y cell line.

FA was negative at concentrations ranging between 25-500 µg/mL for inducing forward mutations in the presence and absence S9 metabolic activation. The concentrations were chosen to cover a toxicity range from 10% to 20% survival to no apparent effect on growth compared to the vehicle control.

In vivo study (GLP study, conducted by _____)

Study title: *In vivo* mouse micronucleus assay

The objective of this study was to evaluate FA for *in vivo* clastogenic activity and/or disruption of the mitotic apparatus by quantifying micronuclei in polychromatic erythrocyte (PCE) cells in Crl:CD-1(ICR) BR mouse bone marrow.

FA was administered by intraperitoneal injection at 500-2,000 mg/kg to mice. FA induced no signs of clinical toxicity but was cytotoxic to the bone marrow (i.e. a statistically significant decrease in the PCE:NCE [nonchromatic erythrocyte] ratio) in males at 2,000 mg/kg dose level. A significant decrease in the PCE:NCE ratio is direct evidence of bone marrow exposure to the test article.

A statistically significant increase in micronucleated PCEs was not observed at any dose level or harvest timepoint in this test. FA was evaluated as negative in the mouse bone marrow micronucleus assay under the condition of this assay.

The genotoxic potential of the empty Retisert implant

The extracts _____ of empty implant was tested for its genotoxic potential in *in vitro* and *in vivo* systems. The results were negative.

2.6.6.5 Carcinogenicity

Because of the low systemic absorption of FA intravitreal implant, the waiver of carcinogenicity study for FA was granted by the Agency on Dec. 3, 2003.

2.6.6.6 Reproductive and developmental toxicology

Because of the low systemic absorption of FA intravitreal implant, the waiver of reproductive toxicity studies for FA was granted by the Agency on Dec. 3, 2003.

The sponsor submitted reproductive toxicity information for FA from two published articles as follows. In these studies, only one dose level of FA was studied as the reference drug (in a study for another new drug) and no proper dose selections were conducted. It appears that the dose, especially in the rabbit study, was maternal toxic and there were no live births. Therefore, these findings might not be useful for the labeling. The results from the rat study seem acceptable. However, an adequate dose range finding study was not conducted and only one dose level was used in this study.

1. Teratogenicity study of the new glucocorticosteroid budesonide in rabbits, I. Kihlstrom and C. Lundberg, *Arzneim.-Forsch./Drug Res.* 37: 43-6, 1987

FA was used as a reference compound in this study. Only one dose level of FA was studied. FA tested at a subcutaneous dose of 0.13 mg/kg/day (0.28 μ mole/kg/day) during Days 6-18 of pregnancy in rabbits, systemically induced abortion at the end of the third and at the beginning of the fourth gestational week. The fetal loss was 100%. This finding was associated with a dramatic maternal weight loss as early as after 10 days of gestation (corresponding to four days of treatment). Budesonide at high dose (0.29 μ mole/kg/day also produced abortions. At lower dose (0.06 μ mole/kg), budesonide produced delayed development of fetal bones.

2. Toxicological Studies on Halopredone Acetate, L. Casilli et al, *Arzneim.-Forsch./Drug Res.* 27: 2102-8, 1977

FA was used as a reference drug in the rat study. Only one dose level of FA was studied. FA at 50 μ g/kg/day s.c. in rats from Days 1 to 20 of pregnancy resulted in a reduced total number and decreased body weights of viable fetuses. There was also a decrease in the number of implantation sites. Dead fetuses and resorption sites were present and one case of malformation of the skull with presence of cleft palate was also observed.

FA was used as a reference drug in the rabbit study. Only one dose level of FA was studied. FA was administered at 50 μ g/kg/day s.c. in rabbits from Day 8 of pregnancy to the day of delivery. No animals were able to deliver normally and all fetuses were stillborn. There were two cases of skull malformation out of the 32 stillborn fetuses.

2.6.6.7 Local tolerance

The sponsor cited one study from the publication showing that a 0.025% FA ointment applied on skin wounds in hamsters (daily application of a 6 mm diameter area for 5 consecutive days) delayed both the rate of wound contraction and the time to complete healing (Marks, et al., *Clin Res* 1983; 31: 585A). The ocular tolerance of FA implant was tested in long-term toxicity studies in rabbits and dogs shown above.

2.6.6.8 Special toxicology studies

Biocompatibility testing of empty implants

Various implant-extracts (_____) tested negative in mutagenic test, hemolytic test, acute systemic toxicity, delayed dermal

contact sensitivity test, and pyrogenicity test, etc. The studies were conducted in compliance with GLP, and in accordance with the applicable ISO and OECD standards.

