CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-315

SUMMARY REVIEW

Division Director Review for NDA 22-315

Date	June 17, 2009
From	Wiley A. Chambers, M.D.
NDA#	NDA 22-315
Applicant	Allergan, Inc.
Date of Submission	December 23, 2008
Name	Ozurdex (dexamethasone intravitreal implant)
Dosage forms / Strength	intravitreal implant
Proposed Indication(s)	Treatment of macular edema following branch or central retinal vein occlusion
Action:	Approval

1. Introduction

Dexamethasone intravitreal implant is an intraocular drug delivery system developed for treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The active ingredient, dexamethasone, is a corticosteroid with anti-inflammatory activity. Dexamethasone is combined with biodegradable polymers and is extruded into a small implant suitable for delivery into the posterior segment of the eye through a specifically designed applicator.

Dexamethasone intravitreal implant is injected into the posterior segment of the eye and releases a total dose of approximately 0.7 mg dexamethasone. While releasing dexamethasone, the implant gradually degrades completely over time so there is no need to remove the implant.

Two phase 3 studies (206207-008 and 206207-009) support the approval having demonstrated safety and effectiveness in patients with macular edema following CRVO or BRVO. These Phase 3 studies were multicenter, masked, randomized, sham-controlled, studies evaluating Dexamethasone intravitreal implant for 6 months, followed by a 6-month open-label extension period.

The efficacy variable used across studies was best-corrected visual acuity (BCVA) in the study eye measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) method. In both phase 3 studies, the endpoint used to support efficacy was based on time to improvement of 15 letters or more improvement in BCVA. For reference a 3-line worsening of visual acuity is equivalent to a doubling of the visual angle; a 15-letter change with the time to achieve a 15 letter or more improvement from baseline is considered a clinically significant endpoint for drug efficacy.

Throughout this review, OZURDEX (dexamethasone intravitreal implant) may alternately be referred to by various review disciplines as OZURDEX, POSURDEX, Dexamethasone intravitreal implant, Dexamethasone Posterior Segment Drug Delivery System, or DEX PS DDS Applicator System.

2. Background

On January 10, 2005, Fast Track Designation for Dexamethasone intravitreal implant was granted for the indication of macular edema due to CRVO/BRVO. There are no currently approved drug products indicated for patients with macular edema secondary to CRVO or BRVO.

On October 30, 2007, at the pre-NDA meeting, Allergan, Inc. requested a Pediatric Waiver. The Division agreed that studies are impossible or highly impractical because the number of pediatric patients with this diagnosis is so small.

Additional meetings included an End-of-Phase 2 meeting on September 8, 2003, clinical meetings and discussions on December 2003; February 2007; May 2007; June 2007 and July 2008. A second pre-NDA meeting was held on April 23, 2008.

During the course of these meetings, the Division agreed that the primary efficacy comparison would be Dexamethasone intravitreal implant versus sham and that a gate keeping approach. This agreement was based on Phase 2 data that demonstrated Dexamethasone intravitreal implant 0.7 had better efficacy and similar safety to Dexamethasone intravitreal implant 0.35 mg. The two Phase 3 trials (206207-008 and 206207-009) would include both doses of dexamethasone (0.35 mg and 0.7 mg) and a needleless, sham control arm. In July 2008, at the conclusion of study 009 and before the completion of study 008, the applicant discussed with the Division the data from study 009. The data from study 009 identified a clear effect during the first 2 months following injection and a wearing off the effect by 6 months. The Division recommended that the primary efficacy endpoint for study 008 be changed to "time to visual improvement [15 letter improvement], based on the findings from study 009. The applicant submitted an amendment to change the endpoint in August 2008, prior to study 008's completion.

3. CMC

From the CMC Review:

b(4)

The dexamethasone drug substance is covered by a DMF held by [redacted] and a Letter of Authorization to refer to this DMF is supplied. This DMF, as amended, has been reviewed and found to be adequate. There have been no substantive changes since this review. An adequate drug substance specification that is tighter than the current USP specification is provided. The analytical methods are fully described. Satisfactory batch analyses are provided for 7 batches of drug substance. The retest date is [redacted] years when stored at controlled room temperature protected from light. This is based on [redacted] years of satisfactory stability data obtained at 25°C/60% RH.

b(4)

The drug product is an intravitreal implant containing 0.7 mg dexamethasone. Dexamethasone is combined with biodegradable polymers and extruded into a small implant suitable for delivery into the posterior segment of the eye through a specifically designed applicator. The rod-shaped implant is [redacted] in diameter and [redacted] in length. It is loaded into the needle of a single-use applicator that delivers the implant directly to the posterior segment of the eye. This implant is indicated for the treatment of adults with macular edema following branch retinal vein occlusion

b(4)

or central retinal vein occlusion. By weight, the implant is [redacted] dexamethasone, [redacted] b(4)

The polymers are similar. [redacted] Poly (D,L-lactide-co-glycolide), [redacted] PLGA [redacted] Poly (D,L-lactide-co-glycolide), [redacted] PLGA [redacted] is terminated with an acid group. These polymers are used in absorbable sutures and are hydrolyzed in the body to lactic acid and glycolic acid. These polymers have been used in approved US products. The polymers are manufactured by [redacted] under a DMF and a Letter of Authorization is provided. This DMF has been reviewed and the polymers have been found to be suitable for pharmaceutical purposes. Acceptable specifications for these polymers are provided in this NDA. Additionally the analytical methods are fully described and satisfactory batch analyses are provided. b(4)

The applicator consists of a 22-gauge thin-wall hypodermic needle with a plastic handle. To use the safety tab is removed and the needle is inserted into the eye. A button is pressed downwards and this causes a plunger to push the implant into the posterior chamber of the eye.

