

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-315**

**PHARMACOLOGY REVIEW(S)**



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: 22-315  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 12/18/2007  
PRODUCT: Posurdex® (dexamethasone biodegradable  
intravitreal implant) 0.35 mg and 0.7 mg  
INTENDED CLINICAL POPULATION: For treatment of patients with macular edema  
secondary to central retinal vein occlusion or branch  
retinal vein occlusion  
SPONSOR: Allergan, Inc.  
DOCUMENTS REVIEWED: Electronic submission  
REVIEW DIVISION: Division of Anti-Infective and Ophthalmologic  
Products  
PHARM/TOX REVIEWER: Conrad H. Chen, Ph.D.  
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PROJECT MANAGER: Raphael Rodriguez

Date of review submission to Division File System (DFS):

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## **EXECUTIVE SUMMARY**

### **I. Recommendations**

- A. Recommendation on approvability  
The approval of NDA 22315 is recommended.
- B. Recommendation for nonclinical studies  
None
- C. Recommendations on labeling  
The proposed labeling appears adequate.

### **II. Summary of nonclinical findings**

#### **A. Brief overview of nonclinical findings**

Allergan conducted a 10 week study in rabbits to evaluate the primary pharmacodynamics of the 350 µg and 700 µg DEX PS DDS® (Report BIO-05-481). A dose-independent effect was observed in a validated rabbit model of glucocorticoid-sensitive blood-retinal barrier breakdown, vasculopathy, and retinal edema.

In monkey, the majority of dexamethasone was released (>90%) from DEX PS DDS® in monkey vitreous by ~3 months postdose with remaining dexamethasone content gradually released to ~6 months. This long duration of delivery in primates and the low concentrations of dexamethasone required for effect in cell based potency (~1 ng/mL) support the 6-month clinical dosing interval.

In rabbit and monkey, the tissue dexamethasone distribution was higher in the ocular posterior segment after DEX PS DDS® administration.

The ocular and systemic safety of DEX PS DDS implant has been evaluated in rabbits with 3 single-dose toxicity studies and in rabbits and monkeys with repeat-dose (2 injections, 3 months apart) toxicity studies. Transient and expected dexamethasone systemic adverse effects in rabbits, including lower mean body weight, changes to hematological and serum chemistry profiles and/or pathological findings of immune system organs, adrenal (atrophy), and/or liver, were observed in the single-dose studies. In the repeat-dose study in rabbits, transient lower mean body weight and food consumption were observed. Low incidences of drug-induced posterior cortical lens opacities were noted following the second dose in one 700 µg-treated and two 1400 µg-treated eyes. By 12-months, there was evidence of regression in one of the 1400 µg-treated eyes. The repeat-dose toxicity study in monkeys did not reveal any significant systemic or ocular toxicity at doses up to two 700 µg implants, 3 months apart.

#### **B. Pharmacologic activity**

The mechanism of action of dexamethasone in ocular inflammatory disease is most likely due to its potent anti-inflammatory activity and inhibition of the expression of vascular endothelial growth factor (VEGF).

- C. Nonclinical safety issues relevant to clinical use  
It has been recognized that prolonged use of corticosteroid treatment may result in cataract formation. Low incidences of drug-induced posterior cortical lens opacities were noted in the repeat-dose rabbit ocular toxicity study.

**APPEARS THIS WAY  
ON ORIGINAL**

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-315

**Review number:** No.1

**Sequence number/date/type of submission:** SN000/December 14, 2007/Original NDA

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

**Sponsor and/or agent:** Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612

**Manufacturer for drug substance:**

**Manufacturers for DEX PS DDS Applicator System:**

Allergan Pharmaceuticals, Ireland, Castlebar Road, Westport, County Mayo, Ireland

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

**Division name:** Division of Anti-Infective and Ophthalmology Products

**Review completion date:** February 11, 2009

**Drug:**

**Trade name:** Posurdex® (Dexamethasone Posterior Segment Drug Delivery System, DEX PS DDS)

**Generic name:** Dexamethasone

**Chemical name:**

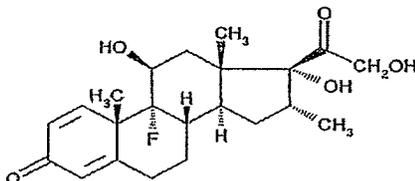
**CAS :** (11 $\beta$ ,16 $\alpha$ )-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione

**IUPAC :** 9 $\alpha$ -Fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\alpha$ -methylpregna-1,4-diene-3,20-dione

**CAS registry number:** 50-02-2

**Molecular formula/molecular weight:** C<sub>22</sub>H<sub>29</sub>FO<sub>5</sub>/392.5

**Structure:**



**Relevant INDs/NDAs/DMFs:** IND 58663, IND 57058

**Drug class:** Corticosteroid

**Intended clinical population:**

For treatment of patients with macular edema secondary to central retinal vein occlusion or branch retinal vein occlusion.

**Clinical formulation:**

The drug component is the drug substance, dexamethasone, dispersed in a poly (D,L-lactide-co-glycolide) (PLGA) biodegradable polymer matrix formed into rod-shaped implants, which are approximately 1 mm in diameter and 10 mm (0.35 mg DEX) to 15 mm (0.7 mg DEX) in length.

**Table 3.2.P.I-2 Quantitative Composition of DEX PS DDS**

Component	% w/w	mg/g	0.35 mg Dose, µg	0.7 mg Dose, µg
Dexamethasone	~%	600	350	700
Poly (D,L-lactide-co-glycolide), PLGA ester	~%			
Poly (D,L-lactide-co-glycolide), PLGA acid	~%			

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The device component is a single-use applicator designed specifically to deliver the rod-shaped implant (Dexamethasone Posterior Segment Drug Delivery System, DEX PS DDS), directly into the posterior segment of the eye. The DEX PS DDS is loaded within the needle of the applicator (DEX PS DDS Applicator System).

**Route of administration:**

Injection of the DEX PS DDS into the posterior segment of the eye using the device component of the system.

**2.6.2 PHARMACOLOGY**

**2.6.2.1 Brief summary**

Dexamethasone, a synthetic derivative of the glucocorticoid hydroxycortisone, has been widely used in human and veterinary medicine for many decades. The mechanism of action of dexamethasone in ocular inflammatory disease is most likely due to its potent anti-inflammatory activity and inhibition of the expression of vascular endothelial growth factor (VEGF).

**2.6.2.2 Primary pharmacodynamics**

Mechanism of action:

Allergan conducted a 10 week study in rabbits to evaluate the primary pharmacodynamics of the 350 µg and 700 µg DEX PS DDS® (Report BIO-05-481). A dose-independent effect was observed in a validated model of glucocorticoid-sensitive blood-retinal barrier breakdown, vasculopathy, and retinal edema as described by Edelman et al. (Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. *Exp Eye Res* 2005;80:249-258). The 350 µg dose completely blocks VEGF-induced blood-retinal barrier (BRB) breakdown in rabbits two weeks after intravitreal drug injection. At the same time, this dose partially inhibits blood-aqueous barrier (BAB; iris) breakdown. Six weeks after injection, the 350 µg dose partially inhibits BRB breakdown but has no effect on BAB breakdown. The efficacy of the 700 µg dose was similar to that

of the lower dose, however, inhibition was more pronounced with the 700 µg dose, and significant effects were observed on all measured responses through six weeks. There was no pharmacologic effect on VEGF-induced responses measured ten weeks after intravitreal injection of either formulation.

