CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-315

PHARMACOLOGY REVIEW(S)
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.
PHARM/TOX SUPERVISOR: Wendelyn Schmidt, Ph.D.
DIVISION DIRECTOR: Wiley A. Chambers, M.D.
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.
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 : (11β,16α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione  
IUPAC : 9α-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione  
CAS registry number: 50-02-2  
Molecular formula/molecular weight: C_{22}H_{29}FO_{5}/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 mm in diameter and mm (0.35 mg DEX) to mm (0.7 mg DEX) in length.

<table>
<thead>
<tr>
<th>Component</th>
<th>%, w/w</th>
<th>0.35 mg Dose, µg</th>
<th>0.7 mg Dose, µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>600</td>
<td>350</td>
<td>700</td>
</tr>
<tr>
<td>Poly (D,L-lactide-co-glycolide)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly (D,L-lactide-co-glycolide)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLGA acid</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 hydrocortisone, 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

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Test System</th>
<th>Method of Administration</th>
<th>Testing Facility</th>
<th>Study Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Pharmacodynamics</td>
<td>Rabbits</td>
<td>Intravitreal</td>
<td>Allergan, Inc. Irvine, California</td>
<td>BIO-05-481</td>
</tr>
<tr>
<td>Secondary Pharmacodynamics</td>
<td>No secondary pharmacodynamic studies were conducted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety Pharmacology</td>
<td>No safety pharmacology studies were conducted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacodynamic Drug Interactions</td>
<td>No pharmacodynamic drug interaction studies were conducted</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 [14C]-dexamethasone. The results indicate no or minimal metabolism of dexamethasone in rabbit, monkey, and human ocular tissues. The sponsor stated that biodegradable polyesters, PLA (polyactic 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.
Table 3.2.P.2.1-2  List of Commercial Medical Products Containing PLA/PLGA Polymers

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Drug Substance</th>
<th>Dosage Form</th>
<th>Mode of Administration</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vieryl®</td>
<td>Ethicon</td>
<td>n/a (69)</td>
<td>n/a (69)</td>
<td>n/a (69)</td>
<td>n/a (69)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Enantone®</td>
<td>Teijin</td>
<td>Leuprolin</td>
<td>Microsphere suspension</td>
<td>Injection (SC or IM)</td>
<td>France 1988</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Italy 1994</td>
</tr>
<tr>
<td>Prostab®</td>
<td>Wyeth</td>
<td>Leuprolin acetate</td>
<td>Microsphere suspension</td>
<td>Injection (SC or IM)</td>
<td>UK 1991</td>
</tr>
<tr>
<td>Bigoniste®</td>
<td>Aventis (Sanofi-Chimie)</td>
<td>Buserelin</td>
<td>Implant</td>
<td>Injection (SC)</td>
<td>France 1993</td>
</tr>
<tr>
<td>Somatoline®</td>
<td>Boehringer-Ingelheim</td>
<td>Lanreotide</td>
<td>Microsphere suspension</td>
<td>Injection (IM)</td>
<td>France 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acetate</td>
<td></td>
<td></td>
<td>UK 1998</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Italy 1999</td>
</tr>
<tr>
<td>Sandostatin®</td>
<td>Novartis</td>
<td>Octreotide acetate</td>
<td>Microsphere suspension</td>
<td>Injection (IM)</td>
<td>USA 1988</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>France 1995</td>
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<td></td>
<td>UK 1998</td>
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<td></td>
<td></td>
<td>Italy 1999</td>
</tr>
<tr>
<td>Zoladex®</td>
<td>Astra Zeneca</td>
<td>Goserelin acetate</td>
<td>Implant</td>
<td>Injection (SC)</td>
<td>USA 1985; 1996</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Italy 1994</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>France 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK 2001</td>
</tr>
<tr>
<td>Rispendal® consta®</td>
<td>Janssen-Cilag</td>
<td>Risperidone</td>
<td>Microsphere suspension</td>
<td>Injection (IM)</td>
<td>USA 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK 2002</td>
</tr>
<tr>
<td>Decapeptyl®</td>
<td>Ipsiva</td>
<td>Triptorelin</td>
<td>Injection (IM)</td>
<td></td>
<td>France 1996</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Italy 1999</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK 2002</td>
</tr>
<tr>
<td>Gonapseryl LP®</td>
<td>Ferring SAS</td>
<td>Triptorelin acetate</td>
<td>Microsphere suspension</td>
<td>Injection (SC or IM)</td>
<td>France 2001</td>
</tr>
<tr>
<td>Gonapseryl Depot®</td>
<td>Ferring Pharmaceutical</td>
<td>Triptorelin</td>
<td>Microsphere suspension</td>
<td>Injection (SC or IM)</td>
<td>UK 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Italy 2003</td>
</tr>
<tr>
<td>Resperidal Costral</td>
<td>Janssen Cilag SA</td>
<td>Risperidone</td>
<td>Injection IM</td>
<td></td>
<td>France 2003</td>
</tr>
</tbody>
</table>