The drug product is manufactured by Allergan Pharmaceuticals, Ireland and [redacted] sterilization is carried out by [redacted]. The drug substance and sterilization facilities were found to be acceptable based on file review, and the manufacturing facility was found to be acceptable based upon an inspection. Sterilization is by [redacted] The commercial batch size is [redacted] which produces [redacted] units for both strengths. The manufacturing process is clearly described in detail. [redacted]

b(4)

[redacted]

1. The in-process controls are clearly explained and serve to adequately control this complex product. The plant and manufacturing process have been inspected by FDA and found to be acceptable.

Drug product specifications for appearance, identity, assay, impurities, insoluble particles, actuation force, drug release, sterility, endotoxins, and content uniformity are provided. As amended, these specifications are acceptable.

The analytical methods are all fully described and have been validated. Drug release [redacted] b(4)

[redacted] This method has been shown to be equivalent to measuring release at a more physiologically relevant 37°C. Measuring release at 37°C would require 21 days which is not practical.

Batch analyses are provided for 17 full scale batches of the 0.7 mg size and 12 full scale batches of the 0.35 mg size. These analyses are generally acceptable although for earlier there are a number of instances where the implant is not present or protrudes from the needle.

For each strength 24 months of stability data obtained at 25°C/60% RH, 12 months of data obtained at 30°C/65% RH, and 6 months of data obtained at 40°C/75% RH are provided for 3 full-scale batches (only 18 months at 25°C/60% RH for one of the 0.35 mg batches, however). One batch was also tested under freeze/thaw and low/high conditions. There are no obvious trends and drug release appears to be smooth and consistent. For the most part there are no out of specification results although the [redacted]s in some cases is of concern. The applicant explains that applicators with missing or protruding implants were from early lots. Since these batches were manufactured the manufacturing process has been refined. These early batches used an [redacted], to retain the implant. This has now been replaced by a sleeve and safety tab. Additionally the assembly process ' b(4)

[redacted] b(4)

Statistical projections support an expiration dating period of 36 months which is acceptable.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

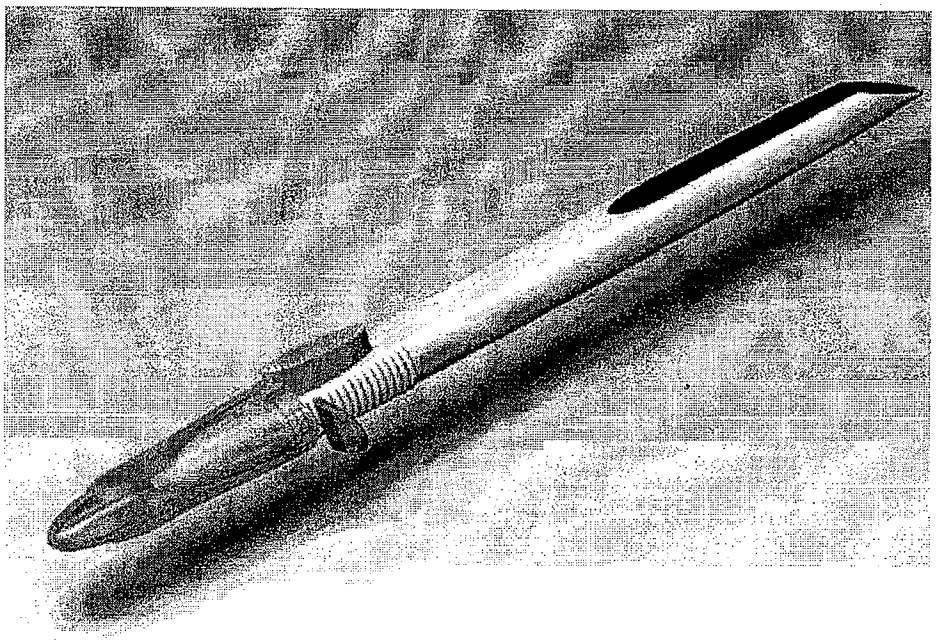
The drug product is an intravitreal implant. Dexamethasone is combined with biodegradable polymers and extruded into a small implant suitable for delivery into the posterior segment of the eye through a specifically designed applicator. The rod-shaped implant is [redacted] in diameter and [redacted] in length. It is loaded into the needle of a single-use applicator that delivers the implant directly to the posterior segment of the eye. This implant is indicated for the treatment of adults with macular edema following branch retinal vein occlusion or central retinal vein occlusion. b(4)

Component	Function	% (w/w)	0.7 mg
Dexamethasone, USP	Active	[redacted]	700 µg
[redacted], Poly (D,L-lactide-co-glycolide), ([redacted] PLGA [redacted]	Biodegradable extended release polymer matrix	[redacted]	
[redacted], Poly (D,L-lactide-co-glycolide), [redacted] PLGA [redacted]	Biodegradable extended release polymer matrix	[redacted]	

b(4)

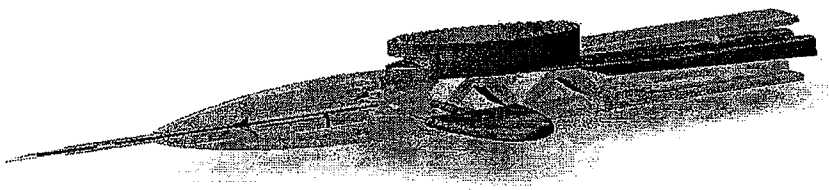
The polymers are similar. [redacted], Poly (D,L-lactide-co-glycolide), ([redacted] PLGA [redacted] Poly (D,L-lactide-co-glycolide), ([redacted] PLGA [redacted] b(4)

The applicator measures [redacted] in length by [redacted] in width.



