PRODUCT MONOGRAPH

# Pr**DUREZOL®**

Difluprednate Ophthalmic Emulsion
0.05% w/v

Professed standard

Topical Corticosteroid

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Ophthalmic (topical) | Emulsion/ 0.05% w/v | Preservative: Sorbic acid<br>*For a complete listing see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

DUREZOL® (difluprednate) ophthalmic emulsion is indicated for the:

- treatment of inflammation and pain associated with post-operative inflammation following cataract surgery
- treatment of endogenous anterior uveitis.

**Geriatrics:**
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

**Pediatrics (0 to 3 years of age):**
Post-operative inflammation following cataract surgery:
DUREZOL® ophthalmic emulsion was studied in 39 children aged 28 days to 3 years with inflammation following cataract surgery. The safety profile of DUREZOL® ophthalmic emulsion administered four times daily for 14 days was found acceptable in these children (see ADVERSE REACTIONS, Post-operative ocular Inflammation and Pain). The efficacy of DUREZOL® ophthalmic emulsion has not been established in children for postoperative inflammation following cataract surgery.

Endogenous Anterior Uveitis:
The safety and efficacy of DUREZOL® ophthalmic emulsion have not been studied in children with endogenous anterior uveitis.

## CONTRAINDICATIONS

DUREZOL® (difluprednate) ophthalmic emulsion is contraindicated in patients with:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section.
- Hypersensitivity to other corticosteroids.
- Suspected or confirmed infection of the eye: viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; acute untreated ocular bacterial infection; mycobacterial infection of the eye, and fungal disease of ocular structures.

## WARNINGS AND PRECAUTIONS

### General

DUREZOL® (difluprednate) ophthalmic emulsion is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. DUREZOL® ophthalmic emulsion is not indicated for intraocular administration.

Prolonged use of ophthalmic corticosteroids may result in cataract and/or glaucoma formation, thus, intraocular pressure should be monitored closely. The use of steroids after cataract surgery may delay wound healing. Corticosteroids should not be used in case of an ocular infection (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Difluprednate has not been studied in pregnant or nursing women, but has been found to be teratogenic in animals. DUREZOL® ophthalmic emulsion should not be used in pregnant or nursing women unless the benefits to the mother clearly outweigh the risk to the foetus or the nursing child. (see WARNINGS AND PRECAUTIONS, Special Populations).

DUREZOL® ophthalmic emulsion should not be instilled while wearing contact lenses (see WARNINGS AND PRECAUTIONS , Ophthalmologic).

### Ophthalmologic

Intraocular pressure (IOP) Increase:
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Intraocular pressure (IOP) should be monitored routinely starting early during treatment with DUREZOL® ophthalmic emulsion. This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. DUREZOL® ophthalmic emulsion is not approved for use in pediatric patients. The risk of corticosteroid-induced raised IOP and/or cataract formation is increased in predisposed patients (e.g. diabetes).

Corticosteroids should not be used in the presence of glaucoma or ocular hypertension (IOP≥ 24 mm Hg) or history of steroid-induced IOP elevation, unless absolutely necessary and under close ophthalmologic monitoring. Caution should be exercised and duration of treatment with DUREZOL® ophthalmic emulsion should be kept as short as possible (usually up to 14 days, and tapered as determined by the treating ophthalmologist).

Cataracts:
Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing:
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. Topical nonsteroidal anti-inflammatory drug (NSAID) medications are also known to slow of delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections:
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral Infections:
The use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections:
Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Contact Lenses:
DUREZOL®ophthalmic emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® ophthalmic emulsion. The preservative in DUREZOL® ophthalmic emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® ophthalmic emulsion.

**Carcinogenesis and Mutagenesis**
There was no evidence of genotoxicity in the relevant *in vitro* and animal *in vivo* tests (see TOXICOLOGY, Genotoxicity). No carcinogenicity studies of difluprednate have been performed.

**Neurologic**
Disturbances and suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis can occur with systemic exposure to corticosteroids. However, given the very low systemic exposure to difluprednate when using DUREZOL® ophthalmic emulsion as directed, these possible effects are not likely (see ACTION AND CLINICAL PHARMACOLOGY).

**Endocrine and Metabolism**
Glucocorticoids, mostly when systemic exposure occurs, decrease the hypoglycemic activity of insulin and oral hypoglycemics, so that a change in dose of the antidiabetic drugs may be needed. In high doses, glucocorticoids also decrease the response to somatotropin. The usual doses of mineralocorticoids and large doses of some glucocorticoids cause hypokalemia and may exaggerate the hypokalemic effects of thiazides and high-ceiling diuretics. In combination with amphotericin-B, they also may cause hypokalemia. Glucocorticoids appear to enhance the ulcerogenic effects of non-steroidal anti-inflammatory drugs. They decrease the plasma levels of salicylates, and salicylism may occur on discontinuing steroids. Glucocorticoids may increase or decrease the effects of prothrombopenic anticoagulants. Estrogens, phenobarbital, phenytoin and rifampin increase the metabolic clearance of adrenal steroids and hence necessitate dose adjustments. However, given the very low systemic exposure to difluprednate when using DUREZOL®ophthalmic emulsion as directed, these possible effects are not likely (see ACTION AND CLINICAL PHARMACOLOGY).

**Immune**
Difluprednate reduced the number of plaque-forming cells (ie, antibody-forming cells) in the spleen of the ICR mice after subcutaneous administration. Cortisol and the synthetic analogs of cortisol have the capacity to prevent or suppress the development of the local heat, redness, swelling, and tenderness by which inflammation is recognized. At the microscopic level, they inhibit not only the early phenomena of the inflammatory process (edema, fibrin deposition, capillary dilation, migration of leukocytes into the inflamed area, and phagocytic activity) but also the later manifestations, such as capillary proliferation, fibroblast proliferation, deposition of collagen, and, still later, cicatrisation.

**Sexual Function/Reproduction**
DUREZOL® ophthalmic emulsion has not been studied in humans. Difluprednate slightly suppressed spontaneous motility of isolated pregnant and nonpregnant rat uterus specimens at concentrations of $10^{-4}$ and $10^{-3}$ g/mL, but not at $10^{-5}$ g/mL (see TOXIOCOLOGY).

Difluprednate was embryotoxic, and teratogenic in animals. See WARNINGS AND PRECAUTIONS, Special Populations - Pregnant Women and TOXICOLOGY.

**Driving and Using Machinery**
DUREZOL® ophthalmic emulsion may cause temporary blurred vision or other visual disturbances, which may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient should be advised to wait until vision clears before driving or using machinery.

## Special Populations

**Pregnant Women:**

Difluprednate has been shown to be embryotoxic (decrease body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies were observed when administered subcutaneously to rabbits at a dose of 10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females.

DUREZOL® ophthalmic emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. Difluprednate has not been studied in pregnant women and the possibility of harm cannot be ruled out. Therefore, DUREZOL® ophthalmic emulsion should be used during pregnancy only if the potential benefits to the mother clearly outweigh the potential risks to the embryo or foetus.

**Nursing Women:**

It is unknown if difluprednate is excreted in human milk following the use of DUREZOL® ophthalmic emulsion. Because many drugs are excreted in human milk, precaution should be exercised. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL® ophthalmic emulsion is administered to a nursing woman.