2.6.6.9 Discussion and Conclusions

In the rabbit study, there was a mild post-operative reaction to implant in the eyes. However, no FA related reactions were observed. Cataracts and corneal opacities were found in dogs treated with FA intravitreal implants. Sponsor explained that the cataracts were caused by mechanical contact between lens and vitreous implant. Since there was no dose-effect relationship and cataracts were also found in the sham-operated eyes. This explanation seems acceptable. Corneal opacities were found only in the FA implanted eyes in dogs. The sponsors stated that these findings were species specific to dogs and have not been found in rabbits or humans. Since the corneal opacities were only found in the FA treated groups, these findings should be considered as drug-related. Canine corneal opacity is often observed with immune-mediated ocular inflammation or ocular infection. Almost all dogs that showed corneal opacities had intra-ocular inflammation. A battery of genotoxicity studies was conducted. FA was negative in the Ames test, mouse lymphoma TK assay, and mouse bone marrow micronucleus assay. The sponsor has submitted information from two published articles regarding the reproductive toxicity for FA. It was reported that FA induced abortion in rabbits when administered at 0.13 mg/kg subcutaneously during Days 6-18 of gestation. When administered at 50 µg/kg/day subcutaneously during organogenesis in pregnant rats and rabbits, FA caused abortions and malformations in fetuses.

2.6.6.10 Tables and Figures:

No information was provided .

2.6.7 TOXICOLOGY TABULATED SUMMARY

In the NDA submission, the sponsor has compiled 44 pages of Tables describing the toxicity studies for FA from the published literature as well as from the sponsor's own works. The studies relevant to this NDA have been evaluated in the current review. Therefore, these Tables are not reproduced here.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This is a 505 (b)(2) application.

Fluocinolone acetonide (FA) is a synthetic corticosteroid with established clinical use to suppress inflammatory changes at various sites in the body. Topical formulations of fluocinolone acetonide are marketed in the US for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

The efficacy of FA in the intravitreal implant has been shown in rabbit model of tuberculin antigen induced uveitis. In addition, there are many published articles reporting the efficacy of corticosteroids in animal models of uveitis.

As a product implanted directly into the vitreous body, at or near the intended site of action of FA, local absorption is not an issue for the FA intravitreal implant. Absorption from inside the eye into the systemic circulation is very low, as plasma and urine levels were below the limit of quantitation (LOQ) of 100-200 pg/mL.

In a one-year rabbit pharmacokinetic study with 0.5 and 2 mg FA intravitreal implants, the followings were observed:

In the vitreous, FA levels were relatively constant and dose-related over the 1-year study period. Concentrations of FA were higher in the vitreous and retina than in the aqueous humor. The vitreous levels were 10.7 to 18.1 ng/g for the 0.5 mg implant and 74.5 to 146 ng/g for the 2 mg implant during the study period.

Ocular tissue concentrations were relatively constant from 2 weeks through 12 months, although there were some increases in the 2 mg implant at 9 and 12 months in some tissues.

In a one-year toxicity study in dogs receiving 0.5 mg and 2 mg FA intravitreal implants, FA levels in all plasma samples obtained at 6 and 12 months time point were below the LOQ (<100 pg/mL).

The route specific intravitreal toxicity studies were conducted for FA implants (0.5 mg, 2 mg, and 6 mg) in rabbits and dogs for up to one year. Significant systemic toxic effects were not observed in both species, except some histopathological changes to the adrenals, liver, and thymus were found in dogs. However, these effects in dogs were probably caused by the long-term supplementary use of topical and systemic corticosteroids in controlling the inflammation by surgery during the study. The systemic effects of FA were ruled out because the total amounts of FA in the implant were small and the daily total FA release from the implant was low (release rates of 0.5 mg and 2 mg implants were 0.76 µg/day and 3.9 µg/day, respectively); therefore, daily systemic exposure to FA was extremely low. This is supported by the fact that the concentrations of FA in the plasma and urine from these animals were below the limit of quantitation (LOQ =100-200 pg/mL).

In the rabbit study, there was a mild post-operative reaction to implant in the eyes. However, no FA related reactions were observed. Cataracts and corneal opacities were found in dogs treated with FA intravitreal implants. Sponsor explained that the cataracts were caused by mechanical contact between lens and vitreous implant. Since there was no dose-effect relationship and cataracts were also found in the sham-operated eyes. This explanation seems acceptable. Corneal opacities were found only in the FA implanted eyes in dogs. The sponsors stated that these findings were species specific to dogs and have not been found in rabbits or humans. Since the corneal opacities were only found in the FA treated groups, these findings should be considered as drug-related. Canine corneal opacity is often observed with immune-mediated ocular inflammation or ocular infection. Almost all dogs that showed corneal opacities had intra-ocular inflammation. Biocompatibility studies were conducted for the extracts of empty implant and results were negative.