**2.6.2.3 Secondary pharmacodynamics**

No secondary pharmacodynamics studies were performed by Allergan with the 350 µg or 700 µg DEX PS DDS® formulations.

**2.6.2.4 Safety pharmacology**

No safety pharmacology studies were conducted with the intravitreal DEX PS DDS® formulations.

**2.6.2.5 Pharmacodynamic drug interactions**

No studies were conducted.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY**

2.6.3.1 Pharmacology Overview Test Article: Dexamethasone

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Primary Pharmacodynamics	Rabbits	Intravitreal	Allergan, Inc. Irvine, California	BIO-05-481
Secondary Pharmacodynamics	No secondary pharmacodynamic studies were conducted			
Safety Pharmacology	No safety pharmacology studies were conducted			
Pharmacodynamic Drug Interactions	No pharmacodynamic drug interaction studies were conducted			

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

### 2.6.4.1 Brief summary

In rabbit, the majority of dexamethasone (>70%) was released from DEX PS DDS® by ~1 month postdose with the remaining dexamethasone content gradually released to ~4 months in rabbit vitreous. A good in vitro-in vivo correlation for DEX PS DDS® release was observed, indicating similarity of implant dissolution in buffer and rabbit vitreous. In monkey, the majority of dexamethasone was released (>90%) from DEX PS DDS® in monkey vitreous by ~3 months postdose with remaining dexamethasone content gradually released to ~6 months. This long duration of delivery in primates and the low concentrations of dexamethasone required for effect in cell based potency (~1 ng/mL) support the 6-month clinical dosing interval.

*In vitro*, dexamethasone was not bound to synthetic melanin (12.5 µg/mL) over a concentration range from \_\_\_\_\_). In rabbit, the tissue dexamethasone exposure was higher in the ocular posterior segment (retina > choroid > sclera) relative to the anterior segment (ciliary body > lens > iris > cornea > AH). In monkey, dexamethasone exposure was also higher in the posterior segment (retina > choroid > sclera) relative to the anterior segment (iris > ciliary body > lens > AH > cornea).

Ocular metabolism studies were conducted *in vitro* in human ocular tissues and *in vivo* in rabbits and monkeys using [<sup>14</sup>C]-dexamethasone. The results indicate no or minimal metabolism of dexamethasone in rabbit, monkey, and human ocular tissues. The sponsor stated that biodegradable polyesters, PLA (polylactic acid) and PLGA, have been approved for human use by the US Food and Drug Administration. PLGA polymers are used in degradable (absorbable) sutures with the trade name Vicryl®, which are frequently used in ophthalmic surgery. According to the sponsor, PLGA polymers have been used for up to 28 years in commercial medical products including sutures, bone screws/rods, soft tissue implants, and drug formulations (for example, Sandostatin Lar Depot®).

The following Table 3.2.P.2.1-2 listed the commercial medical products containing PLA/PLGA polymers.

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Table 3.2.P.2.1-2 List of Commercial Medical Products Containing PLA/PLGA Polymers

Name	Manufacturer	Drug Substance	Dosage Form	Mode of Administration	Registration	
					Country	Year
Vicryl <sup>®</sup>	Ethicon	n/a <sup>(1)</sup>	n/a <sup>(1)</sup>	n/a <sup>(1)</sup>	n/a <sup>(1)</sup>	n/a <sup>(1)</sup>
Suture recommended for ocular surgery first marketed in 1976						
Eunatone <sup>®</sup>	Takeda	Leuprorelin	Microsphere suspension	Injection (SC or IM)	France	1988
					Italy	1994
Prostap <sup>®</sup>	Wyeth	Leuprorelin acetate	Microsphere suspension	Injection (SC or IM)	UK	1991
Bigonist <sup>®</sup>	Aventis (Sanofi-Chimie)	Buserelin	Implant	Injection (SC)	France	1993
Somatuline <sup>®</sup>	Beaufour Ipsen Pharma	Lanreotide acetate	Microparticle suspension	Injection (IM)	France	1994
					UK	1998
Sandostatin <sup>®</sup>	Novartis	Octreotide acetate	Microsphere suspension	Injection (IM)	USA	1988
					France	1995
					UK	1998
					Italy	1999
Zoladex <sup>®</sup>	Astra Zeneca	Goserelin acetate	Implant	Injection (SC)	USA	1989, 1996
					Italy	1994
					France	1996
					UK	2001
Rispedal consta <sup>®</sup>	Janssen-Cilag	Risperidone	Microparticle suspension	Injection (IM)	USA	2003
					UK	2002
Decapeptyl <sup>®</sup>	Ipsen	Triptorelin		Injection (IM)	France	1996
					Italy	1999
					UK	2002
Gonapeptyl LP	Ferring SAS	Triptorelin Acetate	Microparticle suspension	Injection (SC or IM)	France	2001
Gonapeptyl Depot <sup>®</sup>	Ferring Pharmaceutical	Triptorelin acetate	Microparticle suspension	Injection (SC or IM)	UK	2003
					Italy	2003
Rispedal Constal	Janssen Cilag SA	Risperidone		Injection IM	France	2003

<sup>(1)</sup> Not applicable since Vicryl<sup>®</sup> is not a registered medical drug product

PLA and PLGA used as vehicle in DEX PS DDS<sup>®</sup> are known to degrade via backbone hydrolysis (bulk erosion) and the degradation products, lactic acid and glycolic acid, are ultimately metabolized into carbon dioxide and water.

The elimination of dexamethasone from the systemic circulation after intravitreal administration of DEX PS DDS<sup>®</sup> is expected to be similar to that after oral or IV routes of administration. In general, following oral or IV administration, elimination occurs via metabolism and renal excretion.

#### 2.6.4.2 Methods of Analysis

LC/MS/MS analytical instrumentations were used for the determination of dexamethasone concentrations in plasma, ocular fluids and tissues in support of pharmacokinetic studies.  $^{14}\text{C}$ -dexamethasone was synthesized and used in the distribution and metabolism studies.

#### 2.6.4.3 Absorption

Five single-dose ocular absorption and distribution studies with DEX PS DDS<sup>®</sup> in rabbits and one single-dose study in monkeys were conducted.

Following intravitreal implantation of 350  $\mu\text{g}$  and 700  $\mu\text{g}$  DEX PS DDS<sup>®</sup> in rabbits, the VH  $C_{\text{max}}$  levels were 1330 ng/mL (Day 31) and 3520 ng/mL (Day 14), and were detectable up to Day 120 (23.1 ng/mL) and Day 71 (33.3 ng/mL), respectively. The percent dose released was  $23.0 \pm 4.5\%$  and  $10.8 \pm 3.2\%$  at 1 day postdose and  $98.6 \pm 2.1\%$  and  $70.5 \pm 36.9\%$  at 28 days postdose for 350  $\mu\text{g}$  and 700  $\mu\text{g}$  DEX PS DDS<sup>®</sup>, respectively. The remaining dexamethasone content was more gradually released to approximately 4 months. The *in vivo* release profile was consistent with the *in vitro* release profile where  $87.1 \pm 1.8\%$  of DEX PS DDS<sup>®</sup> was released over 28 days.