**Pediatrics (28 days to 3 years of age):**

Post-operative inflammation following cataract surgery:
DUREZOL® ophthalmic emulsion was studied in 39 children age 28 days to 3 years with inflammation following cataract surgery. The safety profile of DUREZOL® ophthalmic emulsion administered QID for 14 days was found acceptable (see ADVERSE REACTIONS, Post-operative ocular Inflammation and Pain).

The risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Endogenous Anterior Uveitis:
The safety and efficacy of DUREZOL®ophthalmic emulsion have not been studied in children with endogenous anterior uveitis.

**Geriatrics**:

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

**Predisposed Patients (e.g. diabetes):**

The risk of corticosteroid-induced raised IOP and/or cataract formation is increased in predisposed patients (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

**Monitoring and Laboratory Tests**

Intraocular pressure should be monitored routinely starting early during treatment with DUREZOL® ophthalmic emulsion. For details regarding patient monitoring after surgery, see WARNINGS AND PRECAUTIONS, Ophthalmologic and ADVERSE REACTIONS.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Ocular adverse events (AEs) generally associated with ophthalmic steroids may include elevated intraocular pressure (IOP) which can be associated with optic nerve damage, punctate keratitis, visual acuity and field defects, posterior subcapsular cataract formation, secondary or reactivation of ocular infection from pathogens including herpes simplex, delayed wound healing, corneal effects, and perforation of the globe where there is thinning of the cornea or sclera.

### Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Overall, a total of 541 patients have been exposed to DUREZOL® (difluprednate) ophthalmic emulsion in 5 uveitis studies (two of which were pivotal: C-10-034, and 001), and 6 post-cataract surgery studies (two of which were pivotal: 002a and 002b). Of these patients, 39 participated in a pediatric study (C-10-004) of inflammation following cataract surgery. In the above-mentioned studies, patients received DUREZOL® ophthalmic emulsion four times daily for at least 14 days followed by a tapering regimen (e.g. halving of the number of doses per day at each step based on medical judgment).

**Post-operative inflammation following cataract surgery**

Two identical pivotal randomized, double-masked, placebo-controlled studies of DUREZOL® ophthalmic emulsion and its vehicle were performed in 219 subjects with ocular inflammation following cataract surgery. Patients had no history of glaucoma, ocular hypertension, steroid-related IOP rise, corneal abrasion/ulceration, and had an IOP <24 mm Hg on Day 1 after surgery (studies 002a and 002b). The patients received 1 drop, either BID or QID of DUREZOL® ophthalmic emulsion, or the placebo, for 14 days followed by a tapering period of up to an additional 14 days. The percentage of patients who completed the study was approximately 90% with DUREZOL® ophthalmic emulsion, and 56% in the placebo group. Withdrawal due to lack of efficacy was more frequent in the placebo group (40%) as compared to the DUREZOL® ophthalmic emulsion QID group (3%), or BID group (8%).

Most frequently reported ocular adverse reactions included corneal and conjunctival edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, and blepharitis. See Table 1 below for rates of adverse events.

Non-ocular adverse reactions that occurred in at least 2% in DUREZOL® ophthalmic emulsion treatment groups (pooled 002a and 002b studies) included headache and diarrhea.

**Table 1: Adverse events (AEs, both related and not related combined) occurring in ≥2% in DUREZOL® ophthalmic emulsion treatment groups (Pooled 002a & 002b studies, safety population)**

| | **DUREZOL® BID N=111** | **DUREZOL® QID N=107** | **Placebo N=220** |
|---|---|---|---|
| **Subjects with at least 1 AE** (ocular and non-ocular) | 66 (59.5%) | 62 (57.9%) | 182 (82.7%) |
| **Congenital, familial, and genetic disorders** | 1 (0.9%) | 0 | 6 (2.7%) |
| Corneal dystrophy | 1 (0.9%) | 0 | 6 (2.7%) |
| **Eye disorders** (any ocular AEs) | 64 (57.7%) | 55 (51.4%) | 178 (80.9%) |
| Posterior capsule opacification | 17 (15.3%) | 12 (11.2%) | 32 (14.5%) |
| Conjunctival hyperemia | 11 (9.9%) | 16 (15.0%) | 76 (34.5%) |
| Punctate keratitis | 8 (7.2%) | 6 (5.6%) | 8 (3.6%) |
| Eye pain | 12 (10.8%) | 5 (4.7%) | 44 (20.0%) |
| Photophobia | 11 (9.9%) | 10 (9.3%) | 45 20.5%) |
| Corneal edema | 12 (10.8%) | 5 (4.7%) | 56 (25.5%) |
| Ciliary hyperemia | 6 (5.4%) | 10 (9.3%) | 62 (28.2%) |
| Conjunctival edema | 7 (6.3%) | 5 (4.7%) | 27 (12.3%) |
| Visual acuity reduced | 6 (5.4%) | 2 (1.9%) | 37 (16.87%) |
| Anterior chamber cell | 5 (4.5%) | 4 (3.7%) | 40 (18.2%) |
| Eye inflammation | 3 (2.7%) | 5 (4.7%) | 17 (7.7%) |
| Vitreous floaters | 3 (2.7%) | 5 (4.7%) | 5 (2.3%) |
| Iritis | 5 (4.5%) | 2 (1.9%) | 3 (1.4%) |
| Foreign body sensation in eyes | 3 (2.7%) | 2 (1.9%) | 16 (7.3%) |
| Vitreous detachment | 3 (2.7%) | 1 (0.9%) | 4 (1.8%) |
| IOP increased (as an AE)* | 3 (2.7%) | 2 (1.9%) | 2 (0.9%) |
| Conjunctival hemorrhage | 2 (1.8%) | 1 (0.9%) | 0 (0.0%) |
| Anterior chamber flare | 3 (2.7%) | 1 (0.9%) | 31 (14.1%) |
| Macular edema | 1 (0.9%) | 2 (1.9%) | 5 (2.3%) |
| Blepharitis | 1 (0.9%) | 2 (1.9%) | 12 (5.5%) |
| Trichiasis | 0 | 2 (1.9%) | 6 (2.7%) |
| Corneal deposits | 0 | 0 | 5 (2.3%) |
| Eyelid edema | 0 | 0 | 5 (2.3%) |

*****: See section below for cases of increase in IOP.

**Table 2: Patients with IOP increase from baseline (pooled studies 002a & 002b)**

| IOP thresholds | Approximate time | DUREZOL® BID (N=111) | DUREZOL® QID (N=107) | Placebo (N=220) |
|---|---|---|---|---|
| **IOP increase ≥ 5 mmHg** | Day 8 | 11(10.0%) | 13(**12.1**%) | 10(4.6%) |
| | Day 15 | 12(10.9%) | 13(**12.1**%) | 11(5.0%) |
| | Day 29 | 11(10.0%) | 14(**13.1**%) | 9(4.1%) |
| | Visit 6 - Follow up | 6/110 (5.5%) | 9/101 (8.9%) | 13/211 (6.2%) |
| **IOP increase ≥ 8 mmHg** | Day 8 | 6(5.5%) | 4(3.7%) | 3(1.4%) |
| | Day 15 | 3(2.7%) | 8(**7.5**%) | 1(0.5%) |
| | Day 29 | 2(1.8%) | 6**(5.6**%) | 2(0.9%) |
| | Visit 6 - Follow up | 1/110 (0.9%) | 1/101 (1.0%) | 4/211 (1.9%) |
| **IOP increase of ≥ 10 mmHg** | Day 8 | 2(1.8%) | 2(1.9%) | 1(0.5%) |
| | Day 15 | 1(0.9%) | 2(1.9%) | 1(0.5%) |
| | Day 29 | 1(0.9%) | 2(1.9%) | 1(0.5%) |
| | Visit 6 - Follow up | 0/110 | 1/101 (1.0%) | 0/211 |

