# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-212**

# SUMMARY REVIEW

# Division Director Review

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| **Date** | June 23, 2008 |
| **From** | Wiley A. Chambers, M.D. |
| **Subject** | Division Director Review |
| **NDA#** | 22-212 |
| **Applicant** | Sirion Therapeutics |
| **Date of Submission** | December 21, 2007 |
| **PDUFA Goal Date** | June 28, 2008 |
| | |
| **Proprietary Name / Established (USAN) names** | Durezol (difluprednate ophthalmic emulsion) 0.05% |
| **Dosage forms / Strength** | ophthalmic emulsion |
| **Proposed Indication(s)** | for the treatment of inflammation and pain associated with ocular surgery |
| **Recommended:** | Approval |

## 1. Introduction

Durezol (ST-601) is a topical formulation of difluprednate (new molecular entity) that is an ophthalmic corticosteroid emulsion for topical ocular instillation. Difluprednate (6α, 9-difluoro-11β,17,21,-trihydroxypregna-1,4-diene-3,20-dione 21 acetate 17-butyrate) is a synthetic, glucocorticoid receptor agonist, a difluorinated derivative of prednisolone that has anti-inflammatory activity.

## 2. Background

Difluprednate was originally developed by Warner-Lambert in 1970, and licensed to Porcher-Lavril in France in 1976, where it was developed as a dermatologic product and first marketed by Clin-Midy as Epitopic cream and ointment in Europe. Currently Epitopic cream, 0.02% and 0.05%, and Epitopic gel, 0.05%, are marketed in Europe by Laboratoire Gerda of France. In 1979, Mitsubishi Yuka-Yakuhin also obtained rights to develop a dermatologic formulation, which was marketed in Japan by Mitsubishi-Tokyo Pharmaceuticals Inc. as Myser cream and ointment (now marketed as Myser, 0.05%, ointment and cream by Mitsubishi Pharma Corporation). These products are used for treating allergic dermatitis, eczema, psoriasis, prurigo, etc, in the same manner as other dermatologic corticosteroids.

The development of difluprednate to treat inflammation in a dermatologic formulation subsequently led to its reformulation as an ophthalmic product by Senju Pharmaceutical Co. In Japan, Senju has conducted non-clinical and clinical ophthalmic studies in patients with ocular inflammation resulting from ocular surgery or from uveitis. Sirion Therapeutics has acquired the US rights to ST-601, and has conducted multiple studies examining its safety and effectiveness in the treatment of post-surgical inflammation. A Phase 3 study by Sirion testing the safety and effectiveness of ST-601 for endogenous anterior uveitis is also underway.

## 3. CMC

**DRUG SUBSTANCE:**
The drug substance is covered by DMF [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. Some details are supplied in the NDA. Difluprednate is 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17- butyrate. It is a [redacted] with a melting point of [redacted] and a specific rotation of [redacted]

**DRUG PRODUCT:**
The product was originally developed by Senju Pharmaceuticals in Japan. Phase 2 and 3 trials were carried out using product manufactured by Senju in Japan. Phase 3 trials were also carried out using product manufactured by [redacted] the proposed commercial manufacturer. The same formulation was used for all clinical trials. The product is isotonic to slightly hypertonic to tears. The product is preserved with 0.1% sorbic acid. The stability of the emulsion is governed by the [redacted]

Drug product manufacturing, packaging, and labeling will be carried out by [redacted] Drug substance testing and drug product release and stability testing will be carried out by [redacted]

George Lunn has reviewed Chemistry, Manufacturing and Controls section of the NDA and recommends approval from his prospective with the concurrence of his supervisory chain. An Establishment Evaluation Request was made via EES and an Overall Recommendation of Acceptable has been made.