The patient contact materials are the plunger (stainless steel), sleeve (silicone with colorant), and needle (stainless steel with [redacted] oil coating). b(4)

A cut-away view is as follows.



To use the safety tab is removed, the needle is inserted into the eye, and the lever is pressed downwards. This causes the linkage to collapse and push the plunger into the needle. In turn this pushes the implant into the posterior chamber of the eye. The lever latches with the housing with an audible click to signal use and prevent re-use. The needle is a standard 22-gauge thin-wall hypodermic needle externally lubricated with [redacted] oil. The needle is fitted b(4)

with a sleeve that also serves to hold the implant in place. The sleeve contacts the outer surface of the eye. Air is vented through a small gap between the implant and the inner needle wall. Because this gap is very small fluid should not leak from the eye.

REGULATORY SPECIFICATIONS:

Test	**Method**	**Acceptance criterion**
Appearance	Visual	White to off-white, rod shaped implant contained in an applicator sealed in a foil patch with a ———
Identity	HPLC	Positive for dexamethasone (retention time ± % of standard)
Identity	TLC	Positive for dexamethasone
Assay	HPLC	——— % (release ——— %)
Impurities	HPLC	
———		
———		
Total		———
Insoluble particles	Light obscuration	
≥ µm		——— particles/mg
≥ µm		——— particles/mg
Actuation force	Method AP-MS014	——— pounds-force
Drug release	USP <724>.App. —	
Average		Day 1 ≤ ——— %; Day 9 ≥ ——— %
Individual		
Level 1 (n=6)		Day 1 ≤ ——— %; Day 9 ≥ ——— %
Level 2 (n=12)		Day 1 ≤ ——— %; Day 9 ≥ ——— %
Level 3 (n=24)		
≤ 2		Day 1 ≤ 25%; Day 9 ≥ ———
None		Day 1 ≤ 35%; Day 9 ≥ ———
Sterility	USP <71>	Conforms
Endotoxins	USP <85>	
Drug		——— EU per implant
Needle		——— EU per needle
Content uniformity	USP <905>	Conforms

b(4)

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b(4)

FACILITIES INSEPCTIONS:
All facilities were found acceptable for NDA 22-315 by Compliance as attached in EER at the end of the original CMC review.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review:

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 [redacted] mm in diameter and [redacted] (0.35 mg DEX) to [redacted] (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). b(4)

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 the monkey, the majority of dexamethasone was released (>90%) from DEX PS DDS® in the 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 [redacted] µM ([redacted] µg/mL). 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). b(4)

Biodegradable polyesters, PLA and PLGA, have been approved for human use. 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 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 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.

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).

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review:

To support product approval, the clinical development program for POSURDEX included initial phase 1 emergency and compassionate use studies, phase 1 and 2 dose-ranging trials, and two phase 3 multicenter, masked, randomized sham-controlled, safety and efficacy studies in patients with macular edema following CRVO or BRVO. The Clinical Pharmacology findings from these studies are summarized as follows:

- A dose-response relationship for efficacy was suggested in both the phase 2 study and the pooled analysis of the two phase 3 trials. In the phase 3 studies 008 and 009, patients treated with either DEX PS DDS containing 700 µg of dexamethasone (DEX 700) or DEX PS DDS containing 350 µg of dexamethasone (DEX 350) experienced better visual acuity based on multiple measures, including time to achieve ≥ 15 letters improvement in BCVA and percent of patients with ≥ 15 letter BCVA improvements. The data presented suggests DEX 700 demonstrated greater efficacy and with a longer duration of effect than DEX 350.
- No dose-response relationship for safety was observed in the pooled phase 3 studies between DEX 700 and DEX 350. The overall incidence of adverse events in the initial treatment period for the pooled phase 3 studies was significantly higher in the DEX 700 group (72.4%) and DEX 350 group (71.8%) compared to sham (57.0%), and there was no significant difference between the 700 and 350 doses of DEX PS DDS.
- The extent of systemic exposure to dexamethasone resulting from delivery of DEX 350 or DEX 700 into the posterior segment of the eye was determined from plasma samples obtained from selected patients in phase 3 studies. In both studies (206207-008 and 206207-009), the majority of plasma dexamethasone concentrations were BLQ (LLOQ = 0.05 ng/mL). Plasma dexamethasone concentrations from 10 of 73 samples in the DEX 700 group and from 2 of 42 samples in the DEX 350 group were above the LLOQ, ranging from 0.0521 ng/mL to 0.0940 ng/mL. Systemic exposure of dexamethasone appears to be minimal but dose dependent following administration of 700 µg DEX PS DDS and 350 µg DEX PS DDS.