Dexamethasone concentrations were generally lower in monkeys compared to rabbits and lasted for a longer period of time. With 700  $\mu\text{g}$  DEX PS DDS<sup>®</sup>, the dexamethasone VH  $C_{\text{max}}$  was 100 ng/mL (Day 42) and was detectable up to Day 91 (5.57 ng/mL). This appears to be due to slower DEX PS DDS<sup>®</sup> release in primate where 24.2% was released at 1 day, 48.4% by 42 days and >90% by 3 months, with detectable levels in VH containing implant remnants to 6 months. The low concentrations of dexamethasone required for effect in cell based potency (EC<sub>50</sub>, 2-3 nM or 0.785-1.18 ng/mL) and long duration of delivery in primate support the 6-month clinical dosing interval.

The systemic use of dexamethasone has been reported for many decades. Following single intravenous (12 mg), oral (12 mg), or multiple-dose topical ocular administration (0.55 mg total eye drop) of dexamethasone or dexamethasone disodium phosphate to humans, maximal plasma concentrations were  $10.5 \pm 2.8$ ,  $8.4 \pm 3.6$ , and  $0.7 \pm 0.4$  ng/mL, respectively. In repeat-dose toxicology studies, the plasma  $C_{\text{max}}$  in rabbit and monkey at the highest DEX PS DDS<sup>®</sup> dose administered were 1.60 and 0.555 ng/mL, respectively. The repeat toxicokinetic profiles were similar to the single-dose, suggesting no potential for ocular or systemic drug accumulation following repeat dosing of DEX PS DDS<sup>®</sup>.

Based on body weight differences between human (~60 kg) and monkey (~3 kg) the systemic exposure of dexamethasone in human is expected to be ~20-fold ( $60 \text{ kg} \div 3 \text{ kg} = 20$ ) lower than in monkey. Therefore, plasma dexamethasone is estimated to be below or at the limit of detection (BLQ < 0.02 ng/mL or  $0.555 \text{ ng/mL} \div 20 = 0.027 \text{ ng/mL}$ ).

In the clinical study report submitted on December 23, 2008, it was reported that the lower limit of quantitation (LLOQ) was 0.05 ng/mL. Almost all plasma dexamethasone concentrations in patients received 700  $\mu\text{g}$  DEX PS DDS were below the LLOQ of 0.05 ng/mL. Only 5 of the 40 samples were slightly above LLOQ ranging from 0.0521 to 0.094 ng/mL.

#### 2.6.4.4 Distribution

*In vitro*, dexamethasone was not bound to synthetic melanin (12.5 µg/mL) over a concentration range from ~~1 to 100 µg/mL~~ when incubated for 60 minutes at 37°C and therefore not expected to accumulate in pigmented ocular tissues. Ocular distribution studies were conducted in rabbits and monkeys using <sup>14</sup>C-dexamethasone and 700 µg DEX PS DDS®. In rabbit, the tissue dexamethasone exposure was higher in the ocular posterior segment (retina > choroid > sclera) relative to the anterior segment (ciliary body > lens > iris > cornea > AH). The overall rank order of dexamethasone exposure was: retina > VH > choroid > ciliary body ≥ sclera > lens > iris > cornea > AH.

In monkey, dexamethasone exposure was also higher in the posterior segment (retina > choroid > sclera) relative to the anterior segment (iris > ciliary body > lens > AH > cornea). However, the overall rank order of dexamethasone exposure was different with higher exposure in iris and ciliary body: retina > iris ≥ ciliary body ≥ choroid ≥ VH > lens > sclera > AH > cornea. The higher iris and ciliary body exposure may in part be due to placement of the intravitreal injection, with the injection being made more posterior in rabbits compared to monkeys to avoid nicking the large rabbit lens.

#### 2.6.4.5 Metabolism

Dexamethasone is known to undergo metabolism by liver CYP450 (CYP3A4) enzymes to form lipid and water-soluble oxidative metabolites (6-hydroxy-dexamethasone) that can be excreted in bile and urine.

Ocular metabolism studies were conducted *in vitro* in human ocular tissues and *in vivo* in rabbits and monkeys using [<sup>14</sup>C]-dexamethasone. For human ocular metabolism studies, human donor enucleated eyes were dissected into cornea, iris-ciliary body, choroid, retina, VH, and sclera and loaded onto titanium screen holders in standard 6-well plates. In this system there was no observable metabolism in any tissue relative to positive and negative controls. In rabbits and monkeys, following [<sup>14</sup>C]-dexamethasone intravitreal administration (~70 µg/10 µCi/eye) with and without 21 day pre-exposure to 700 µg DEX PS DDS® to rabbit and monkey, no ocular metabolites were observed in any ocular tissue except for aqueous humor at 2 hours postdose Day 21 in monkey wherein a small metabolite peak proposed as mono-oxygenated dexamethasone was observed. The metabolite peak represented less than 1% of the radioactivity in the sample. The results indicate no or minimal metabolism of dexamethasone in rabbit, monkey, and human ocular tissues.

Over the past few decades, biodegradable polyesters, such as poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) have been among the most extensively investigated polymers for drug delivery purposes. The biodegradable polyester family has been regarded as one of the few synthetic biodegradable polymers with controllable biodegradability, excellent biocompatibility, and high safety. PLA and PLGA have been approved for human use by the US Food and Drug Administration. PLA and PLGA used as vehicle in DEX PS DDS® are known to degrade via backbone hydrolysis (bulk erosion) and the degradation products, lactic acid and glycolic acid, are ultimately metabolized into carbon dioxide and water.

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*References:*

*Gilding DK. Biodegradable Polymers. In: Williams DF, ed. Biocompatibility of Clinical Implant Materials. Volume II. Boca Raton, Florida: CRC Press, Inc.; 1981:210-232.*  
*Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev 1997;28:5-24.*

**2.6.4.6 Excretion**

In monkeys, dexamethasone was rapidly cleared from retina, choroid, sclera, ciliary body, iris, cornea, and AH with  $t_{1/2}$  ranging from 3.35 to 5.61 hours on Day 1, and 3.65 to 5.67 hours on Day 21. The  $t_{1/2}$  in lens was 10.6 hours on Day 1 and 9.73 hours on Day 21. The elimination of dexamethasone from the systemic circulation after intravitreal administration of DEX PS DDS® is expected to be similar to that after oral or IV routes of administration. In general, following oral or IV administration, elimination occurs via metabolism and renal excretion.

**2.6.4.7 Pharmacokinetic drug interactions**

No ocular drug-drug interaction studies have been conducted for DEX PS DDS.

**2.6.4.8 Other Pharmacokinetic Studies**

No data was submitted.

**2.6.4.9 Discussion and Conclusions**

The systemic use of dexamethasone has been reported for many decades. Following single intravenous (12 mg), oral (12 mg), or multiple-dose topical ocular administration (0.55 mg total eye drop) of dexamethasone or dexamethasone disodium phosphate to humans, maximal plasma concentrations were  $10.5 \pm 2.8$ ,  $8.4 \pm 3.6$ , and  $0.7 \pm 0.4$  ng/mL, respectively. In repeat-dose toxicology studies, the plasma  $C_{max}$  in rabbit and monkey at the highest DEX PS DDS® dose administered (1400 µg/eye and 700 µg/eye, respectively) were 1.60 and 0.555 ng/mL, respectively. The repeat toxicokinetic profiles were similar to the single-dose, suggesting no potential for ocular or systemic drug accumulation following repeat dosing of DEX PS DDS®.