Study C-10-004

In this randomized active-controlled study, 39 pediatric patients aged 28 days to 3 years were administered DUREZOL® ophthalmic emulsion QID for 14 days (and tapered thereafter). Overall, the adverse events profile was not significantly different from that of Prednisolone acetate ophthalmic suspension 1% QID administered to the controls (N=40). However, there were one case of corneal edema, and two cases of IOP increased assessed as related to DUREZOL® ophthalmic emulsion, one of which was serious (IOP increase of +17 mmHg, with IOP reaching 30 mmHg).

**Endogenous Anterior Uveitis**

Two randomized, double blind, controlled clinical trials (studies C10-034 and 001) were the main data source for the indication. A total of 200 subjects with mild to moderate endogenous anterior uveitis participated in these studies, of which 106 were exposed to DUREZOL® ophthalmic emulsion and 94 to prednisolone acetate 1% ophthalmic suspension. Subjects were exposed to study drug for a period of 14 days followed by 14 days of tapering and an additional 14 days of follow-up. Very common adverse reactions in subjects exposed to DUREZOL® ophthalmic emulsion occurring in ≥ 10% were punctate keratitis and increased IOP. Punctate keratitis was mild to moderate and assessed as not related to study drug according to the investigators. IOP should be monitored and managed during treatment. No subject was withdrawn from the studies due to these two AEs (see Table 3).

**Table 3: Adverse Events (AEs, both related and not related combined) With Rates of 2% or More Occurring in the Study Eye of Subjects in Either Treatment Group (Safety Population – Pooled Pivotal Studies)**

| System Organ Class<br>Preferred Term | Number of Subjects Reporting AEs (% of Subjects at Risk)<br>DUREZOL®<br>QID<br>(N = 106) | <br><br>Prednisolone<br>(N = 94) |
|---|---|---|
| **Subjects reporting any AEs** | **49 (46.2%)** | **37 (39.4%)** |
| **Congenital, familial and genetic disorders** | 1 (0.9%) | 2 (2.1%) |
| Corneal dystrophy | 1 (0.9%) | 2 (2.1%) |
| **Eye disorders** | 44 (41.5%) | 33 (35.1%) |
| Punctate keratitis | 11 (10.4%) | 5 (5.3%) |
| Uveitis | 7 (6.6%) | 4 (4.3%) |
| Conjunctival hyperaemia | 6 (5.7%) | 7 (7.4%) |
| Eye irritation | 6 (5.7%) | 1 (1.1%) |
| Eye pain | 6 (5.7%) | 3 (3.2%) |
| Limbal hyperaemia | 6 (5.7%) | 5 (5.3%) |
| Vision blurred | 6 (5.7%) | 3 (3.2%) |
| Anterior chamber flare | 4 (3.8%) | 1 (1.1%) |
| Dry eye | 4 (3.8%) | 0 |
| Photophobia | 4 (3.8%) | 3 (3.2%) |
| Visual acuity reduced | 4 (3.8%) | 4 (4.3%) |
| Anterior chamber inflammation | 3 (2.8%) | 4 (4.3%) |
| Corneal oedema | 3 (2.8%) | 0 |
| Iridocyclitis | 3 (2.8%) | 2 (2.1%) |
| Iritis | 3 (2.8%) | 3 (3.2%) |
| Anterior chamber cell | 1 (0.9%) | 3 (3.2%) |
| Corneal deposits | 1 (0.9%) | 3 (3.2%) |
| Ocular hyperaemia | 1 (0.9%) | 3 (3.2%) |
| Vitreous floaters | 1 (0.9%) | 2 (2.1%) |
| Photopsia | 0 | 2 (2.1%) |
| Scleritis | 0 | 2 (2.1%) |
| **Infections and infestations** | 2 (1.9%) | 1 (1.1%) |
| **Investigations** | 11 (10.4%) | 6 (6.4%) |
| Intraocular pressure increased | 11 (10.4%) | 6 (6.4%) |
| Clinical significant IOP increase* | 12 (11.3%) | 8 (8.5%) |

AE: adverse event, N: number of subjects in the safety population.
At each level of summarization, subjects reporting more than 1 event were only counted once.
Within system organ class, preferred terms are presented by descending incidence in the difluprednate treatment group.
AEs were coded using MedDRA version 10.
*Clinical significant IOP increase was defined as an observed value ≥21 mmHg which also represent a change from baseline of at least 10 mmHg

**Less Common Clinical Trial Adverse Drug Reactions (<5%)**

*Inflammation following post-cataract surgery*

In the pivotal trials, ocular adverse events occurring in < 2% of subjects treated with DUREZOL® ophthalmic emulsion QID included two cases (1.9%) each of anterior capsule contraction, macular edema, blepharitis, lacrimation increased, trichiasis, and uveitis. In the supportive trials, the most frequently reported AEs were IOP increase and punctate keratitis.

Among all the 300 patients treated with DUREZOL® ophthalmic emulsion QID, eight subjects (2.7%) had one serious AE each: iris adhesions, maculopathy, retinal detachment were considered not related to treatment and only one case of iris adhesions was considered possibly related to DUREZOL® ophthalmic emulsion. The other four events were non-ocular and unrelated to treatment.

*Endogenous Anterior Uveitis*

Serious AEs (SAEs) were found in 3 (2.8%) subjects in the pivotal studies: necrotizing retinitis, hypertension, and chest pain (noncardiac). In the supplemental uveitis studies, SAEs were reported in 2 (2.1%) subjects: necrotizing retinitis and monoarthritis. None of the events was considered related to the study drug by the investigators.

Abnormal Hematologic Findings

Three abnormal findings were reported in three subjects: one case of reduction in platelet count reversible 8 days after completion of dosing. One case of elevated white blood cell (WBC) count; and one case of WBC count elevation that reached Grade 1 (also with a fever).

Abnormal Clinical Chemistry Findings

Clinical chemistry conducted in some of the supplemental studies revealed the following abnormal findings: one case of elevated aspartate transaminase [AST] and alanine transaminase [ALT]; one case of elevated blood glucose levels, and one case of elevated AST, ALT, and gamma glutamyl transferase [γ-GTP] levels.

**Post-Market Adverse Drug Reactions**

In over four years of post-marketing experience, over 1.5 million units of DUREZOL® ophthalmic emulsion have been sold and over 2.6 million units of DUREZOL® ophthalmic emulsion have been distributed in the United States. During that time there was no individual event that would be indicative of an overall product problem, and no issues or trends were identified that would represent a previously unknown concern. The most commonly reported adverse events include eye irritation, eye pain, headache, IOP increased, and vision blurred.