Based on the assessment of systemic exposure information from the Phase 3 multicenter, masked, randomized, sham-controlled, safety and efficacy studies in patients with macular edema following CRVO or BRVO, the regulatory requirement for submission of in vivo bioavailability data has been addressed.

6. Sterility Assurance

From the Product Quality Microbiology Review:

There are no microbiology deficiencies identified.

The bulk drug components (dexamethasone and polymers) are [redacted] b(4)

b(4)

The product specification includes the test methods and acceptance criteria shown in Table 3 which are indicators of the microbiological quality of the subject drug product.

Table 3. Microbiological Tests and Acceptance Criteria

Test	Method	Release & Stability Acceptance Criteria
Sterility	—, based on USP<71>	Meets Compendial Acceptance Criteria
Bacterial Endotoxins	—, based on USP<85>	Drug Component: ≤ — EU/DEX PS DDS Device Component: ≤ — EU/Needle Assembly

b(4)

The applicant will test the drug product at release and on stability for bacterial endotoxins using the gel clot method according to USP<85>. The applicant has proposed the following limits for endotoxin:

- Drug Component: ≤ —EU/DEX PS DDS.
- Device Component: ≤ —EU/Needle Assembly.

b(4)

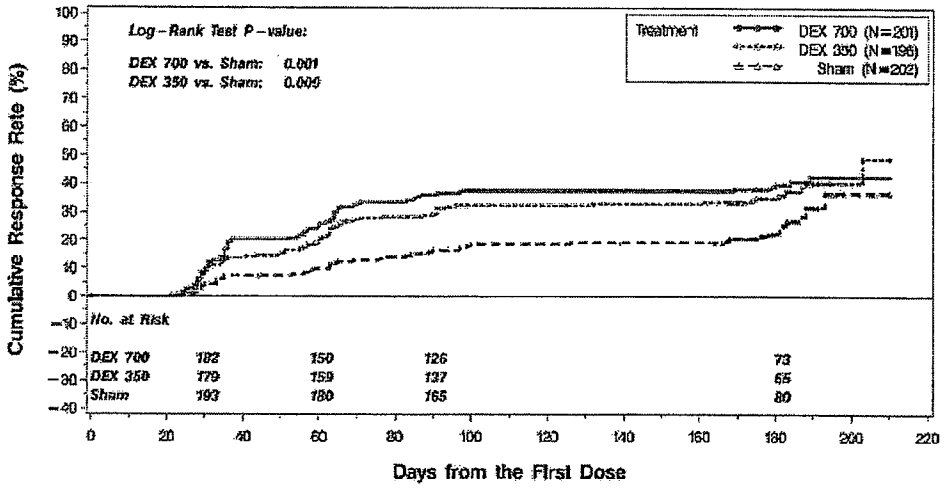
7. Clinical/Statistical - Efficacy

From the Medical Officer Review:

The applicant conducted two adequate and well controlled clinical trials. Studies 206207-008 and 206207-009 compared two active treatment groups, dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg, to the control group that received a sham needleless injection. These studies were designed as 6-month masked treatments followed by 6-month open label periods. At day 180, qualifying patients who remained unaware of the initial randomized treatment (up to 100 subjects) were eligible to receive treatment with an open-label dexamethasone intravitreal implant 0.7 mg. No sham or 0.35 mg implant procedures were conducted at this visit.

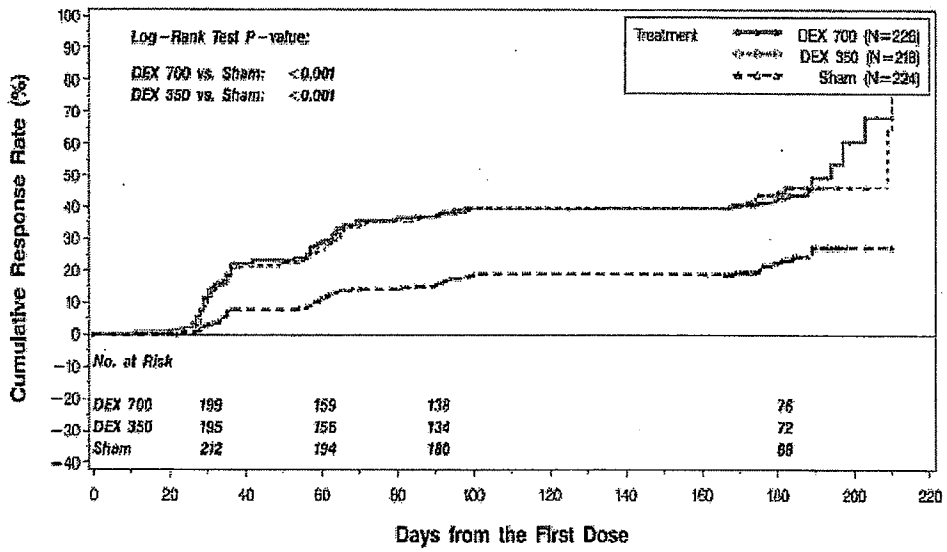
One hundred subjects from these studies received an open-label dexamethasone intravitreal implant 0.7 mg for the 6-month open-label treatment period. The safety data from these 100 subjects with 12 month follow-up are included in the Medical Officer's safety review.