Based on body weight differences between human (~60 kg) and monkey (~3 kg) the systemic exposure of dexamethasone in human is expected to be ~20-fold ( $60 \text{ kg} \div 3 \text{ kg} = 20$ ) lower than in monkey. Therefore, plasma dexamethasone is estimated to be below or at the limit of detection ( $\text{BLQ} < 0.02 \text{ ng/mL}$  or  $0.555 \text{ ng/mL} \div 20 = 0.027 \text{ ng/mL}$ ).

In the clinical study report submitted on December 23, 2008, it was reported that the lower limit of quantitation (LLOQ) was 0.05 ng/mL. Almost all plasma dexamethasone concentrations in patients received 700 µg DEX PS DDS were below the LLOQ of 0.05 ng/mL. Only 5 of the 40 samples were slightly above LLOQ ranging from 0.0521 to 0.094 ng/mL.

**2.6.4.10 Tables and figures to include comparative TK summary**

The tables are included in the Toxicology section as appropriate.

**2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

Test Article: Dexamethasone

Overview

2.6.5.1 Pharmacokinetics

Type of Study	Test System	Method of Administration	Testing Facility	Report Number
Absorption	Rabbits	Intravitreal implantation by sclerotomy	_____	OPF 257
72-Hour comparison <sup>a</sup>	Rabbits	Intravitreal implantation by sclerotomy	Oculex	TR2003-10
28-Day comparison	Rabbits	Intravitreal implantation by sclerotomy	_____	OPF 258
84-Day comparison <sup>a</sup>	Rabbits	Intravitreal implantation by injection	Allergan, Inc.	PK-07-017
31-Day vitrectomy	Rabbits	Intravitreal implantation by injection	_____	PK-05-178/
6-Month comparison <sup>a</sup>	Monkeys	Intravitreal implantation by injection	_____	PK-07-050
6-Month comparison <sup>a</sup>	Monkeys	Intravitreal implantation by injection	_____	PK-06-115/
Toxicokinetic <sup>b</sup>	Rabbits	Intravitreal implantation by injection	_____	PK-07-095
Toxicokinetic <sup>a</sup>	Monkeys	Intravitreal implantation by injection	_____	PK-06-020
Distribution	Synthetic	In vitro	_____	PK-07-102
In vitro melannin binding	Rabbits	Intravitreal injection	_____	PK-07-060
In vivo rabbit ocular metabolism	Monkeys	Intravitreal injection	_____	PK-07-063
In vivo monkey ocular metabolism	Human	In vitro	Allergan, Inc.	PK-07-108
Metabolism				
In vitro human ocular metabolism				

a - Report contains a GLP Compliance Statement.

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## 2.6.6 TOXICOLOGY

### 2.6.6.1 Overall toxicology summary

#### General toxicology:

In ophthalmology, dexamethasone has been widely used for over 40 years (Gordon, 1959 *Am J Ophthalmol* 1959;48:656-660). Dexamethasone, at concentrations up to 0.1% alone, or in combination with antibiotic agents such as tobramycin or ciprofloxacin, has been approved for topical use (Decadron® package insert, 2004; TobraDex® package insert, 2000). To date, the upper limit of dose-dependent toxicity has not been established. In animal studies, the maximum reported doses without adverse ocular findings for single intravitreal (IVT) injection (4,800 µg) and for implanted sustained-release dexamethasone devices (5,000 µg) are much higher than the total dose delivered with the dexamethasone posterior segment drug delivery system (DEX PS DDS®) (350 µg or 700 µg) (Cheng et al, 1995, *Invest Ophthalmol Vis Sci* 1995;36:442-453; Kwak and D'Amico, 1992, *Arch Ophthalmol* 1992;110:259-266; Nabih et al, 1991, *Int Ophthalmol* 1991;15:233-235). It has been recognized that prolonged use of corticosteroid treatment may result in cataract formation. Intraocular pressure (IOP) elevation may occur much earlier, however, reports have varied about the time point of observable significant IOP increase. On average, IOP elevation has been found to be significant following 1 to 2 weeks of corticosteroid treatment (Foster CS, *Massachusetts Eye & Ear Infirmary Immunology Service* 1998; Schwartz B, *Ophthalmol Clin North Am* 1996;6:929-989).

The ocular and systemic safety of DEX PS DDS® implant has been evaluated in rabbits with 3 single-dose toxicity studies and in rabbits and monkeys with repeat-dose (2 injections, 3 months apart) toxicity studies. Transient and expected dexamethasone systemic adverse effects in rabbits, including lower mean body weight, changes to hematological and serum chemistry profiles and/or pathological findings of immune system organs, adrenal (atrophy), and/or liver, were observed in the single-dose studies. In the repeat-dose study in rabbits, transient lower mean body weight and food consumption were observed. Low incidences of drug-induced posterior cortical lens opacities were noted following the second dose in one 700 µg-treated and two 1400 µg-treated eyes. By 12-months, there was evidence of regression in one of the 1400 µg-treated eyes. However, corticosteroid-induced cataract is well established. The repeat-dose toxicity study in monkeys did not reveal any significant systemic or ocular toxicity at doses up to two 700 µg implants, 3 months apart.

#### Genetic toxicology:

Studies evaluating mutagenic potential of dexamethasone in bacteria and mammalian cells *in vitro* have been negative (European Medicines Agency (EMA), 2001). An *in vivo* mouse micronucleus test was also negative (EMA, 2001).

EMA 2001: *European Medicines Agency, Dexamethasone Summary Report (2). Maximum Residual Limits: 2001*

#### Carcinogenicity:

No carcinogenicity studies on dexamethasone or the DEX PS DDS® implant have been

performed.

Reproductive toxicology:

No additional data have been generated on the effects of dexamethasone, the DEX PS DDS® implant, or PLGA on fertility and general reproduction, embryo-fetal development, or pre/post-natal development. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application. In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. (Decadron® package insert, 2004). Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1.0 mg/kg/day every other day for 28 days or at 10.0 mg/kg/day once or every other day on 3 or 5 days between gestation Days 23 and 49 had fetuses with findings limited to minor cranial abnormalities (Jerome and Hendrickx, 1988, J. Med. Primatol. 17:195-203 (1988)). A 1.0 mg/kg/day dose in pregnant rhesus monkeys would be approximately 85 times higher than a 700 µg DEX PS DDS® implant in humans (assuming 60 kg body weight).

Special toxicology:

The POSURDEX® applicator system was found to be easy to operate when used to insert DEX PS DDS® implants into the posterior segment of the eyes of rabbits. The traumatic cataracts observed in this study were likely related to the anatomical dimensions of the rabbit eye and not associated with the POSURDEX® applicator system. PLGA is a biodegradable component used in the drug product. PLGA polymers, the copolymers of lactide and glycolide monomers, have applications in surgery and in drug delivery. PLA and PLGA have been approved for human use by the US Food and Drug Administration. PLA and PLGA used as vehicle in DEX PS DDS® are known to degrade via backbone hydrolysis (bulk erosion) and the degradation products, lactic acid and glycolic acid, are ultimately metabolized into carbon dioxide and water. Based on its well established clinical safe use and the lack of any adverse ocular findings in the chronic toxicity studies (Reports TX05029 and TX05030), the PLGA polymers used to make the implants are not expected to produce any toxic effects.

**2.6.6.2 Single-Dose Toxicity**

Two GLP single-dose toxicity studies were conducted to evaluate the ocular and systemic effects of DEX PS DDS® implant following a single sclerotomy implantation in rabbits (Reports X7I062G and X8I310G).