A battery of genotoxicity studies was conducted. FA was negative in the Ames test, mouse lymphoma TK assay, and mouse bone marrow micronucleus assay.

The waivers for carcinogenicity study and reproductive toxicity study have been granted by the Agency because the systemic absorption of FA intravitreal implant is small. The sponsor has submitted information from two published articles regarding the reproductive toxicity for FA. It was reported that FA induced abortion in rabbits when administered at 0.13 mg/kg subcutaneously during Days 6-18 of gestation. When administered at 50

µg/kg/day subcutaneously during organogenesis in pregnant rats and rabbits, FA caused abortions and malformations in fetuses.

In this NDA, the sponsor is applying for approval of 0.59 mg fluocinolone acetonide intravitreal implant (Retisert) for the treatment of non-infectious posterior uveitis. According to the sponsor, the 0.5 mg FA implants used in non-clinical studies were almost identical to the implants intended for marketing. The 2 mg implants used in non-clinical and early clinical studies have since been redesigned. Non-clinical studies with the redesigned 2 mg implant have not been performed. The 6 mg implants were only used in the first part of clinical studies, as well as in the one-year rabbit study and the two dog studies (1-month and 1-year). Although the designs of the implants were different, it appears that the inactive ingredients in the formulations were similar. Since 0.59 mg implant for marketing is similar to 0.5 mg implant which was studied in animals, the results from the earlier animal studies can be directly used in the safety evaluation of the product.

Unresolved toxicology issues (if any): None

Recommendations:

FA intravitreal implant caused cataracts and corneal opacities in dogs in the one year study. Similar effects were not found in the one-year rabbit study. Cataracts were probably caused by mechanical contact between the implant and the lens. Cataracts were also found in the sham-operated (with empty implant) control eyes, the sponsor attributed the formations of cataracts to mechanical contact between the implant and the lens. Corneal opacities were not found in the human clinical studies. The sponsor speculated that these findings were species specific to the dog. However, corneal opacities were found only in the FA treated dogs and were drug-related. Canine corneal opacity is often observed with immune-mediated ocular inflammation or ocular infection. Almost all dogs that showed corneal opacities had intra-ocular inflammation. Other ocular findings in dogs, such as vitreal hemorrhage, retinal detachment, corneal ulcers, and lateral canthotomy dehiscence were probably induced during placement of implant by surgery. The findings of corneal opacities in dog studies have been conveyed to the medical reviewer. Medical reviewer thought that there have been adequate human data for the evaluation of FA intravitreal implant. The findings in one species of animals will not affect the outcome of clinical evaluation of the product.

Because of findings in the dog, the pharmacology reviewer would recommend the approval of this NDA if clinical benefits outweigh the possible risks.

If approved, the corneal opacities should be closely monitored during post-marketing.

Suggested labeling:

1. Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect of fertility of fluocinolone acetonide.
Fluocinolone acetonide was not genotoxic in vitro in the Ames test, the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.
2. Pregnancy: Teratogenic effects: Pregnancy Category C.

No adequate animal reproduction studies have been conducted with fluocinolone acetonide.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Fluocinolone acetonide when administered subcutaneously at dose of 0.13 mg/kg/day (approximately 10,000* times the daily clinical dose of Retisert), during Days 6 to 18 of pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week. When administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 µg/kg/day (approximately 4,000* times the clinical dose of Retisert), fluocinolone acetonide caused abortion and malformations in a few surviving fetuses.

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

Note: A class labeling for corticosteroids is used. Additional information for FA was taken from the published literature and the dose used in the study was maternal toxic.

*The calculation is based on the release rate of 0.5 mg implant, 0.76 µg/day/person.

0.76 µg/day ÷ 60 kg = 0.0127 µg/kg/day; 0.13 mg/kg/day = 130 µg/kg/day; 130 ÷ 0.0127=10,000 times; 50 µg/kg/day ÷ 0.0127 = 4,000 times.

Signatures (optional):

Reviewer Signature _____
Conrad H. Chen, Ph.D.

Supervisor Signature _____ Concurrency Yes ___ No ___
Josie Yang, Ph.D.

APPENDIX/ATTACHMENTS

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/s/

Conrad Chen

10/19/04 10:41:02 AM

PHARMACOLOGIST

The pharmacologist recommends approval if the clinical benefits outweigh
the possible risks.

Josie Yang

10/19/04 04:57:06 PM

PHARMACOLOGIST

Review of Pharmacology and Toxicology Data

IND number: IND 60000

Review number: No.2

Sequence number/ date/ type of submission: SN 126/ 6-05-03/ Waiver request for carcinogenicity and reproductive toxicity studies.

Information to sponsor: Yes (x), No ()

Sponsor and/ or agent: Bausch & Lomb, Inc.