1) Not applicable since Vieryl® is not a registered medical drug product.

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.
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. $^{14}$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® in rabbits
and one single-dose study in monkeys were conducted.
Following intravitreal implantation of 350 µg and 700 µg DEX PS DDS® in rabbits, the
VH C$_{max}$ 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 ± 4.5% and 10.8 ± 3.2% at 1 day postdose and 98.6 ±
2.1% and 70.5 ± 36.9% at 28 days postdose for 350 µg and 700 µg DEX PS DDS®,
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 ± 1.8% of DEX PS DDS® 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 µg DEX PS DDS®, the dexamethasone VH
C$_{max}$ 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® 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 (EC50, 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 ± 2.8, 8.4 ± 3.6, and 0.7 ± 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 administrered 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 kg/3 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 ng/mL/~20= 0.027 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.
2.6.4.4 Distribution

In vitro, dexamethasone was not bound to synthetic melanin (12.5 μg/mL) over a concentration range from —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 ^14^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 ^14^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 ^14^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.
References:

2.6.4.6 Excretion
In monkeys, dexamethasone was rapidly cleared from retina, choroid, sclera, ciliary body, iris, cornea, and AH with t1/2 ranging from 3.35 to 5.61 hours on Day 1, and 3.65 to 5.67 hours on Day 21. The t1/2 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 ± 2.8, 8.4 ± 3.6, and 0.7 ± 0.4 ng/mL, respectively. In repeat-dose toxicology studies, the plasma Cmax 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 kg/3 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 ng/mL/20= 0.027 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
### 2.6.5.1 Pharmacokinetics

#### Overview

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Test System</th>
<th>Method of Administration</th>
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<td>In vitro human ocular metabolism</td>
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<sup>a</sup> - Report contains a GLP Compliance Statement.

<sup>b</sup> - Additional tests are required for toxicokinetics.
2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicity 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 (EMEA), 2001). An in vivo mouse micronucleus test was also negative (EMEA, 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 X71062G and X81310G).
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 X71062G) 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 X81310G).
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
lymphototoxicity 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 lymphototoxicity, 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 #: 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 2nd 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 1st injection on Days 2, 8, 15, 22, 29, 36, 61, and 89, and post 2nd 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 1st dose and 9 months observation period following the 2nd 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 1st dose and 0.71 vs. 1.33 ng/mL post 2nd dose). The extent of systemic exposure (AUC_{0-\infty}) appeared to be dose proportional (9.78 vs. 19.6 ng-days/mL post 1st dose and 7.40 vs. 18.4 ng-days/mL post 2nd 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 1st dose and 24.0 vs. 24.0 days (post 2nd 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
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 1st dose and 9 months observation period following the 2nd 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-\infty}) 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

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<th>Dose (mg/eye)</th>
<th>( C_{max}) (ng/mL)</th>
<th>( T_{max}) (day)</th>
<th>AUC_{0-\infty} (ng·day/mL)</th>
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<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>0b (Placebo)</td>
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* = 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 toxicity
Studies evaluating mutagenic potential of dexamethasone in bacteria and mammalian cells in vitro have been negative (European Medicines Agency (EMEA), 2001). An in vivo mouse micronucleus test was also negative (EMEA, 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 (Tobralex® 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 #: 
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 glyoxyxylate, 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® 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
Posuradex® (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 < 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).

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 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 1. 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 [14C]-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 ± 2.8, 8.4 ± 3.6, and 0.7 ± 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 Cmax 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 kg ÷ 3 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 ng/mL ÷ 20 = 0.027 ng/mL) and ~400 times (0.7 mg/mL ÷ 1.6 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 (EMEA), 2001). An in vivo mouse micronucleus test was also negative (EMEA, 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 µg+11.67 µg) than a 700 µg (or 11.67 µg/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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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