Rabbits were surgically (sclerotomy) implanted with 700 µg (1 implant), 1400 µg (2 implants), or 2100 µg (3 implants) dexamethasone into the posterior segment of the right and left eyes. Placebo-treated (1 placebo implant) and untreated control eyes were also included. Due to endophthalmitis observed in the first study (Report X7I062G) and per recommendation from the FDA reviewers during the Pre-IND meeting, the study was repeated with a similar study design.

Procedures designed to assure the sterility of the surgical suite were incorporated, and no cases of endophthalmitis were observed in the repeat study (Report X8I310G). Surgical-related findings including squinting, decreases in intraocular pressure (IOP), focal granulomatous or chronic inflammation in the sclera and/or conjunctiva associated

with silk sutures, and focal mild disruption of the subjacent retina were observed in all treatment groups including placebo-treated eyes.

Microcysts were detected sporadically in 14% (5/36) of eyes treated with DEX PS DDS® implants from rabbits euthanized on Day 28 and none (0/24) from rabbits euthanized on Day 42, suggesting that the changes were reversible. A decrease in body weight (0.1 to 0.3 kg), an expected dexamethasone effect in rabbits, was observed over the first 28 days in rabbits receiving the DEX PS DDS®. In addition, increased thymic atrophy was observed in the drug-treated rabbits when compared to the control animals.

In another study (Report P0701002), rabbits received a single sclerotomy implantation of placebo (1 implant), 700 µg (1 implant), 1400 µg (2 implants), or 2100 µg (3 implants) DEX PS DDS® into the posterior segment of the right eye and were observed up to 23 weeks post-implantation. There was no evidence of drug-related ocular toxicity as a result of POSURDEX® applicator system implantation. Ophthalmic findings such as cataract formation observed during the study were the result of the surgical procedure and were not related to the test article because eyes with test and placebo implants, and sham surgery were similarly affected. No drug-related elevation in IOP occurred, and histopathology confirmed that test article implants did not cause ocular toxicity up to 164 days after implantation. Dexamethasone-related systemic effects included lymphotoxicity and decreased body weight. These dose-dependent effects were most evident 30 days after implantation, were generally diminished at 2 months after implantation, and were absent at subsequent timepoints.

When the intravitreal dose of dexamethasone administered is expressed relative to body weight, each 700 µg DEX PS DDS® implant unit would be equivalent to approximately 0.2 mg/kg body weight in rabbits, which is approximately 20 times higher than the expected therapeutic dose for man (assuming 60 kg body weight). Therefore, the systemic effects occurring in the rabbit studies are not expected to occur in humans using the 700 µg DEX PS DDS® implant.

In summary, no drug-related ocular toxicity was observed. Dexamethasone-related systemic effects, including lymphotoxicity, decreased body weight, and adrenal and liver pathological findings, were observed during the study as a result of implantation of DEX PS DDS® units into the posterior segment of the eyes of rabbits. Lymphoid depletion was seen in the thymus, cecal tonsils, and spleen. In liver, dose-dependent hepatocellular cloudy swelling and hydropic degeneration occurred. These dose-dependent effects were most evident 30 days after implantation, were generally diminished at 2 months after implantation, and were absent at later intervals. When the intravitreal dose of dexamethasone administered is expressed relative to body weight, each 700 µg DEX PS DDS® implant unit would be equivalent to approximately 0.2 mg/kg body weight in rabbits, which is 20 times higher than the expected therapeutic dose for man based on body weight (assuming 60 kg body weight), therefore, systemic effects are not expected to be seen in humans.

#### 2.6.6.3 Repeat-Dose Toxicity

**Study title:** Posurdex: Chronic Intravitreal Ocular Toxicity Study in Rabbits

**Key study findings:** In this study, female New Zealand White rabbits received a unilateral intravitreal insertion of a PS DDS needle (sham procedure), or Posurdex PS DDS at a dose level of 0 (placebo), 0.7 mg (1 implant) or 1.4 mg (2 implants)/ eye and were observed for 3 or 12 months. Those animals followed for 12 months received a second treatment at 3 months. Transient, procedural-related conjunctival congestion and swelling in all groups and transient lower mean body weight and food consumption in both drug-treated groups were observed. In general, the implants were well tolerated within the eye. Three incidences of small posterior cortical lens opacities were noted following the second dose, two at 5 months post dose and another at 9 months, representing one 0.7 mg eye and two 1.4 mg eyes. By 12 months, there was evidence of regression in one of the 1.4 mg eyes. Based on the transient lower mean body weight and food consumption and the presence of the small lens opacity at the 0.7 mg/eye dose level, a no-effect level was not established. However, the opacity appeared to be reversible.

**Study no.:** TX05030

**Volume #, and page #:**

**Conducting laboratory and location:** \_\_\_\_\_

b(4)

**Date of study initiation:** September 6, 2005

**GLP compliance:** Yes

**QA report:** yes (x) no ( )

**Drug, lot #, and % purity:** 12500A1

**Methods**

Doses: 0 (sham), 0 (placebo), 0.7 mg, and 2x0.7 mg DEX PS DDS implants using Posurdex applicator system to the right eyes; the left eyes were untreated

Species/strain: New Zealand White rabbit

Number/sex/group or time point (main study): 12 females/group

Route, formulation, volume, and infusion rate: On Day 1, all animals received one implant; on Day 92, 8 animals in high dose group received a 2<sup>nd</sup> implant

Age: 5-6 months of age

Weight: 2.7 to 3.6 kg

Sampling times: 4/group (13-week necropsy) and 8/group (52-week necropsy); blood samples were collected Post 1<sup>st</sup> injection on Days 2, 8, 15, 22, 29, 36, 61, and 89, and post 2<sup>nd</sup> injection on Days 93, 99, 116, 123, 130, 137, 162 and 181.

Unique study design or methodology (if any): None

**Observations and times:** 3 months observation period following the 1<sup>st</sup> dose and 9 months observation period following the 2<sup>nd</sup> dose. Rabbits (4/group) were sacrificed and necropsied 3 months following treatment. The remaining 8 rabbits/group received a second treatment as previously described and were necropsied after 9 months. All eyes and associated ocular tissues (optic nerve, extraocular muscles, Harderian gland, lacrimal gland, nictitating membrane, upper and lower eyelids) were prepared for

histopathological examination by embedding in paraffin wax, sectioning and staining with hematoxylin and eosin. Remaining tissues were retained in fixative but was not examined.

### Results

There was no drug-related mortality or drug-related effects on clinical observations, electroretinography, tonometry, hematology, serum chemistry, macroscopic observations or organ weights.

Procedure-related gross ocular effects including transient congestion and swelling were observed in treated eyes from all groups including the sham procedure, placebo and drug-treated animals following the first and second injections. The changes generally resolved in most animals within approximately two weeks following dosing. Slight and transient, dose-related lower mean body weight, relative to sham control, was observed in rabbits given 0.7 mg (4-8%) or 1.4 mg (4-12%) dexamethasone.

Mean food consumption was transiently reduced (7% to 48% lower relative to sham control) in rabbits given 0.7 or 1.4 mg dexamethasone commencing approximately 4 weeks following the first dose and 4 to 5 weeks post second dose.