Study 008, ITT Population: Time to Achieve 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity



In Study 206207-008, the time to achieve a treatment response of ≥15 letters improvement from baseline BCVA was evaluated over the entire initial treatment period using survival analysis methods. Overall the cumulative response rate curves were significantly different for the dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg groups compared to the Sham group ($p < 0.001$). Response rates were consistently higher with dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg compared to sham throughout the 180-day initial treatment period. There was a separation of curves as early as day 30, without crossover at any subsequent visit. The effect of dexamethasone intravitreal implant treatment was also similar in the BRVO and CRVO patients.

Study 009, ITT Population: Time to Achieve 15 or More Letters Improvement from Baseline



In study 206207- 009, analysis of time to treatment response of ≥ 15 letters improvement from baseline BCVA in the study eye was determined. Overall, the cumulative response rate curves were significantly different for the dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg groups compared to the Sham group ($p < 0.001$). Response rates were consistently higher with dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg than with sham, with separation of curves as early as day 30 and no crossover during the initial treatment period. The effect of dexamethasone intravitreal implant treatment was also similar in the BRVO and CRVO patients.

Analysis of Additional Endpoints

Efficacy endpoints included the proportion of patients with BCVA improvement of 15 or more letters.

Proportion of patients with BCVA Improvement of 15 or More Letters from Baseline Best Corrected Visual Acuity in the Study Eye

Visit	Study 206207-009			Study 206207-008			Pooled 008 and 009		
	Posurdex 0.7 mg N=226	Posurdex 0.35 mg N=218	Sham N=224	Posurdex 0.7 mg N=210	Posurdex 0.35 mg N=196	Sham N=202	Posurdex 0.7 mg N=427	Posurdex 0.35 mg N=414	Sham N=426
Day 30	22.6%[a]	20.6%[a]	7.6	19.9%[a]	14.8%[e]	7.4%	21.3%[a]	17.9[a]	7.5%
Day 60	29.6%[a]	31.2[a]	12.1	28.9%[a]	25.5%[a]	10.4%	29.3%[a]	28.5%[a]	11.3%
Day 90	21.2[b]	25.7%[c]	13.8%	22.4%[d]	20.9%[f]	12.4%	21.8%[a]	23.4%[a]	13.1%
Day 180	23.5%	22.0%	17.0%	19.4%	16.3%	18.3%	21.5%	19.3%	17.6%

a Proportion significantly higher with TRADENAME compared to Sham ($p < 0.001$)
b Proportion significantly higher with TRADENAME compared to Sham ($p = 0.039$)
c Proportion significantly higher with TRADENAME compared to Sham ($p = 0.002$)
d Proportion significantly higher with TRADENAME compared to Sham ($p = 0.008$)
e Proportion significantly higher with TRADENAME compared to Sham ($p = 0.019$)
f Proportion significantly higher with TRADENAME compared to Sham ($p = 0.022$)

In each of the phase 3 studies, patients receiving Dexamethasone intravitreal implant achieved significantly higher rates of 15 or more letters improvement in BCVA from baseline compared to sham in the first 3 months.

In each individual study and in a pooled analysis, time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with Dexamethasone intravitreal implant compared to sham ($p < 0.01$), with Dexamethasone intravitreal implant-treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a ≥15 letter (3 line) improvement in BCVA with Dexamethasone intravitreal implant occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately one to three months after onset of this effect.

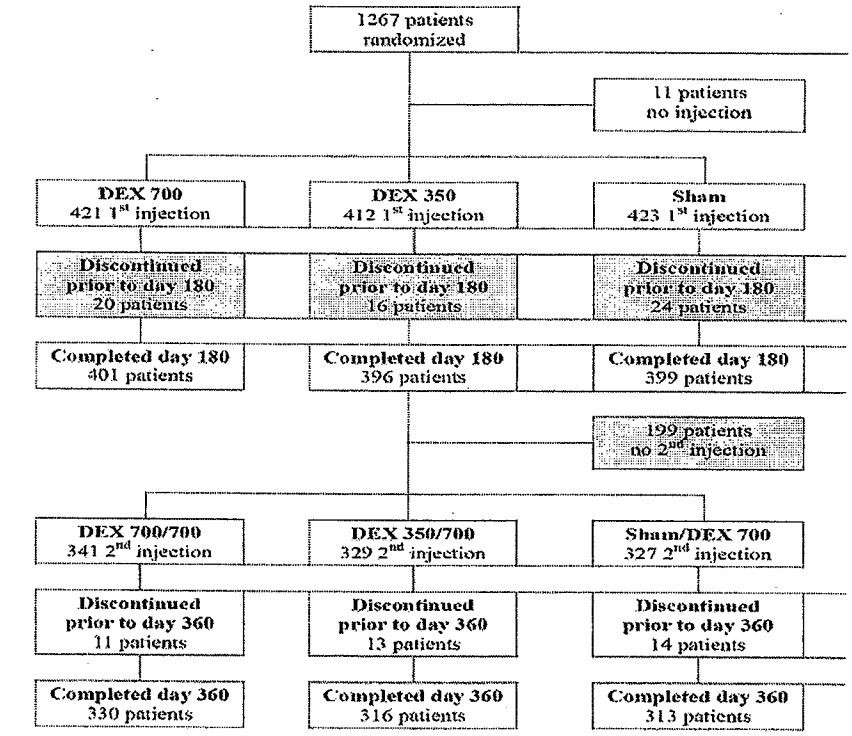
8. Safety

The safety and efficacy effects seen with this product are class effects related to steroids.