Serious AEs reported included: IOP increased , conjunctival erosion , corneal perforation foreign body sensation, cataract subcapsular, iris disorder, iritis, vision blurred, visual acuity reduced and drug ineffective, rebound effect, eye excision, and off label use.

Other AEs reported included: dizziness, ulcerative keratitis, skin depigmentation and increased heart rate.

## DRUG INTERACTIONS

### Overview

Specific interaction studies have not been conducted with DUREZOL® (difluprednate) ophthalmic emulsion.

Topical ophthalmic corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are known to slow or delay healing. Concomitant use of topical steroids and topical NSAIDs may increase the potential for healing problems (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

The preservative in DUREZOL® ophthalmic emulsion, sorbic acid, can interact with soft contact lenses. DUREZOL® ophthalmic emulsion should not be instilled while wearing contact lenses (see DOSAGE AND ADMINISTRATION, Administration).

Drug-drug, Drug-Food, Drug-Herb, Drug-Laboratory, Drug-Lifestyle interactions were not studied.

## DOSAGE AND ADMINISTRATION

### Recommended Dose and Dosage Adjustment

**Post-operative inflammation following cataract surgery**
Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period, then taper as determined by the treating physician based on the clinical response.

**Endogenous Anterior Uveitis**
Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

### Missed Dose

If a dose is missed, it should be taken as soon as possible or should be resumed at the usual dosing schedule. A double dose should not be taken.

### Administration

To prevent contamination of the dropper tip and emulsion, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Do not use DUREZOL® (difluprednate) ophthalmic emulsion if the vial is cracked or damaged in any way.

If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

DUREZOL® ophthalmic emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® ophthalmic emulsion. The preservative in DUREZOL® ophthalmic emulsion, sorbic acid, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® ophthalmic emulsion.

## OVERDOSAGE

There were no cases of overdose reported. There is no specific antidote for DUREZOL® (difluprednate) ophthalmic suspension overdose. A topical overdose is not likely to be associated with toxicity.

| |
|---|
| For management of a suspected drug overdose, contact your regional Poison Control Centre. |

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action and Pharmacodynamics

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and may delay or slow healing. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

### Pharmacokinetics

Difluprednate (DFBA, 6α,9-difluoro-11β,17,21,-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate) undergoes deacetylation *in vivo* to 6α,9-difluoroprednisolone 17-butyrate (DFB), an active metabolite of difluprednate.

Clinical pharmacokinetic studies of difluprednate after repeat ocular instillation of 2 drops of difluprednate (0.01% or 0.05%) four times per day for 7 days showed that DFB levels in blood were below the quantification limit (50 ng/mL) at all-time points for all subjects, indicating the systemic absorption of difluprednate after ocular instillation of DUREZOL® (difluprednate) ophthalmic emulsion is limited.

The binding of radiolabeled difluprednate to human serum protein has been determined to be 73% *in vitro*.

**Special Populations and Conditions**

**Pediatrics:** DUREZOL® ophthalmic emulsion was evaluated in a 3-month, multicenter, double-masked, active-controlled trial in 79 pediatric patients 28 days to 3 years of age (39 DUREZOL® ophthalmic emulsion; 40 prednisolone acetate) for the treatment of inflammation following cataract surgery. See ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions.

**Geriatrics:** No overall differences in safety or effectiveness have been observed between elderly and younger adult patients for both indications.

**Gender or Race:** Not studied for the indication of inflammation following cataract surgery.

For the treatment of endogenous (non-infectious) anterior uveitis, subgroup analyses were conducted in C-10-034 and Study 001 by gender (male and female), age (< 65 years and ≥ 65 years), race (white and non-white) and iris pigmentation (light and dark) for the primary efficacy endpoint (observed and change from baseline in AC cell grade at Day 14) based on the per protocol (PP) population with last observation carried forward (LOCF) applied.

In Studies C-10-034 and 001, no significant differences were observed between DUREZOL® ophthalmic emulsion and Prednisolone Acetate 1% Ophthalmic Suspension in any of the subgroups at the primary time point, Day 14.

**Renal Insufficiency & Hepatic Insufficiency:**
There were no specific studies in patients with renal insufficiency or with hepatic insufficiency

**Genetic Polymorphism:** No data are available.

## STORAGE AND STABILITY

Store at 15 - 25°C (59 - 77°F). Do not freeze. Protect from light. When not in use, keep the bottles in the protective carton.

## SPECIAL HANDLING INSTRUCTIONS

None.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

DUREZOL® (difluprednate) ophthalmic emulsion is a sterile, aqueous topical ophthalmic emulsion supplied in a carton containing an opaque plastic bottle with a controlled drop tip and a pink cap in the following size:

5 mL in an 8 mL bottle

Each mL contains: ACTIVE: difluprednate 0.5 mg (0.05%); INACTIVE: boric acid, castor oil, glycerin, sodium acetate, sodium EDTA, sodium hydroxide (to adjust the pH), polysorbate 80 and water for injection. The emulsion is essentially isotonic with a tonicity of 304 to 411 mOsm/kg. PRESERVATIVE: sorbic acid 0.1%.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

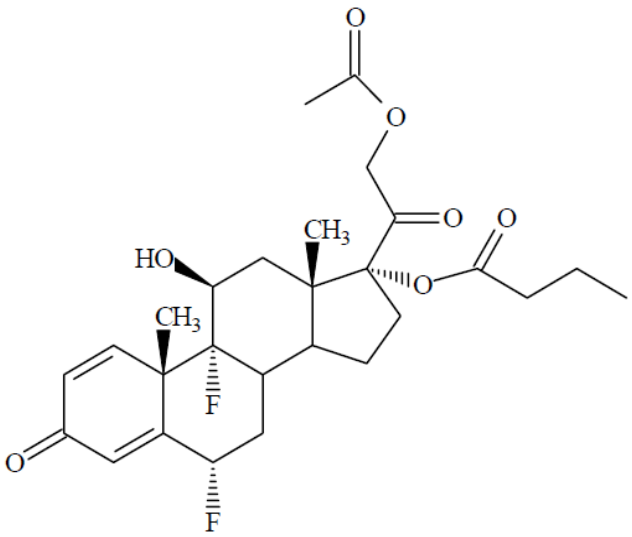
### Drug Substance

Common name: difluprednate

Chemical name: 6α,9-Difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate.

Molecular formula and molecular mass: $C_{27}H_{34}F_2O_7$ ; 508.56

Structural formula:




Physicochemical properties: Freely soluble in acetonitrile and chloroform; soluble in methanol, ethanol and dioxane; slightly soluble in ether; practically insoluble in water.

*Melting point:* Between 186°C and 196°C

## CLINICAL TRIALS

### Study demographics and trial design

A total of two pivotal (endogenous anterior) uveitis studies, and 2 pivotal post-cataract surgery studies contributed significantly to establishing the efficacy of DUREZOL® (difluprednate) ophthalmic emulsion in these two indications.