There were no drug-related effects observed during the ophthalmology examinations up to 3 months following the first dose. After the second dose, there was a low incidence of small posterior cortical lens opacities observed in a total of three eyes. This was first observed approximately 1.5 months after insertion (5 months after injection of the first implants) in one eye at each dose level. A comparable lesion was identified four months later in another treated eye from the 1.4 mg/dose group (total of 2.8 mg/eye).

By 12 months, there was evidence in one eye from the 1.4 mg/eye group that this lesion was regressing. Microscopic evaluation did not elucidate these opacities. Healing at the site of DEX PS DDS application system insertion, characterized as a transcleral gap closed up by scar tissue (fibroplasia/fibrosis) was observed in all groups.

Peak dexamethasone plasma concentrations were observed approximately 19-24 days after intravitreal injection of DEX PS DDS in both treatment groups and during both treatment periods. The plasma  $C_{max}$  values were similar between both treatment groups for both treatment periods (1.01 vs. 1.60 ng/mL post 1<sup>st</sup> dose and 0.71 vs. 1.33 ng/mL post 2<sup>nd</sup> dose). The extent of systemic exposure ( $AUC_{0-t}$ ) appeared to be dose proportional (9.78 vs. 19.6 ng·days/mL post 1<sup>st</sup> dose and 7.40 vs. 18.4 ng·days/mL post 2<sup>nd</sup> dose) and the duration of plasma drug concentrations was longer for 1.4 mg dose group compared to the 0.7 mg dose group. The  $T_{max}$  were 19.8 vs. 19.3 days (post 1<sup>st</sup> dose and 24.0 vs. 24.0 days (post 2<sup>nd</sup> dose), respectively.

**Study title:** Posurdex: Chronic Intravitreal Ocular Toxicity Study in Monkey

**Key study findings:** Male and female Cynomolgus monkeys received two unilateral intravitreal insertions, 3 months apart, of PS DDS needle (sham), placebo implant, or Posurdex implant (0.35 or 0.7 mg of dexamethasone) and were observed for 3 or 9 months following the second insertion. The implants were well tolerated and no drug-related ocular or systemic toxicity was observed.

**Study no.:** TX05029

b(4)

**Volume #, and page #:****Conducting laboratory and location:** \_\_\_\_\_**Date of study initiation:** October 14, 2005**GLP compliance:** Yes**QA report:** yes (x) no ( )**Drug, lot #, and % purity:** 12501A1 (0.35 mg) and 12500A1 (0.7 mg)**Methods**

Doses: 0 (sham), 0 (placebo), 0.35 mg, and 0.7 mg; all groups received injections on Day 1 and Day 92

Species/strain: Cynomolgus monkeys

Number/sex/group or time point (main study): 26-week necropsy, 3/sex/group; 52-week necropsy, 1/sex/group

Route, formulation, volume, and infusion rate: the right eye received the treatment, the left eye remained untreated; a new DEX PS DDS application system was used for each injection

Satellite groups used for toxicokinetics or recovery:

Age: 3 to 3.5 years of age

Weight: male, 2.3 to 2.9 kg; females 2.0 to 2.7 kg

Sampling times: Blood samples: Post 1st injection on Days 2, 8, 15, 22, 36, 61, and 89, and post 2nd injection on Days 93, 99, 116, 123, 137, 162 and 181; terminal sacrifice, 26-week and 52-week

Unique study design or methodology (if any):

**Observations and times:** 3 months observation period following the 1<sup>st</sup> dose and 9 months observation period following the 2<sup>nd</sup> dose. Animals (3/sex/group) were sacrificed and necropsied 3 months following the second treatment (26 weeks). The remaining 1 animal/sex/group was necropsied 9 months after the second treatment (52-weeks). All tissues (full panel) were prepared for histopathological examination by embedding in paraffin wax, sectioning and staining with hematoxylin and eosin and examined.

**Results**

There was no drug-related mortality or drug-related effects on clinical observations, body weight, body weight gains, food consumption, gross ocular observations, ophthalmology, electroretinography, tonometry, hematology, serum chemistry, urinalysis, organ weights, macroscopic observations, or microscopic observations.

Procedural-related effects included swelling and redness of the conjunctiva in the treated eyes following dosing on Days 1 and/or 92 in the sham, placebo and drug-treated monkeys. These changes were generally transient, and were resolved in most animals within approximately one week following the respective injection.

Ophthalmology evaluation showed that the eyes were relatively unaffected during the three months following implantation on Day 1 and following the second implantation on Day 92, with no evidence of adverse effects on any of the ocular structures. The appearance of the implants and the time course of their dissolution were comparable after each treatment.

When visible 2 weeks post implantation, there was little change in the size and appearance of the dexamethasone implants, in contrast to the placebo implants which were swollen. This difference in appearance between implants persisted two to three months after implantation. Most implants eventually became shrunken and sometimes fragmented. The position of the implants within the vitreous remained fairly constant in many eyes from one examination to the next for as long as the implants could be visualized.

Microscopically, intravitreal administration procedures related findings included healing at the site of DEX PS DDS application system insertion, characterized as fibrosis at the implant (injection) site in all groups including sham control at the end of 26 week and 52 week sacrifices.

Peak dexamethasone plasma concentrations were observed 40 to 51 days after intravitreal injection for the first implantation and 3 months later for the second implantation of DEX PS DDS in both treatment groups and during both treatment periods. Plasma  $C_{max}$  values increased with dose between both treatment groups for both treatment periods. The extent of systemic exposure ( $AUC_{0-t}$ ) increased with dose and the duration of plasma drug concentrations was longer for 0.7 mg dose group compared to the 0.35 mg dose group. No gender related differences were observed for the treatment groups after post first implantation and post second implantation.

Text Table 1 Summary of Overall TK Data

Dose (mg/eye)	$C_{max}$ (ng/mL)	$T_{max}$ (day)	$AUC_{0-t}$ (ng•day/mL)
Post 1 <sup>st</sup> Injection*			
0a (Sham)	BLQ	NC	NC
0b (Placebo)	BLQ	NC	NC
0.35	0.213	40.1	5.65
0.7	0.555	51.1	19.1
Post 2 <sup>nd</sup> Injection*			
0a (Sham)	BLQ	NC	NC
0b (Placebo)	BLQ	NC	NC
0.35	0.357	45.0	5.29
0.7	0.535	45.0	16.8

\* = For toxicokinetic analysis, time after dosing was used

N = 4 sex/group/timepoint for both post first implantation and post second implantation

a = Sham (applicator with TAB - no implant)

b = Posurdex PS DDS Placebo, Lot. No. 1255A1

BLQ = Below Limits of Quantitation

NC = Not calculable

#### 2.6.6.4 Genetic toxicology

Studies evaluating mutagenic potential of dexamethasone in bacteria and mammalian cells *in vitro* have been negative (European Medicines Agency (EMA), 2001). An *in vivo* mouse micronucleus test was also negative (EMA, 2001). No studies of the

mutagenic potential of DEX PS DDS® implant or its polymeric components have been conducted

Committee for veterinary medicinal products, dexamethasone, summary report (2), EMEA/MRL/195/97-CORRIGENDUM March 1997 (Corrigendum dated September 2001)

**2.6.6.5 Carcinogenicity**

No carcinogenicity studies on dexamethasone or the DEX PS DDS® implant have been performed.

**2.6.6.6 Reproductive and developmental toxicology**

Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application (Tobradex® package insert, tobramycin and dexamethasone ophthalmic ointment). In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. (Decadron® package insert, 2004).