**DRUG PRODUCT COMPOSITION:**

| | |
|---|---|
| Difluprednate | 0.05% |
| Glycerin | 2.2% |
| Sodium acetate | 0.05% |
| Boric acid | 0.1% |
| Castor oil | 5% |
| Polysorbate 80 | 4% |
| Sodium edetate | 0.02% |
| Sorbic acid | 0.1% |
| NaOH | To adjust pH |
| Water | qs |

## 4. Nonclinical Pharmacology/Toxicology

Difluprednate (DFBA) is rapidly metabolized by deacetylation (at 21-position) in the rabbit eye tissues to the metabolite DFB (active metabolite), which is in turn converted to DF. No quantifiable difluprednate or DFB reaches the blood following a single ocular instillation (50 μL/eye) of difluprednate 0.05% in rabbits. The $C_{max}$ in the eye was observed within 1 hour of $^{3}$H-difluprednate instillation. The assay method using $^{3}$H-difluprednate is sensitive enough to measure difluprednate and its metabolites at the levels of 0.3 ng equivalent/gm tissue. By autoradiography, difluprednate was cleared from the ocular tissues after a single instillation within 24 hours. Over 99% of radioactivity was excreted within 7 days.

Difluprednate has been marketed as a topical dermatological ointment in Japan. The toxicity data from the completed dermatological studies in animals were for a longer duration than the ophthalmic studies. The NOELs in the 6-month dermatological studies in rats and dogs were 1 μg/kg/day and 1.25 μg/kg/day, respectively. Neither deaths nor serious toxicologic findings were noted in the studies. Many changes at higher doses were those generally observed in glucocorticoid-treated animals. Ocular administration of 0.05% difluprednate ophthalmic emulsion (0.1 ml/eye) QID for up to 4 weeks in dogs and in rabbits did not cause any significant ocular toxicity. Instillation of heat-degraded difluprednate 0.05% in rabbits was tolerated as well as the normal difluprednate 0.05%. The instillation of polysorbate 80 excipient for 7 days was tolerated at concentrations up to 4% in rabbit eyes. Mutagenesis and chromosomal aberration tests of difluprednate and difluprednate metabolites were negative. In the bacterial reverse mutation tests and the *in vitro* mammalian cell clastogenicity tests, difluprednate, metabolites, degradants, and impurities (DF17C, DF21B, and DFB) were all negative. An *in vivo* micronucleus test of difluprednate in mice was also negative. No carcinogenicity studies of difluprednate have been performed.

Reproductive toxicity studies conducted in Japan (in 1981- 1984) during the development of dermatologic formulation of difluprednate were submitted in this NDA. Reproductive toxicity tests were performed with difluprednate in rats and rabbits. Fetal death and malformations such as cleft palate (commonly associated with high-dose administration of GCs) were observed during the organogenic period in rabbits. The effects of difluprednate on rat fetuses were weak; fetal death and/or malformed fetuses were not found.

## 5. Clinical Pharmacology/Biopharmaceutics

To support product approval, two clinical pharmacology studies of ST-601 were conducted as sub-studies of a single Phase 1 trial (Study 9): a pharmacokinetic study evaluating systemic exposure following repeated ocular instillation, and a pharmacodynamic study examining the effect of repeated ocular instillation on serum cortisol levels in the same subjects.

Difluprednate has negligible systemic absorption following multiple ocular instillation of difluprednate 0.01% and 0.05% for 7 days, as evidenced by undetectable concentrations of the active metabolite 6α,9-difluoroprednisolone 17-butyrate (DFB).

The product was recommended for approval from a Pharmacology/Toxicology Prospective by Conrad Chen with concurrence of his supervisor.

## 6. Sterility Assurance

The drug product will be ——— processed and packaged using ——— technology at ——————————— No product quality microbiology deficiencies were identified based upon the information provided. The product was recommended for approval from a Sterility Assurance Prospective by Stephen E. Langille with concurrence of his supervisor.

## 7. Clinical/Statistical - Efficacy

Two phase 3, double-masked, randomized, vehicle-controlled clinical trials evaluating ST-601 in the treatment of inflammation and pain following cataract surgery. Each study was conducted under an identical but geographically separate protocols, with sites located north of latitude 37° in Study 002b and sites located south of latitude 37° in Study 002a. (ST-601A-002a and ST-601A-002b). In each study, patients were dosed either BID or QID for 14 days.