**Table 4: Pivotal efficacy and safety clinical trials**

| Study ID/ Protocol No. | Study Design–Subject Population | Treatment Topical instillation | No. Entered Each Treatment | Duration of Treatment |
|---|---|---|---|---|
| **Indication: Endogenous (noninfectious) anterior uveitis** | | | | |
| **C-10-034** | Randomized, double-masked, parallel-group, active-controlled | DUREZOL® :<br>1 drop QID<br>PF 1 drop 8 times daily<br>14 days of full dose + 14 day taper | ITT population: 110 subjects<br>Durezol: 57<br>PF: 53<br>PP population:<br>Durezol: 46<br>PF: 47 | Up to 14 days (study period), with an additional 14 days for the tapering period |
| **001** | Randomized, double-masked, parallel-group, active-controlled | DUREZOL® :<br>1 drop QID<br>PF 1 drop 8 times daily<br>14 days of full dose + 14 day taper | ITT population: 90 subjects<br>Durezol: 50<br>PF: 40<br>PP population<br>Durezol: 48<br>PF:39 | Up to 14 days (study period), with an additional 14 days for the tapering period |
| **Indication: Post-surgical ocular inflammation** | | | | |
| **002a** | Randomized, double-masked, parallel-group, placebo-controlled | DUREZOL®:<br>1 drop BID<br>1 drop QID<br>Placebo:<br>1 drop BID;<br>1 drop QID | 219 subjects<br>Durezol<br>BID: 57<br>QID: 55<br>Placebo: 107 | Up to 14 days (study period), with an additional 14-day tapering period |
| **002b** | Randomized, double-masked, parallel-group, placebo-controlled | DUREZOL® :<br>1 drop BID,<br>1 drop QID;<br>Placebo:<br>1 drop BID;<br>1 drop QID | 219 subjects<br>Durezol<br>BID: 54<br>QID: 52<br>Placebo: 113 | Up to 14 days (study period), with an additional 14-day tapering period |

BID, twice daily; QID, 4 times daily; PF, Prednisolone Acetate 1% Ophthalmic Suspension

**Post-surgical inflammation:**

Two identical pivotal randomized, double-masked, placebo-controlled studies of DUREZOL® ophthalmic emulsion and its vehicle were performed in 219 subjects with ocular inflammation following cataract surgery (anterior chamber cell count ≥11). Patients had no history of glaucoma, ocular hypertension, steroid-related IOP rise, corneal abrasion/ulceration, and had an IOP <24 mm Hg on Day 1 after surgery (studies 002a and 002b). The patients received 1 drop, either BID or QID of DUREZOL® ophthalmic emulsion, or the placebo, (starting one day after surgery), for 14 days followed by a tapering period of up to an additional 14 days.

The main efficacy parameter was the proportion of patients with anterior chamber (AC) cell count =0. The main secondary parameter was the proportion of Pain/Discomfort Free patients. As shown below, DUREZOL® ophthalmic emulsion administered QID was superior to placebo in clearing AC cells and reducing pain/discomfort starting on day 8.

**Table 5: Demographics and baseline characteristics (pooled pivotal studies 002a and 002b, ITT population)**

| Parameter | Demographics | DUREZOL® QID (N = 107) | Placebo (N = 220) |
|---|---|---|---|
| Gender (n, %) | Female | 60 (56.1%) | 121 (55.0%) |
| Age, yrs. | Mean (SD) | 68.2 (11.21) | 69.5 (10.63) |
| | Median (range) | 70.0 (24–87) | 71.0 (32–96) |
| Race (n) | White | 95 (88.8%) | 196 (89.1%) |
| | African-American | 11 (10.3%) | 14 (6.4%) |
| | Am Native or Asian | 0 | 4 (1.8%) |
| Iris Color (n) | Blue | 31 (29.0%) | 71 (32.3%) |
| | Brown | 43 (40.2%) | 83 (37.7%) |
| | Green | 10 (9.3%) | 19 (8.6%) |
| | Hazel | 18 (16.8%) | 37 (16.8%) |
| | Gray | 2 (1.9%) | 7 (3.2%) |
| | Unknown | 3 (2.8%) | 3 (1.4%) |
| Surgery | Cataract | 104 (97.2%) | 216 (98.2%) |
| | Other* | 3 (2.8%) | 4 (1.8%) |

* Other surgeries included: Kelman phacoemulsification (n=2), Extracapsular cataract extraction (n=1), Aqualase (n=1), Vitrectomy (n=5), Iridoplasty (n=1), Wound modification (n=1)

**Table 6: Overall Summary of efficacy findings**

**(Pooled pivotal studies 002a and 002b, ITT population with LOCF)**

| Parameter & approximate time | | DUREZOL® QID (N=107) | Placebo (N=220) | Difference(1), p-value |
|---|---|---|---|---|
| **AC cell =0** | | | | |
| | Day 08 | 24 (22.4%) | 17 (7.7%) | 14.7%, 0.0002 |
| | Day 15 | 44 (41.1%) | 25 (11.4%) | 29.8%, <.0001 |
| **Pain/Discomfort Free** | | | | |
| | Day 08 | 62 (57.9%) | 59 (26.8%) | 31.1%, <.0001 |
| | Day 15 | 67 (62.6%) | 76 (34.5%) | 28.1%, <.0001 |
| **AC cell =0 and Pain/Discomfort Free** | | | | |
| | Day 08 | 16 (15.0%) | 12 (5.5%) | 9.5%, 0.0040 |
| | Day 15 | 34 (31.8%) | 15 (6.8%) | 25.0%, <.0001 |

(1) Difference in percent (difluprednate - placebo, positive values favor difluprednate), p-value (chi²) is 2-sided; Significance level is 0.05).

DUREZOL® administered four times daily

AC: anterior chamber; N = number of subjects in the ITT Population;

LOCF: last observation carried forward

**Endogenous anterior uveitis:**

Studies C-10-034 and 001 were randomized, controlled, double-masked, active-controlled Phase 3 non-inferiority trials; 200 subjects with endogenous anterior uveitis were randomized, and 106 subjects received DUREZOL® ophthalmic emulsion 4 times daily. The Per Protocol population used in the efficacy analysis (non-inferiority), consisted of 180 subjects (DUREZOL® ophthalmic emulsion 94 and prednisolone 86). Patients with mild to moderate endogenous anterior uveitis were dosed with DUREZOL® ophthalmic emulsion 0.05% 4 times daily or prednisolone acetate 1% 8 times daily for 14 days. On Day 14 and for the following 2 weeks, subjects began graduated tapering of study drugs, successively halving the number of doses per day at each step. From Day 28 + additional treatment was at the investigator's discretion.