**2.6.6.7 Local tolerance**

Local tolerance was assessed in the ocular toxicity study in rabbits and monkeys described in Sections 2.6.6.2 Single-Dose Toxicity and 2.6.6.3 Repeat-Dose Toxicity.

**2.6.6.8 Special toxicology studies**

**Study title:** Evaluation of the DDS applicator functionality and safety for insertion and dispensability in the eyes of New Zealand White rabbits

**Key study findings:** The POSURDEX® applicator system was found to be easy to operate when used to insert the DEX PS DDS® implant into the posterior segment of rabbit eyes.

**Study no.:** PO902001

**Volume #, and page #:**

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**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** November 20, 2002

**GLP compliance:** Yes

**QA reports:** yes (x) no ( )

**Formulation, Drug, lot #, and % purity:** DDS Applicator Lot No. 255-01a; DEX PS DDS Lot No. 255-01c

**Methods**

The objective of this study was to evaluate the safety and performance of the DEX PS DDS Applicator System, developed by Oculex Pharmaceuticals, Inc. Four treatment regimens were randomly assigned to the eyes of 30 rabbits, resulting in a total of 60 eyes treated.

**Study design:**

- POSURDEX® Applicator System: 700 µg DEX PS DDS® implant delivery from the POSURDEX® applicator system into the posterior segment of the eye.
- POSURDEX® Applicator system: POSURDEX® applicator system was used to puncture the eye but no DEX PS DDS® implant was delivered.
- Surgical: 700 µg DEX PS DDS® implant delivery using a surgical incision and forceps.
- Sham Surgery: A surgical incision was made but DEX PS DDS® implant was not inserted.

Immediately after surgical implantation of the DEX PS DDS® implant, the surgical implantation methods were rated using a standardized scoring system. Post surgical care and ophthalmic observations were performed. Animals were euthanized on Day 15 following final ophthalmic observations.

**Results:**

The POSURDEX® applicator system was found to be easy to operate when used to insert the DEX PS DDS® implant into the posterior segment of rabbit eyes. The surgeon rated the performance of the POSURDEX® applicator system (with or without implantation of DEX PS DDS® implant) as easy (6/30 eyes, 20%) or very easy (24/30 eyes, 80%). The surgeon rated surgical implantation of DEX PS DDS® implant as difficult (4/15 eyes, 27%), easy (10/15 eyes, 67%), or very easy (1/15 eyes, 7%). At all time points, DEX PS DDS® implants were observed in all eyes implanted with the POSURDEX® applicator system or surgically.

The sponsor stated that the traumatic cataracts observed in this study are likely related to the anatomical dimensions of the rabbit eye and not associated with the DEX PS DDS® applicator. However, it is well known that the intravitreal treatment of corticosteroid will cause the formation of the cataract.

**Study title:** Safety evaluation of poly (lactic--glycolic) acid (PLGA)

**Key study findings:** Based on its well established clinical safe use and the lack of any adverse ocular findings in the chronic toxicity studies (Reports TX05029 and TX05030), the PLGA polymers used to make the implants are not expected to produce any toxic effects.

**Methods and Results (from published information)**

PLGA is a biodegradable component used in the drug product. PLGA polymers, the copolymers of lactide and glycolide monomers, have applications in surgery and in drug delivery. Several researchers have developed and tested drug delivery systems for the eye and reported the feasibility of this approach.

PLGA polymers have been used safely for up to 28 years in a number of commercial medical products including sutures, bone screws/rods, soft tissue implants, and drug formulations.

In addition, PLGA polymers are currently used in degradable (absorbable) sutures with the trade name, Vicryl® (Vicryl® package insert, 1996) in ophthalmic surgery. In general, PLGA polymers used in absorbable sutures are generally metabolized to lactic acid and

glycolic acid residues. Thereafter, lactic acid takes part in the tricarboxylic acid cycle and is consequently exhaled via respiration. Glycolic acid is transformed by glycolate oxidase to glyoxylate, which reacts with glycine transaminase, and results in the formation of glycine. Glycine can be used in protein synthesis such as serine, which may be employed in the tricarboxylic acid cycle after transformation into pyruvate (Hollinger, 1983). Therefore, based on its well established clinical safe use and the lack of any adverse ocular findings in the chronic toxicity studies (Reports TX05029 and TX05030), the PLGA polymers used to make the implants are not expected to produce any toxic effects.

#### 2.6.6.9 Discussion and Conclusions

The ocular and systemic safety of DEX PS DDS<sup>®</sup> implant has been evaluated in rabbits with 3 single-dose toxicity studies and in rabbits and in monkeys with repeat-dose (2 injections, 3 months apart) toxicity study each. Ocular findings of endophthalmitis and cataract noted in these studies were attributed to the surgical procedures. However, corticosteroid-induced cataract is well established. Transient and expected dexamethasone systemic adverse effects in rabbits, including lower mean body weight, changes to hematological and serum chemistry profiles and/or pathological findings of immune system organs, adrenal (atrophy), and/or liver, were observed in the single-dose studies. In the repeat-dose study in rabbits, Transient lower mean body weight and food consumption were observed. Low incidences of drug-induced posterior cortical lens opacities were noted following the second dose in one 700 µg-treated and two 1400 µg-treated eyes. By 12-months, there was evidence of regression in one of the 1400 µg-treated eyes. The repeat-dose toxicity study in monkeys did not reveal any significant systemic or ocular toxicity at doses up to two 700 µg implants, 3 months apart.

#### 2.6.6.10 Tables and Figures

Tables and figures are directly included in text above as appropriate.

### 2.6.7 TOXICOLOGY TABULATED SUMMARY

#### OVERALL CONCLUSIONS AND RECOMMENDATIONS

Posurdex<sup>®</sup> (Dexamethasone Posterior Segment Drug Delivery System, DEX PS DDS) is indicated for treatment of patients with macular edema secondary to central retinal vein occlusion or branch retinal vein occlusion. The drug component, dexamethasone, is dispersed in a poly (D,L-lactide-co-glycolide) (PLGA) biodegradable polymer matrix formed into rod-shaped implants, which are approximately — mm in diameter and — mm (0.35 mg DEX) to 4 mm (0.7 mg DEX) in length. The device component is to be delivered by a single-use applicator directly into the posterior segment of the eye. The DEX PS DDS is loaded within the needle of the applicator (DEX PS DDS Applicator System).

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Allergan conducted a 10 week study in rabbits to evaluate the primary pharmacodynamics of the 350 µg and 700 µg DEX PS DDS<sup>®</sup> (Report BIO-05-481). A

dose-independent effect was observed in a validated rabbit model of glucocorticoid-sensitive blood-retinal barrier breakdown, vasculopathy, and retinal edema.

In rabbit, the majority of dexamethasone (>70%) was released from DEX PS DDS® by ~1 month postdose with the remaining dexamethasone content gradually released to ~4 months in rabbit vitreous. A good *in vitro-in vivo* correlation for DEX PS DDS® release was observed, indicating similarity of implant dissolution in buffer and rabbit vitreous. In monkey, the majority of dexamethasone was released (>90%) from DEX PS DDS® in monkey vitreous by ~3 months postdose with remaining dexamethasone content gradually released to ~6 months. This long duration of delivery in primates and the low concentrations of dexamethasone required for effect in cell based potency (~1 ng/mL) support the 6-month clinical dosing interval.