**Complete Clearing of Anterior Chamber Cells - Study 002a [Grade 0 = 0 cells], ITT**

| Subjects Cleared | ST-601 BID (N=57) | ST-601 QID (N=55) | Vehicle (N=107) | ST-601 BID P value | ST-601 QID P value |
|---|---|---|---|---|---|
| Day 3 | 3 | 4 | 0 | 0.02 | 0.01 |
| Day 8 (LOCF) | 9 (15.8%) | 13 (23.6%) | 11 (10.3%) | 0.36 | **0.03** |
| Day 15 (LOCF) | 25 | 25 | 15 | **<0.01** | **<0.01** |
| Day 29 (LOCF) | 35 | 32 | 26 | **<0.01** | **<0.01** |
| Follow-up | 35 | 36 | 51 | 0.22 | **0.01** |

**Study 002b [Grade 0 = 0 cells] ITT Population**

| Subjects Cleared | ST-601 BID (N=54) | ST-601 QID (N=52) | Vehicle (N=113) | ST-601 BID P value | ST-601 QID P value |
|---|---|---|---|---|---|
| Day 3 | 1 | 1 | 2 | 0.87 | 1.00 |
| Day 8 (LOCF) | 10 (18.9%) | 11 (21.2%) | 6 (5.3%) | **<0.01** | **<0.01** |
| Day 15 (LOCF) | 20 | 19 | 10 | **<0.01** | **<0.01** |
| Day 29 (LOCF) | 29 | 33 | 20 | **<0.01** | **<0.01** |
| Follow-up | 33 | 32 | 48 | **0.02** | **0.01** |

**Study 002a: Proportion of Patients with a Pain/Discomfort Score of 0, ITT**

| | ST-601 BID (N=57) | ST-601 QID (N=55) | Vehicle (N=107) | ST-601 BID P value | ST-601 QID P value |
|---|---|---|---|---|---|
| Day 3 | 23 (40.4%) | 27 (50%) | 29 (27.6%) | 0.08 | <0.01 |
| Day 8 (LOCF) | 23 (40.4%) | 38 (69.1%) | 32 (30.5%) | 0.22 | **<0.01** |
| Day 15 (LOCF) | 36 (63.2%) | 42 (76.4%) | 47 (44.8%) | **0.02** | **<0.01** |
| Follow-up | 41 | 44 | 75 | 0.40 | 0.25 |

**Study 002b: Proportion of Patients with a Pain/Discomfort Score of 0, ITT**

| | ST-601 BID (N=54) | ST-601 QID (N=52) | Vehicle (N=113) | ST-601 BID P value | ST-601 QID P value |
|---|---|---|---|---|---|
| Day 3 | 19 (35.8%) | 21 (40.4%) | 25 (22.1%) | 0.08 | **0.01** |
| Day 8 (LOCF) | 23 (43.4%) | 24 (46.2%) | 27 (23.9%) | **0.01** | **<0.01** |
| Day 15 (LOCF) | 23 (43.4%) | 25 (48.1%) | 29 (25.7%) | **0.01** | **<0.01** |

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|---|---|---|---|---|---|
| Follow-up | 30 | 36 | 56 | 0.43 | **<0.01** |

The QID dosing is clearly superior to BID dosing. In the treatment of ocular inflammation, it is important to clear as much inflammation as quickly as possible and therefore the QID dosing regimen will be recommended for approval.

Christopher Kadoorie has reviewed the clinical studies from a statistical prospective and concluded that the overall findings from studies 002A and 002B provided adequate evidence of efficacy in the QID regimen but not the BID regimen. Overall findings were primarily based on an analysis of 'the proportion of ITT subjects with complete clearing (count = 0) of anterior chamber cells by day 8' which had been previously recommended by the Agency as a clinically meaningful primary endpoint. For the QID regimen, this endpoint was significant in Studies 002A and 002B. For the BID regimen, this endpoint was significant in Study 002A but not significant in Study 002B. Sonal Wadhwa has reviewed the clinical studies from a clinical prospective and concluded that the studies support a QID regimen.