Ocular steroids are contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and thus increase the hazard of secondary ocular infections. Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. Acute purulent infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

Patient Disposition (Pooled Studies 008 and 009)



Shaded boxes comprise the single-treatment population.

Serious Adverse Events in Any Treatment Group
(Studies 206207-008 and 206207-009, Initial 6-Month Period)

System Organ Class Preferred Term[a]	TRADENAME 0.7 mg N = 421	TRADENAME 0.35 mg N = 412	Sham N = 423
Ocular Events			
Intraocular pressure Increased	2 (0.5%)	3 (0.7%)	0 (0.0%)
Ocular hypertension	1 (0.2%)	0 (0.0%)	0 (0.0%)
Retinal vein occlusion	0 (0.0%)	1 (0.2%)	0 (0.0%)
Blindness	0 (0.0%)	1 (0.2%)[b]	0 (0.0%)
Glaucoma	0 (0.0%)	1 (0.2%)[b]	1 (0.2%)
Non-Ocular Events[c]			
Cardiac Disorders			
Myocardial infarction	2 (0.5%)	5 (1.2%)	0 (0.0%)
Angina pectoris	2 (0.5%)	1 (0.2%)	0 (0.0%)
Cardiac failure congestive	1 (0.2%)	0 (0.0%)	2 (0.5%)
General Disorders			
Chest pain	0 (0.0%)	0 (0.0%)	2 (0.5%)
Infections			
Urinary tract infection	0 (0.0%)	0 (0.0%)	2 (0.5%)
Nervous System Disorders			
Cerebrovascular accident	1 (0.2%)	2 (0.5%)	1 (0.2%)
Syncope	0 (0.0%)	1 (0.2%)	2 (0.5%)

a Preferred terms based on MeDRA, version 11.0.
b Events occurred in same patient eye
c Events listed occurring in 2 or more subjects

The rates of ocular serious events and non-ocular serious events were similar among the 3 treatment groups.

There were three deaths that occurred during study 206207-008 and one death that occurred during study 206207-009.

In study 206207-008, one subject died due to accidental drowning and two due to myocardial infarctions. In study 206207-009, the subject died due to a myocardial infarction.

None of these deaths were considered to be related to study treatment.

Adverse Events Occurring in > 2 % of Patients in Any Treatment Group (Studies 206207-008 and 206207-009, Initial 6-month Period)

System Organ Class Preferred Term[a]	Ozurdex 0.7 mg N = 421	TRADENAME 0.35 mg N = 412	Sham N = 423
Ocular Events			
Intraocular pressure increased[b]	106 (25.2%)	102 (24.8%)	5 (1.2%)
Conjunctival hemorrhage	85 (20.2%)	72 (17.5%)	63 (14.9%)
Eye pain	31 (7.4%)	17 (4.1%)	16 (3.8%)
Conjunctival hyperemia	28 (6.7%)	27 (6.6%)	20 (4.7%)
Maculopathy	19 (4.5%)	22 (5.3)	23 (5.4%)
Ocular hypertension[c]	17 (4.0%)	16 (3.9%)	3 (0.7%)
Cataract	15 (3.6%)	7 (1.7%)	6 (1.4%)
Vitreous floaters	13 (3.1%)	5 (1.2%)	6 (1.4%)
Vitreous detachment	12 (2.9%)	12 (2.9%)	8 (1.9%)
Retinal hemorrhage	12 (2.9%)	8 (1.9%)	10 (2.4%)
Foreign body sensation	11 (2.6%)	7 (1.7%)	11 (2.6%)
Vitreous hemorrhage	10 (2.4%)	13 (3.2%)	12 (2.8%)
Retinal exudates	10 (2.4%)	4 (1.0%)	14 (3.3%)
Conjunctival edema	9 (2.1%)	16 (3.9%)	7 (1.7%)
Visual acuity reduced	7 (1.7%)	7 (1.7%)	9 (2.1%)
Retinal neovascularization	3 (0.7%)	4 (1.0%)	11 (2.6%)
Non-ocular events			
Influenza	9 (2.1%)	4 (1.0%)	2 (0.5%)
Headache	14 (3.3%)	10 (2.4%)	7 (1.7%)
Hypertension	17 (4.0%)	13 (3.2%)	15 (3.5%)

a Preferred terms based on MeDRA, version 11.0.
b P-value < 0.001 for DEX 700 vs Sham; < 0.001 for DEX 350 vs Sham; and 0.888 for DEX 700 vs DEX 350
c P-value 0.004 for DEX 700 vs Sham; 0.006 for DEX 350 vs Sham; and 0.909 for DEX 700 vs DEX 350

The overall incidence of adverse events in the initial treatment period for the pooled phase 3 studies was significantly higher in the dexamethasone intravitreal implant 0.7 mg group (72.4%) and dexamethasone intravitreal implant 0.35 mg (71.8%) compared to sham (57.0%). There was no significant difference between the dexamethasone intravitreal implant 0.7 mg and dexamethasone intravitreal implant 0.35 mg doses. Ocular adverse events were likewise more commonly reported with dexamethasone intravitreal implant 0.7 mg (64.1%) and dexamethasone intravitreal implant 0.35 mg (64.6%) than with sham (45.4%). The adverse event profile was similar between the 3 treatment groups, aside from the expected increase in intraocular pressure associated with intravitreal injection of a steroid.