*In vitro*, dexamethasone was not bound to synthetic melanin (12.5 µg/mL) over a concentration range from \_\_\_\_\_ . In rabbit, the tissue dexamethasone exposure was higher in the ocular posterior segment (retina > choroid > sclera) relative to the anterior segment (ciliary body > lens > iris > cornea > AH). In monkey, dexamethasone exposure was also higher in the posterior segment (retina > choroid > sclera) relative to the anterior segment (iris > ciliary body > lens > AH > cornea).

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Ocular metabolism studies were conducted *in vitro* in human ocular tissues and *in vivo* in rabbits and monkeys using [<sup>14</sup>C]-dexamethasone. The results indicate no or minimal metabolism of dexamethasone in rabbit, monkey, and human ocular tissues.

Biodegradable polyesters, PLA and PLGA, have been approved for human use by the US Food and Drug Administration. PLA and PLGA used as vehicle in DEX PS DDS® are known to degrade via backbone hydrolysis (bulk erosion) and the degradation products, lactic acid and glycolic acid, are ultimately metabolized into carbon dioxide and water. The elimination of dexamethasone from the systemic circulation after intravitreal administration of DEX PS DDS® is expected to be similar to that after oral or IV routes of administration. In general, following oral or IV administration, elimination occurs via metabolism and renal excretion.

The systemic use of dexamethasone has been reported for many decades. Following single intravenous (IV), oral, or multiple-dose topical ocular administration of dexamethasone or dexamethasone disodium phosphate to humans, maximal plasma concentrations were  $10.5 \pm 2.8$ ,  $8.4 \pm 3.6$ , and  $0.7 \pm 0.4$  mg/mL, respectively. Oral and IV doses may range from 6 up to 8 mg with subsequently higher human exposure. In repeat-dose toxicology studies, the plasma  $C_{max}$  in rabbit and monkey at the highest DEX PS DDS® dose administered were 1.60 and 0.555 ng/mL, respectively. The repeat toxicokinetic profiles were similar to the single-dose, suggesting no potential for ocular or systemic drug accumulation following repeat dosing of DEX PS DDS®.

Based on body weight differences between human (~60 kg) and monkey (~3 kg) the systemic exposure of dexamethasone in human is expected to be ~20-fold ( $60 \text{ kg} \div 3 \text{ kg} = 20$ ) lower than in monkey. Therefore, plasma dexamethasone is estimated to be below or at the limit of detection ( $BLQ < 0.02 \text{ ng/mL}$  or  $0.555 \text{ ng/mL} \div 20 = 0.027 \text{ ng/mL}$ ) and ~400 times ( $0.7 \text{ mg/mL} \div 1.6 \text{ ng/mL} = 437$ ) lower exposure compared to topical ocular administration and even lower exposure compared to IV or oral administration.

In ophthalmology, dexamethasone has been widely used for over 40 years (Gordon, 1959 *Am J Ophthalmol* 1959;48:656-660). Dexamethasone, at concentrations up to 0.1% alone, or in combination with antibiotic agents such as tobramycin or ciprofloxacin, has been approved for topical use (Decadron® package insert, 2004; TobraDex® package insert, 2000). To date, the upper limit of dose-dependent toxicity has not been established. In animal studies, the maximum reported doses without adverse ocular findings for single intravitreal (IVT) injection (4,800 µg) and for implanted sustained-release dexamethasone devices (5,000 µg) are much higher than the total dose delivered with the dexamethasone posterior segment drug delivery system (DEX PS DDS®) (350 µg or 700 µg) (Cheng et al, 1995, *Invest Ophthalmol Vis Sci* 1995;36:442-453; Kwak and D'Amico, 1992, *Arch Ophthalmol* 1992;110:259-266; Nabih et al, 1991, *Int Ophthalmol* 1991;15:233-235). It has been recognized that prolonged use of corticosteroid treatment may result in cataract formation. Intraocular pressure (IOP) elevation may occur much earlier, however, reports have varied about the time point of observable significant IOP increase. On average, IOP elevation has been found to be significant following 1 to 2 weeks of corticosteroid treatment (Foster CS, *Massachusetts Eye & Ear Infirmary Immunology Service* 1998; Schwartz B, *Ophthalmol Clin North Am* 1996;6:929-989).

The ocular and systemic safety of DEX PS DDS implant has been evaluated in rabbits with 3 single-dose toxicity studies and in rabbits and in monkeys with repeat-dose (2 injections, 3 months apart) toxicity study each. Ocular findings of endophthalmitis and cataract noted in these studies were attributed to the surgical procedures. Transient and expected dexamethasone systemic adverse effects in rabbits, including lower mean body weight, changes to hematological and serum chemistry profiles and/or pathological findings of immune system organs, adrenal (atrophy), and/or liver, were observed in the single-dose studies. In the repeat-dose study in rabbits, Transient lower mean body weight and food consumption were observed. Low incidences of drug-induced posterior cortical lens opacities were noted following the second dose in one 700 µg-treated and two 1400 µg-treated eyes. By 12-months, there was evidence of regression in one of the 1400 µg-treated eyes. The repeat-dose toxicity study in monkeys did not reveal any significant systemic or ocular toxicity at doses up to two 700 µg implants, 3 months apart.

Studies evaluating mutagenic potential of dexamethasone in bacteria and mammalian cells *in vitro* have been negative (European Medicines Agency (EMA), 2001). An *in vivo* mouse micronucleus test was also negative (EMA, 2001). No carcinogenicity studies on dexamethasone or the DEX PS DDS® implant have been performed. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application. In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. (Decadron® package insert, 2004). Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1.0 mg/kg/day every other day for 28 days or at 10.0 mg/kg/day once or every other day on 3 or 5 days between gestation Days 23 and 49

had fetuses with findings limited to minor cranial abnormalities (Jerome and Hendrickx, 1988, J. Med. Primatol. 17:195-203 (1988)). A 1.0 mg/kg/day dose in pregnant rhesus monkeys would be approximately 85 times higher ( $1000 \mu\text{g} \div 11.67 \mu\text{g}$ ) than a 700  $\mu\text{g}$  (or  $11.67 \mu\text{g}/\text{kg}$ ) DEX PS DDS® implant in humans (assuming 60 kg body weight). The POSURDEX® applicator system was found to be easy to operate when used to insert the DEX PS DDS® implant into the posterior segment of rabbit eyes. PLGA is a biodegradable component used in the drug product. Based on its well established clinical safe use and the lack of any adverse ocular findings in the chronic toxicity studies (Reports TX05029 and TX05030), the PLGA polymers used to make the implants are not expected to produce any toxic effects.

**Conclusions:**

The non-clinical issues for DEX PS DDS® have been properly addressed and discussed in the NDA 22315.

Unresolved toxicology issues (if any):

None

**Recommendations:**

The approval of NDA 22315 is recommended.

**Suggested labeling:**

The proposed labeling appears adequate.

Signatures (optional):

Reviewer Signature Conrad H. Chen, Ph.D.

Supervisor Signature Wendelyn Schmidt, Ph.D.

Concurrence Yes  No

**APPENDIX/ATTACHMENTS**

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this page is the manifestation of the electronic signature.**  
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/s/  
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Conrad Chen  
4/14/2009 02:21:35 PM  
PHARMACOLOGIST  
The approval of NDA 22315 is recommended.

Wendelyn Schmidt  
4/29/2009 01:32:08 PM  
PHARMACOLOGIST