Manufacturer for drug substance:

Reviewer name: Conrad H. Chen, Ph.D.

Division name: Anti-inflammatory, Analgesic, and Ophthalmic Drug Products.

HFD #: 550

Review completion date: December 3, 2003

Drug: Fluocinolone Acetonide Intravitreal Implant (FAII).

Relevant INDs/ NDAs/ DMFs:

_____, N-20569

Drug class: Corticosteroid

Indication: 1. Non-infectious uveitis affecting the posterior segment of the eye.

Clinical formulation: 0.5 mg and 2 mg Fluocinolone Acetonide Intravitreal Implants (Retisert).

Route of administration: Intravitreal implant.

Previous clinical experience: The clinical study has been ongoing since the submission of IND 60000 in March 2000.

Purpose of this submission: In this submission, the sponsor is requesting the waiver for carcinogenicity and reproductive toxicity studies for Fluocinolone Acetonide Intravitreal Implant.

Background: In a pre-meeting package submitted on 1-16-03 (SN 090), the sponsor proposed to file the NDA as a 505 (b)(2) relying on previous fluocinolone acetonide NDA for drug substance safety including non-clinical toxicology and PK studies. A sponsor/FDA meeting took place on 2-12-03. The list of non-clinical studies that will be submitted included the following:

- Four-week intravitreal implant toxicity study in beagle dogs.
- One-year intravitreal implant toxicity study in beagle dogs.
- One-year ocular pharmacokinetics study of fluocinolone acetonide 0.5 and 2mg intravitreal implants in pigmented rabbits; including a subset evaluation of one-year ocular toxicity of 0.5, 2mg and 6mg.
- Genotoxicity studies: in vivo mouse micronucleus assay, Salmonella-Escherichia coli reverse mutation assay, and L5178Y TK+/- mouse lymphoma forward mutation assay.
- Several biocompatibility studies of the implant construction materials.

Based on this list, it was concluded that the type of non-clinical studies conducted was adequate for the NDA.

In this submission (SN 126), the sponsor presented information from the literature to justify the waiver request for carcinogenicity and reproductive toxicity studies for FAII.

Evaluation and Comment:

Carcinogenicity studies: According to the sponsor's analysis of literature reports, Fluocinolone Acetonide (FA) was both non-carcinogenic as well as an inhibitor of DNA synthesis and an inhibitor of tumor promotion. However, these cited studies were not designed for the evaluation of carcinogenicity potential of FA; hence, they could not be used in the labeling. The sponsor also stated that FA was devoid of mutagenic potential based on the literature.

The sponsor stated that the animal (dogs and rabbits) and human pharmacokinetic data showed negligible systemic absorption of FA from the implants. Urine and plasma values collected from the one-year rabbit study were below the lower limit of quantitation (200 pg/mL). Plasma samples from the one-year dog study were below the limit of quantitation (100 pg/mL). The human plasma samples from clinical study also showed the values were below the limit of quantitation (200 pg/mL). Based on these findings, the sponsor requests the need for carcinogenicity study be waived.

It is concluded that the systemic exposure to FA from FAII appears to be negligible. It is recommended that the waiver request be granted based on the ICH guideline (S1A).

Reproductive and developmental studies:

According to sponsor's analysis of the available literature, some assessment of the teratogenic potential of FA at higher dose can be discerned. It was reported that a daily subcutaneous (s.c.) dose of 0.13 mg/kg (during D6-D18 of gestation) in rabbits induced abortion, maternal weight loss, and a possible teratogenic effect.

FA at 50 µg/kg/day s.c. in rats (during D1-D20 of gestation) reduced number and body weights of viable fetuses, and decreased number of implantation sites. Dead fetuses, resorption sites and one case of skull malformation with cleft palate were also found.

FA at 50 µg/kg/day s.c. in rabbits (from D8 to delivery) produced skull malformations in two stillborns. No animals were able to perform a normal delivery and no viable rabbits were observed in these litters.

This reviewer would not request for any new reproductive study to be conducted. However, the available information in the literature should be stated in the labeling.

Recommendation:

The waiver request for carcinogenicity and reproductive toxicity studies should be granted. However, available information from the literature must be included in the "carcinogenicity, mutagenesis, and impairment of fertility" and "Pregnancy" sections of the labeling.

Conrad H. Chen, Ph.D.
Reviewing Pharmacologist

Concurrence by: Josie Yang, Ph.D.
Pharmacology Team Leader

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this page is the manifestation of the electronic signature.**

/s/

Conrad Chen

12/5/03 04:11:34 PM

PHARMACOLOGIST

The waiver request for carcinogenicity and reproductive toxicity studies
is granted. However, the available information from the
literature should be included in the labeling.

Josie Yang

12/8/03 09:02:40 AM

PHARMACOLOGIST