**Table 7: Demographics for Pooled Pivotal Studies (C-10-034 and 001) Intent-to-Treat**

| **Parameters** | **DUREZOL® QID (N=106)** | **Prednisolone (N=94)** |
|---|---|---|
| **Gender, n (%)** | | |
| Male | 48 (45.3) | 40 (42.6) |
| Female | 58 (54.7) | 54 (57.4) |
| **Age (Years), n(%)** | | |
| <65 | 93 (87.7) | 78 (83.0) |
| >=65 | 13 (12.3) | 16 (17.0) |
| Mean (SD) | 48.2 (15.2) | 44.4 (17.1) |
| Median | 50.0 | 45.0 |
| (Min, Max) | (11, 87) | (4, 76) |
| **Race, n (%)** | | |
| White | 66 (62.3) | 65 (69.1) |
| Black/African American | 33 (31.1) | 25 (26.6) |
| American Indian/Alaskan Native | 1 (0.9) | |
| Asian | 4 (3.8) | 1 (1.1) |
| Other | 2 (1.9) | 3 (3.2) |
| **Ethnicity, n(%)** | | |
| Hispanic or Latino | 7 (6.6) | 14 (14.9) |
| Not Hispanic or Latino | 99 (93.4) | 80 (85.1) |
| **Iris Color, n(%)** | | |
| Blue | 22 (20.8) | 16 (17.0) |
| Brown | 61 (57.5) | 57 (60.6) |
| Green | 6 (5.7) | 5 (5.3) |
| Hazel | 17 (16.0) | 14 (14.9) |
| Gray | | 1 (1.1) |
| Other | | 1 (1.1) |

The primary efficacy endpoint was the change from baseline in anterior chamber cell grade on Day 14 between DUREZOL® ophthalmic emulsion and prednisolone ophthalmic suspension 1%. Anterior chamber cell grade was determined using a 5 unit scale ranging from 0 (≤ 1 cell) to 4 (> 50 cells). The noninferiority margin used was 0.5 units, meaning that the upper limit of the two-tailed 95% confidence interval must have been less than 0.5 to establish noninferiority.

Study C10-034:

**Table 8: Change From Baseline in Anterior Chamber Cell Grade Per Protocol (LOCF) Population**

| Study Visit | DUREZOL® QID (N = 46) | Prednisolone (N = 47) | Estimate of Difference, Difluprednate Minus Prednisolone (95% CL)[a] |
|---|---|---|---|
| Baseline/Day 0 | 2.6 | 2.6 | |
| Change from Baseline | | | |
| Day 3 | -1.1 | -1.0 | -0.02 (-0.38, 0.34) |
| Day 7 | -1.8 | -1.6 | -0.18 (-0.44, 0.09) |
| Day 14 | -2.2 | -2.0 | -0.22 (-0.53, 0.09) |
| Day 21 | -2.4 | -2.1 | -0.29 (-0.57, -0.01) |
| Day 28 | -2.3 | -2.1 | -0.20 (-0.49, 0.10) |
| Day 35 | -2.3 | -2.1 | -0.21 (-0.53, 0.11) |
| Day 42 | -2.3 | -2.1 | -0.12 (-0.45, 0.22) |

CL, confidence limits; LOCF, last observation carried forward; N, number of subjects in the per protocol population.
[a] Estimate from ANCOVA with treatment and investigative site as fixed factors and baseline score as a covariate in the model.
Difluprednate = Difluprednate ophthalmic emulsion, 0.05%
Prednisolone = Prednisolone acetate ophthalmic suspension, 1%

Study 001:

**Table 9: Change From Baseline in Anterior Chamber Cell Grade Per Protocol (LOCF) Population**

| | Baseline Value and Change From Baseline in Mean AC Cell Grade | | |
|---|---|---|---|
| Study Visit | DUREZOL® QID (N = 48) | Pred Forte (N = 39) | Estimate of Difference, Difluprednate Minus Pred Forte (95% CL)[a] |
| Baseline/Day 0 | 2.5 | 2.4 | - |
| Day 3 | -0.9 | -1.0 | 0.07 (-0.24, 0.37) |
| Day 7 | -1.8 | -1.7 | -0.03 (-0.33, 0.28) |
| Day 14 | -2.1 | -1.9 | -0.07 (-0.35, 0.22) |
| Day 21 | -2.2 | -2.0 | -0.09 (-0.37, -0.19) |
| Day 28 | -2.2 | -2.1 | -0.04 (-0.32, 0.24) |
| Day 35 | -2.2 | -2.0 | -0.11 (-0.39, 0.18) |
| Day 42 | -2.2 | -1.9 | -0.20 (-0.52, 0.11) |

AC, anterior chamber; CL, confidence limits; LOCF, last observation carried forward; N, number of subjects in the per protocol population.
[a] Estimate of the difference between difluprednate and Pred Forte and t-test on difference adjusted least means square on change from baseline from ANCOVA with treatment and investigative site as fixed factors and baseline score as a covariate in the model.
Source: Table 14.2.1.1.1 and Appendix 16.2.6.1

Sensitivity analyses on the primary efficacy endpoint were performed based on three different approaches for handling missing data and were consistent with the original results: Available case analysis, Likelihood-based analysis, and Multiple imputation analysis.

The proportion of subjects anterior chamber (AC) clearing cells (cell count =0) at Day 14 was 52% of patients in both studies. At Day 42 clearing rates were 62% and 70% of patients in Study 001 and C10-034, respectively.

Relapse was defined as an AC cell count ≤5 at Day 14 that increased to an AC cell count >10 at subsequent visits. Overall, few subjects (7) relapsed in these studies (4 in the prednisolone group and 3 in the DUREZOL® ophthalmic emulsion group). Relapses in the DUREZOL® ophthalmic emulsion treatment group occurred at Day 21 and Day 42, and in the prednisolone group at Day 35 and 42, reaching similar cell grades (grades 2 -3) as in baseline values.

## DETAILED PHARMACOLOGY

### Animal Pharmacodynamics

*In Vivo Pharmacodynamics*

The inhibitory effect of difluprednate by topical instillation on experimental melanin-protein-induced uveitis (EMIU) in rats was examined, and the difference of effect between difluprednate 0.05% and betamethasone 0.1%, was compared. Difluprednate exerted its anti-inflammatory effect in a concentration-dependent manner, and difluprednate 0.05% and difluprednate 0.01%, had a greater inhibiting effect on inflammation compared with saline ($P<0.01$). The peak values showed that betamethasone 0.1%, suppressed inflammation better than saline ($P<0.05$), the efficacy of difluprednate 0.01%, was comparable with betamethasone 0.1%, and difluprednate 0.05% significantly inhibited uveitis better than betamethasone 0.1% ($P<0.01$).

The inhibitory effect of difluprednate ophthalmic emulsions on experimental uveitis in rabbits after instillation four times a day was examined, and the difference of effect between difluprednate 0.05% and betamethasone 0.1%, was compared. Betamethasone 0.1%, had a significantly greater inhibitory effect compared with saline, difluprednate 0.05% had a greater inhibitory effect than betamethasone ($P<0.01$). These results indicate that the optimum concentration of difluprednate 0.05% for treating rabbit experimental uveitis was 0.05%.

The inhibitory effect of difluprednate ophthalmic emulsions on rabbit paracentesis model was examined, and the difference between the effect of inflammation between difluprednate 0.05% and betamethasone 0.1%, was evaluated by comparing their respective AUCs. The saline group had the highest flare value, and the difluprednate flare values decreased as difluprednate concentrations increased. Compared with saline, the low-concentration of difluprednate, 0.002%, had no significant effect on flare value. However, at higher concentrations of 0.01% and 0.05%, difluprednate significantly reduced the flare values ($P$<0.01 and $P$<0.001, respectively). Furthermore, difluprednate 0.05% seemed to be more effective in reducing inflammation than difluprednate 0.01%. The anti-inflammatory response of difluprednate showed a dose response. The AUCs between betamethasone 0.1%, and difluprednate 0.05%, were not significantly different. This result shows that difluprednate 0.05%, is as effective in suppressing inflammation as betamethasone 0.1%.