The adverse event profile for the BRVO patients was generally similar to that observed for CRVO, and to the overall population. The greatest percentage events reported in the drug treatment groups were an increase in intraocular pressure and conjunctival hemorrhage that were reported in more than 20 % of patients. These events are expected given the route of administration of the drug product is an intravitreal injection. The adverse events reported were not significantly different between the two clinical trials (-008 and -009).

A total of 1267 patients were randomized to studies 008 and 009. Of these, 11 patients did not receive study treatment and are excluded from the safety population. 2 patients randomized to

DEX 700 actually received DEX 350 (1 patient) and Sham (1 patient). Safety data were analyzed using actual treatment received.

The re-treated population consists of patients who received DEX 700, DEX 350, or Sham as their first injection, completed the initial treatment period day 180, and then received DEX 700 as their second injection. There were 997 patients: 341 in the DEX 700/700 group, 329 in the DEX 350/700 group, and 327 in the Sham/DEX 700 group.

Safety Update: Ocular Adverse Events in the Study Eye Reported by Greater Than 2% of Patients Over the 1-Year Study (Re-Treated Population)

System Organ Class Preferred Term [a]	Initial Treatment plus Open-Label Extension DEX 700/700 N = 341	 DEX 350/700 N = 329	 Sham/DEX 700 N = 327
Investigations (study eye)			
intraocular pressure increased	109 (32.0%)	119 (36.2%)	88 (26.9%)
Eye Disorders (study eye)			
conjunctival haemorrhage	84 (24.6%)	73 (22.2%)	73 (22.3%)
eye pain	33 (9.7%)	24 (7.3%)	25 (7.6%)
conjunctival hyperaemia	29 (8.5%)	30 (9.1%)	26 (8.0%)
cataract	39 (11.4%)	26 (7.9%)	9 (2.8%)
ocular hypertension	18 (5.3%)	16 (4.9%)	16 (4.9%)
vitreous detachment	18 (5.3%)	17 (5.2%)	10 (3.1%)
retinal haemorrhage	19 (5.6%)	14 (4.3%)	18 (5.5%)
foreign body sensation in eyes	12 (3.5%)	11 (3.3%)	13 (4.0%)
vitreous floaters	15 (4.4%)	12 (3.6%)	13 (4.0%)
retinal exudates	14 (4.1%)	8 (2.4%)	20 (6.1%)
macular oedema	24 (7.0%)	21 (6.4%)	25 (7.6%)
vitreous haemorrhage	12 (3.5%)	13 (4.0%)	16 (4.9%)
conjunctival oedema	11 (3.2%)	17 (5.2%)	15 (4.6%)
maculopathy	18 (5.3%)	22 (6.7%)	20 (6.1%)
cataract subcapsular	44 (12.9%)	20 (6.1%)	11 (3.4%)
vision blurred	8 (2.3%)	3 (0.9%)	6 (1.8%)
visual acuity reduced	9 (2.6%)	12 (3.6%)	17 (5.2%)
eye irritation	7 (2.1%)	4 (1.2%)	8 (2.4%)
ocular discomfort	4 (1.2%)	8 (2.4%)	7 (2.1%)
cataract cortical	10 (2.9%)	5 (1.5%)	9 (2.8%)
cataract nuclear	10 (2.9%)	8 (2.4%)	5 (1.5%)
optic disc vascular disorder	9 (2.6%)	9 (2.7%)	11 (3.4%)
dry eye	8 (2.3%)	5 (1.5%)	11 (3.4%)
retinal neovascularisation	5 (1.5%)	5 (1.5%)	8 (2.4%)
retinal vascular disorder	4 (1.2%)	5 (1.5%)	8 (2.4%)
retinal pigment epitheliopathy	5 (1.5%)	2 (0.6%)	8 (2.4%)
blepharitis	5 (1.5%)	8 (2.4%)	12 (3.7%)

Over the 1-year study period, the overall incidence of ocular adverse events in the study eye was similar among the 3 regimens: DEX 700/700 (77.7%), DEX 350/700 (79.3%), and Sham/DEX 700 (71.9%). The incidence of intraocular pressure increased in the study eye was higher in the DEX 350/700 group (36.2%) compared to DEX 700/700 (32.0%) or Sham/DEX 700 (26.9%). The incidence of cataracts, particularly subcapsular cataracts, was higher in

patients who had received 2 doses of DEX compared to patients who had received Sham in the initial treatment period followed by DEX 700 in the open-label extension

9. Safety Summary

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Dexamethasone intravitreal implant, dosed when macular edema is present following branch retinal or central retinal vein occlusion, is safe for the treatment of macular edema provided the implant is adequately labeled.

10. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for Dexamethasone intravitreal implant.

11. Pediatrics

On October 30, 2007, at the pre-NDA meeting, Allergan, Inc. requested a Pediatric Waiver. The Division agreed that studies are impossible or highly impractical because the number of pediatric patients with this diagnosis is so small.

Safety and effectiveness of Dexamethasone intravitreal implant in pediatric patients has not been established.

12. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested.

Per the DSI review finalized 5/27/09:

The clinical investigator (CI) sites that were requested for inspections were those with the highest enrollment numbers at domestic centers for each study. Field inspections of these pivotal studies was considered important as: 1) this is the first Application for use of dexamethasone with this intraocular drug delivery device, and 2) there are no other approved drug products for treatment of macular edema following branch or central retinal vein occlusion (this Application has been granted a priority review based on this basis).