## 8. Safety

Seven clinical trials were used to support safety of difluprednate. Studies 1, 2, 3, and 4 were in patients following cataract surgery with moderate inflammation. Studies 6, 7, and 11 were conducted in patients with a diagnosis of endogenous anterior uveitis or panuveitis.

The studies raised no new safety concerns about the product beyond those known to occur with the ophthalmic use of corticosteroids. The model studied (post cataract inflammation) does not permit adequate evaluations of the potential to cause cataracts, to increase intraocular pressure, increase the risk of secondary infections or to delay wound healing. These issues will be described in the labeling of the product. Sonal Wadhwa has reviewed the safety information from the clinical studies from a clinical prospective and concluded that the studies support a QID regimen.

## 9. Advisory Committee Meeting

An advisory committee meeting was held on May 29, 2008. The committee concurred with the potential approval of the application and raised no new issues of safety or efficacy.

## 10. Pediatrics

Sirion has not conducted any clinical studies in pediatric patients. In their June 10, 2008, submission, Sirion committed to conducting a post-marketing study of difluprednate ophthalmic emulsion in pediatric subjects as described below.

**Protocol Submission Date:** 10/26/2008
**Study Start Date:** 01/26/2009
**Final Report Submission:** 06/26/2011

As described in PREA, because the application is otherwise being recommended for approval in adults, the pediatric requirements will be deferred to the dates listed above.

## 11. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was requested. The inspection for this NDA consisted of two US clinical sites in addition to the sponsor inspection. The deficiencies noted at the two clinical sites were minor in nature and appeared to be isolated occurrences. The inspectional findings limited to a few minor, apparently isolated deficiencies support the validity of the data submitted by the sponsor under this NDA.

Sirion Therapeutics 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 study were impacted by any financial payments.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "Durezol." The results of the Proprietary Name Risk Assessment found that the proposed name, Durezol, is vulnerable to name confusion that could lead to medication errors with the name [redacted], is not approved and the action date for [redacted] is scheduled after the action date for Durezol.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed [redacted] proposed product labeling (PI) for this application submitted to the Agency on [redacted]

## 12. Labeling

NDA 22-212 is recommended for approval for the treatment of ocular inflammation and pain associated with ocular surgery with the labeling submitted by Sirion Therapeutics on June 23, 2008, and found in the Cross-Discipline Team Leader Review.

## 13. Recommendations/Risk Benefit Assessment

**RECOMMENDED REGULATORY ACTION:**

NDA 22-212 is recommended for approval for the treatment of ocular inflammation and pain associated with ocular surgery.

The labeling submitted by Sirion Therapeutics on June 23, 2008, and found in the Cross-Discipline Team Leader Review is acceptable for approval.

**RISK BENEFIT ASSESSMENT:**

Overall findings from studies 002A and 002B provided adequate evidence of efficacy in the QID regimen but not the BID regimen. For the QID regimen, this endpoint was significant in Studies 002A and 002B. For the BID regimen, this endpoint was significant in Study 002A but not significant in Study 002B. For the QID regimen, both studies 002A and 002B also showed significance in a key secondary endpoint, 'the proportion of ITT subjects with pain/discomfort score of 0 on Day 3.' Based on the FDA recommended primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QID regimen but not the BID regimen as an effective treatment in subjects with inflammation following ocular surgery.

The application supports the safety of Durezol (difluprednate ophthalmic emulsion) 0.05% for the treatment of ocular inflammation and pain associated with ocular surgery. Overall, Durezol was safe and well tolerated. Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Clinical, CMC, Pharmacology/Toxicology, and Clinical Pharmacology 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
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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