Difluprednate 0.05% suppressed uveitis in a dose-dependant manner, and that difluprednate 0.05% suppressed uveitis better than betamethasone 0.1% in all 3 animal uveitis models. Difluprednate in concentrations greater than or equal to 0.01% suppressed post-surgical inflammation, and difluprednate 0.05% exerted the strongest effect (an effect comparable to that of betamethasone 0.1%).

Glucocorticoid (GC) receptor binding activity of ocular tissues and plasma after instillation of difluprednate ophthalmic emulsions in the rabbit was measured in the aqueous humor and iris/ciliary body; the dose-dependency of difluprednate receptor binding was measured; and the GC binding activities of difluprednate and betamethasone were compared. The GC binding inhibitory rate of difluprednate in the aqueous humor was dose dependent, and difluprednate 0.05%, showed the highest GC binding activity at all-time points ($P$<0.05). The time to maximum GC binding activity ($T_{max}$) was 30 to 60 minutes after instillation for each difluprednate dose, indicating a quick transfer of difluprednate into the anterior chamber. The difluprednate binding activity was constant up 120 minutes after instillation. The Tmax for betamethasone 0.1% was 120 minutes. The binding activity of difluprednate 0.05% was significantly higher than that of the betamethasone 0.1% treated groups at 30 and 60 minutes after instillation ($P$<0.05).

The GC receptor binding activity in the iris/ciliary body for the difluprednate 0.05% treated group was significantly higher than the difluprednate 0.002% and 0.01% treated groups at all-time points up to 120 minutes after instillation ($P$< 0.05). At 240 minutes, the difference in GC receptor binding was minimal for all difluprednate concentrations. The $T_{max}$ for difluprednate 0.05% and betamethasone 0.1%, in the iris/ciliary body was 30 and 120 minutes respectively. Although betamethasone 0.1%, had similar receptor binding activity as the difluprednate 0.002% and 0.01% groups, the GC receptor inhibitory activity for betamethasone 0.1%, was significantly lower than difluprednate 0.05% for the first 240 minutes after instillation ($P$<0.05).

The potential effect of difluprednate on body weight in EMIU rats was examined, and the difference of effect between difluprednate 0.05% and betamethasone 0.1% was compared, body weights were measured before antigen administration, then once a week thereafter.

Although difluprednate 0.05% suppressed body weight gain in this study; it was not significantly different from the saline group. Compared with saline, betamethasone 0.1%, significantly suppressed body weight gain of rats ($P<0.01$). Furthermore, betamethasone 0.1% had a stronger effect on suppressing body weight compared with difluprednate 0.05%.

The effect of difluprednate on body weight in bovine serum albumin-induced uveitis (BIU) rabbits was examined, and the difference of effect between difluprednate 0.05% and betamethasone 0.1% was compared, body weights were recorded on Days 0 (day prior to antigen injection), 7, 14, and 20. In the BIU rabbits, difluprednate 0.05% and betamethasone 0.1% similarly suppressed weight gain. These results suggest that based on relative potency of the 2 drugs, difluprednate may have less adverse impacts than betamethasone for weight gain. No abnormalities were observed in the general condition of the rabbits for either treatment.

Difluprednate exerted no effects on spontaneous motor activity, rotor rod test, pentetrazole-induced convulsions, and maximum electric shock–induced convulsions in mice; body temperature in rats; or spontaneous brain waves in rabbits. Although difluprednate prolonged the thiopental-induced sleeping time and appeared to exert a protective effect on mortality due to methamphetamine toxicity after subcutaneous administration of difluprednate at a dose of 100.0 mg/kg, none of these effects were found at doses of 10. 0 to 30.0 mg/kg. In comparison with the anti-inflammatory effects seen in nonclinical studies (at doses of 10.0 to 100.0 μg/kg by subcutaneous administration), effects of difluprednate on the central nervous system (CNS) were observed at 1000 to 10,000- fold higher doses.

Difluprednate was considered to exert no effects on heart rate, blood pressure, respiration, or the electrocardiogram in dogs; no effects on the isolated atrium of guinea pigs; and no effects on norepinephrine-induced vasoconstriction in rats.

**Table 10: Summary List of Safety Pharmacological Test Results of Difluprednate**

| Examination Items | | Species, Sex | No. of Animals | Route | Dose (mg/kg) | Results |
|---|---|---|---|---|---|---|
| Central Nervous System | General symptoms | ICR mice, M | 5 | SC | 100 | No effects other than a slight diuretic effect. |
| | Spontaneous motor activity (squirrel cage) | ICR mice, M | 10 | SC | 100 | No effects. |
| | Rotor rod test | ICR mice, M | 8 | SC | 30, 100 | Positive in 1/8 cases at 100 mg/kg.<br>No effects at 30 mg/kg. |
| | Sleep enhancement | ICR mice, M | 10 | SC | 1, 10, 100 | Prolongation of sleeping time at 100 mg/kg. No effects at 1 mg/kg and 10 mg/kg. |
| | Pentetrazole-induced convulsions | ICR mice, M | 8 | SC | 30, 100 | No effects. |
| | Electric shock-induced convulsions | ICR mice, M | 8 | SC | 30, 100 | No effects. |
| | Methamphetamine toxicity | ICR mice, M | 10 | SC | 30, 100 | Significant decrease in mortality at 100 mg/kg. No effects at 30 mg/kg. |
| | Body temperature | Rats, M | 8 | SC | 30, 100 | No effects. |
| | Analgesic effects | ddy mice, M | 10 | SC | 30, 100 | No effects. |
| | Spontaneous brain wave | Rabbits, M | 3 | IV | 3 | No effects. |
| Somatic Nervous System | Muscle relaxation | ICR mice, M | 8 | SC | 30, 100 | No effects. |
| | Neuromuscular specimen | Rats, M | 3* | In vitro | $10^{-3}$ g/mL | No effects. |
| | Spinal reflex | Rats, M | 10 | IV | 3 | No effects. |
| | Surface anesthesia (corneal reflex) | Guinea pigs, M | 3 | Topical | 1, 10 mg/site | No effects. |
| Autonomic Nervous System | Isolated trachea | Guinea pigs, M | 2* | In vitro | $10^{-5}$, $10^{-4}$, $10^{-3}$ g/mL | No effects. |
| | Charcoal transit | ddy mice, M | 10 | SC | 100 | No effects. |
| | Gastric secretion | Rats, M | 8 | SC | 30, 100 | No effects. |
| | Isolated ileum (spontaneous motility) | Rabbits, M | 4* | In vitro | $10^{-3}$ g/mL | No effects. |
| | Isolated ileum | Guinea pigs, M | 4* | In vitro | $10^{-5}$, $10^{-4}$, $10^{-3}$ g/mL | Weak suppression of Ach and His-induced contraction at $10^{-4}$ and $10^{-3}$g/mL.Weak suppression of Ba-induced contraction at $10^{-3}$g/mL..<br>No effects at $10^{-5}$g/mL. |