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
James H. Miller, MD Southeastern Retina Associates, PC 1124 Weisgarber Road, Suite 207 Knoxville, TN 37909	Protocol #206207-008 Site #4280 13 Subjects	04/08/2009- 04/14/2009	Pending (Preliminary classification of NAI)
Derek Y. Kunimoto, MD (replaced Scott R. Sneed MD who was PI from 06/15/2004 to 6/05/2007 at same address) Retinal Consultants of Arizona, Ltd 1101 East Missouri Ave Phoenix, AZ 85014	Protocol #206207-009 Site #9341 (Sneed #4300) 24 Subjects	03/25/2009- 04/08/2009	VAI

In general, Protocol #206207-008 and Protocol #206207-009 appear to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Clinical Investigator inspection of Dr. Kunimoto is Voluntary Action Indicated (VAI). While regulatory violations occurred at Dr. Kunimoto's site, the safety and efficacy data from this site are considered reliable. These violations consisted of:

- Inclusion of one subject that had a history of glaucoma, contrary to protocol eligibility criteria.
- Failure to obtain fundus photography on Day 90 of the Initial Treatment phase for one subject (it was obtained approximately 7 weeks late).
- Failure to report a vitreous hemorrhage as an adverse event for one subject (this finding was recorded on the examination portion of the case report form).
- Failure to document that Subject #2000 received the protocol required perioperative ophthalmic antibacterial treatment.

The preliminary classification of the Clinical Investigator inspection of Dr. Miller is NAI. Upon receipt of the EIR for Dr. Miller an addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

FINANCIAL DISCLOSURE

Allergan, Inc. has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that the results of the studies were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) objected to the use of the originally proposed proprietary name, POSURDEX, for this product. Per the DMEPA review finalized 5/14/2009, the Proprietary Name Risk Assessment findings indicate that the proposed name, POSURDEX, is vulnerable to name confusion that could lead to medication errors with the currently marketed product, PRECEDEX. As such, the DMEPA staff objects to the use of the proprietary name, POSURDEX, for this product.

DMEPA notified the Division of Anti-Infective and Ophthalmologic Products via email on the unacceptability of the proposed proprietary name, POSURDEX, on March 30, 2009. Per email correspondence on April 14, 2009, the Division of Anti-Infective and Ophthalmologic Products (DAIOP) provided the following comments to DMEPA on the proposed proprietary name:

> "We do not agree. We think the differentiating product characteristics will be enough to mitigate the potential for a medication error reaching the patient. We agree that the names are close and may cause confusion in ordering the product, but Posurdex is an implant which comes with a pen injector. It is easily recognized from a solution for injection. It would not reach the patient.
>
> If our policy is going to be we are trying to prevent ordering errors, we concur that there is the potential for name confusion. If our policy is that there should be a risk that the patient will receive the wrong product, we do not believe that this is the case here."

In a letter to Allergan, Inc., dated 5/20/2009, DMEPA concluded that the name Posurdex is unacceptable because the proposed name is orthographically and phonetically similar to the currently marketed product PRECEDEX (dexmedetomidine hydrochloride injection).

In a submission to the NDA dated 5/6/2009, Allergan submitted the following three alternate tradenames for consideration. These names were listed in the order of preference (after POSURDEX).

1. OZURDEX
2. [redacted] b(4)
3. [redacted]

OSE reviewed the trademark "Ozurdex" and considered it acceptable. DAIOP concurred.

BIOSTATISTICS

The Biostatistics consultative review states that this submission did not provide statistically persuasive evidence of DEX 700 on a sustained response, though an early but short term improvement was observed. The Dexamethasone intravitreal implant is not considered a "cure" for macular edema; it is considered a treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The treatment effect is expected to wear off. The PLGA matrix of the implant slowly degrades to lactic acid and glycolic acid.

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Office DirectorMemo-*1

b(4)

14. REGULATORY ACTION:

I concur with the approval recommendation from the Cross Discipline Team Leader that NDA 22-315 should be approved for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

The labeling submitted by Allergan, Inc., on June 11, 2009, and listed below is acceptable for approval.

RISK BENEFIT ASSESSMENT:

The application supports the safety and efficacy of Dexamethasone intravitreal implant for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Studies 206207-008 and 206207-009 demonstrate superiority over Sham injections for the efficacy endpoint of Time to Improvement of 15 or more letters of best corrected visual acuity (BCVA); these adequate and well controlled studies support the efficacy of Dexamethasone intravitreal implant for the treatment of macular edema following BRVO and CRVO.

Aside from the expected increase in intraocular pressure associated with an intravitreal injection of a steroid that was reported in the dexamethasone intravitreal implant groups, pooled adverse event data for these trials demonstrate the adverse event profile was similar between the 3 treatment groups (dexamethasone intravitreal implant 0.7 mg versus dexamethasone intravitreal implant 0.35 mg versus Sham injections). Increased intraocular pressure occurred in 25.2 % versus 24.8 % % versus 1.2 % for the dexamethasone intravitreal implant 0.7 mg group, dexamethasone intravitreal implant 0.35 mg group, and the Sham group, respectively. Per the labeling, the most common adverse reactions reported by $\geq$ 20% of patients included increased intraocular pressure and conjunctival hemorrhage. The increase of intraocular pressure is to be expected secondary to the effects of the steroid class.

CMC, Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology, and the Medical Officer have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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