

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-212**

**OFFICE DIRECTOR MEMO**

## Office Director Memo

**Applicant:** Sirion Therapeutics

**NDA #:** 22-212

**Established Name:** difluprednate ophthalmic emulsion

**Trade Name:** Durezol

**Dosage Form and Strength:** ophthalmic emulsion, 0.05%

### Proposed Indication and Usage Section

Durezol (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery

### Proposed Dose

Instill one drop into the conjunctival sac of the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

**Date of Initial Submission:** December 26, 2007 (stamp date)

**PDUFA Goal Date:** June 26, 2008

### Regulatory Action: Approval

Durezol (difluprednate ophthalmic emulsion) 0.05% is a corticosteroid for topical ophthalmic use for the treatment of inflammation and pain following ocular surgery.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of difluprednate for the treatment of inflammation and pain following ocular surgery. For a detailed discussion of NDA 22-212, the reader is referred to the individual discipline specific reviews. In addition, Dr. Boyd's Cross Discipline Team Leader's Memo and Dr. Chamber's Acting Division Director's Memo summarize key issues in the NDA submission. This memorandum will focus on selected issues from the application.

### Chemistry Manufacturing Controls and Product Quality Microbiology

The chemistry manufacturing and controls are summarized in the Chemist's review which recommends approval from the standpoint of CMC for Durezol. Facilities

inspections were performed and found to be acceptable. The recommendation with regards to microbiology product quality is for approval.

### **Pharmacology Toxicology**

The pharmacology toxicology of difluprednate is reviewed in Dr. Chen's pharmacology toxicology review. The recommendation from the standpoint of pharmacology/toxicology is for approval.

### **Clinical Pharmacology**

The clinical pharmacology of difluprednate is discussed in the clinical pharmacology and biopharmaceutics review which notes that the information provided by the applicant is acceptable. The levels of difluprednate detected in the systemic circulation following ocular administration were below the limit of detection of 50 ng/mL.

Two dosing regimens were carried into the phase 3 trial. There was an apparent dose response between the QID regimen and the BID regimen (see below).

### **Clinical Efficacy and Safety**

Difluprednate ophthalmic emulsion 0.05% was evaluated in two phase 3 clinical trials of identical design. Both studies were double-masked placebo controlled studies that enrolled patients after ocular surgery. The primary efficacy endpoint was complete clearing of anterior chamber cells by day 8. The applicant studied both a regimen of QID for two weeks and then BID for 1 weeks followed by QD for one week (referred to as the QID regimen) and also a regimen of BID for two weeks followed by QD for two weeks (referred to as the BID regimen). Tapering in both arms was dependent upon satisfactory response. In both studies the QID regimen achieved its primary endpoint. The BID regimen achieved its primary endpoint in one of the studies, but not in the second study. Likewise, for the analysis of relief of pain/discomfort as the endpoint at day 3, the QID regimen achieved statistical significance in both studies and the BID regimen did not. The recommendation from the clinical, statistical, cross discipline team leader, and acting division director is for approval of the QID regimen.

The safety profile of difluprednate was evaluated from data across the studies in the clinical trial program. Safety assessments included collection of adverse events, corneal endothelial cell counts, IOP, BCVA, slit lamp examination, and ophthalmoscopy. The safety data did not raise concerns beyond what is known for topical ophthalmic corticosteroids. The product labeling will include a Contraindication for use in the setting of herpes simplex keratitis, vaccinia, varicella, and other active infections (viral, mycobacterial, and fungal). The labeling also includes Warnings and Precautions information on the potential to increase intraocular pressure, cataract formation, delayed healing, bacterial infection, viral infection, and fungal infections. The labeling adequately describes the safety profile of difluprednate.

### **DSI Inspections / DDMAC / DMETS**

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name Durezol. There is another product with a similar name, but the goal date for this other application is after the goal date for Durezol.

The Division of Scientific Investigations performed inspections of four sites and did not identify any significant observations that would compromise the integrity of the data.

Pediatric studies required under PREA are included as postmarketing requirements in the approval letter. The postmarketing requirement is to study patients between 0 to 3 years undergoing cataract surgery.

#### **Advisory Committee**

Durezol (difluprednate ophthalmic emulsion) 0.05% was presented before the Dermatologic and Ophthalmic Drugs Advisory Committee on May 29, 2008. The Committee voted in favor of approval.

#### **Risk Benefit Summary**

The overall risks and benefits of Durezol (difluprednate ophthalmic emulsion) 0.05% for the treatment of inflammation and pain associated with ocular surgery when used as a QID regimen for 2 weeks followed by a week of BID use and then an appropriate taper is satisfactory based upon the findings from the two phase 3 studies in post surgical patients and the additional safety data.

#### **Postmarketing Study Requirements & Commitments**

The postmarketing study commitments include a requirement for a study in pediatric patients 0 to 3 years of age undergoing cataract surgery.

#### **Summary**

I concur with the assessment of the review team, the cross discipline team leader, and the acting division director that adequate safety and efficacy information have been provided for Durezol (difluprednate ophthalmic emulsion) 0.05% for the treatment of inflammation and pain associated with ocular surgery when used as a QID regimen for 2 weeks followed by a week of BID use, and then an appropriate taper.

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6/23/2008 04:57:21 PM  
MEDICAL OFFICER