| Examination Items | | Species, Sex | No. of Animals | Route | Dose (mg/kg) | Results |
|---|---|---|---|---|---|---|
| Cardiovascular System | Isolated atrium | Guinea pigs, M | 3* | In vitro | $10^{-3}$ g/mL | No changes in heart rate and cardiac contractile force. |
| | Blood vessel | Rats, M | 3* | In vitro | $10^{-6}$, $10^{-5}$, $10^{-4}$, g/mL | No effects. |
| | Respiration, blood pressure, electrocardiogram | Dogs, M/F | 3 | IV | 3 | Slight changes in heart rate, blood pressure, respiration, and electrocardiogram, comparable to those caused by administration of 60% DMF. |
| Urinary/Reproductive Organ System | Diuretic effect | Rats, M | 7 | SC | 100 | Urine volume was increased, but there were no changes in $Na^+$ and $K^+$ concentrations. |
| | Isolated uterus (pregnant, non-pregnant) | Rats, M | 3–4* | In vitro | $10^{-5}$, $10^{-4}$, $10^{-3}$ g/mL | No effects on both the pregnant and non- pregnant uterus at $10^{-5}$g/mL, but mild suppression at $10^{-4}$ and $10^{-3}$g/mL.. |
| Others | Blood coagulation system | Rats, M | 5 | SC | 10, 100 | No effects on the whole blood coagulation time. |
| | Drug-metabolizing enzymes | Rats, M | 8 | SC | 0.01, 0.1, and 1, 7-day repeated administration | No induction but mild inhibition of drug-metabolizing enzymes. |
| | PFC (plaque-forming cell) | ICR mice, M | 5 | SC | 0.0001–100 | Suppression of PFC formation<br>ED50: 0.24 mg/kg. |
| Metabolites | Spontaneous motor activity (squirrel cage) | ddy mice, M | 5 | SC | 100 | Any of DFBA, DFB, DF, HFB, HF, DF20H, and HF20H exerted no effects. |
| | Charcoal transit | ddy mice, M | 10 | SC | 100 | Any of DFBA, DFB, DF, HFB, HF, DF20H, and HF20H exerted no effects. |
| Related Substances | Spontaneous motor activity (squirrel cage) | ddy mice, M | 5 | SC | 100 | Any of DFBA, CFBA, DFB, and DF exerted no effects. |
| | Charcoal transit | ddy mice, M | 10 | SC | 100 | Any of DFBA, CFBA, DFB, and DF exerted no effects. |

* Number of specimens; DFB, DF, HFB, HF, DF20H, and HF20H=metabolites of difluprednate, DMF= dimethylformamide, IV=intravenous, PFC= plaque-forming cell, SC=subcutaneous.

## Human Pharmacokinetics

*In Vivo* Studies

In the Phase 1 repeated-dosing study conducted with difluprednate 0.05% on healthy male Japanese subjects, the blood concentration of DFB (a rapidly-created active metabolite of difluprednate) was below the quantification limit (50 ng/mL) at all-time points for all subjects. Because the systemic levels of difluprednate or its active metabolite, DFB, are low to undetectable after 7 days of ocular instillation of difluprednate 0.05%, the systemic effects of ocular instillation of difluprednate 0.05% are likely to be minimal or nonexistent.

**Animal Pharmacokinetics**

*Single Dose in Rabbits:*

The purity of $^{3}$H-difluprednate and pharmacokinetics of difluprednate was evaluated after a single instillation of 3H-difluprednate ophthalmic emulsion into the rabbit eye. One 50 μL dose (25 μg/50 μL) of 3H-difluprednate emulsion was instilled into the right eye of 31 male Dutch rabbits; 28 of these rabbits were split into 7 groups of 4 rabbits each. 3H-dfluprednate levels were measured in the blood, plasma, aqueous humor, accessory lacrimal gland, extraocular muscle, conjunctiva, lacrimal gland, cornea, iris or ciliary body, lens, vitreous body, anterior retinal choroid, posterior retinal choroids, and sclera at the time points after instillation.

Pharmacokinetic parameters such as maximum radioactivity levels ($C_{max}$), time to reach that level ($T_{max}$), and elimination half-life ($T_{1/2}$) are summarized in Table 11.

**Table 11: Pharmacokinetic Parameters of Radioactivity in Ocular Tissues After Single Instillation of 3H-Difluprednate to the Right Eye of Male Dutch Rabbits (Dose: 25 µg/50 µL per Eye)**

| Tissue | $C_{max}$ | $T_{max}$ (h) | AUC 0-finite | SD (AUC 0-finite) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| Plasma (dry) | 3 | 0.5 | 28 | 0 | 1.9 (1–4) |
| Plasma (wet) | 3 | 0.5 | 175 | 1 | 4.9 (1–8) |
| Blood | 3 | 1 | 11 | 0 | 1.9 (1–4) |
| Aqueous humor | 144 | 0.5 | 431 | 18 | 1.5 (1–8*) |
| Conjunctiva | 330 | 0.5 | 1146 | 187 | 0.5 (0.5–2)<br>48.5 (4–168*) |
| Extraocular muscle | 17 | 0.5 | 45 | 4 | 2.6 (0.5–8*) |
| Cornea | 2081 | 0.5 | 4278 | 278 | 1.1 (0.5–2)<br>5.8 (4–24*) |
| Iris or ciliary body | 926 | 0.5 | 2044 | 129 | 0.9 (0.5–4)<br>49.0 (8–168*) |
| Lens | 15 | 0.5 | 88 | 14 | 0.9 (0.5–2)<br>14.9 (4–24*) |
| Vitreous body | 1 | 0.5 | NC | NC | NC |
| Anterior retinal choroid | 359 | 1 | 897 | 88 | 4.4 (1–24*) |
| Posterior retinal choroid | 59 | 1 | 160 | 21 | 6.1 (1–24*) |
| Sclera | 222 | 0.5 | 383 | 32 | 3.3 (0.5–24*) |
| Lacrimal gland | 11 | 0.5 | 37 | 2 | 3.3 (0.5–8*) |
| Sublacrimal gland | 7 | 0.5 | 24 | 0 | 2.5 (1–8*) |

Figures in parentheses represent the time period of calculation in hours
*Finite. NC=Not calculated; SD=Standard deviation
AUC 0-finite: ng eq h/g or mL; Cmax: ng eq/g or mL

*Repeated Dose in Rabbits:*

The pharmacokinetics of repeated instillations of difluprednate was evaluated after multiple doses of $^{3}$H-difluprednate ophthalmic emulsion into the rabbit eye. Twenty-eight male Dutch rabbits were split into 7 groups of 4 rabbits each, and 50 µL (25 µg/50 µL) of $^{3}$H-difluprednate was instilled into the right eye of each rabbit QID, for 3 days (12 doses) or 7 days (28 doses). Pharmacokinetic parameters such as $C_{max}$, $T_{max}$, and $T_{1/2}$ were calculated and are summarized in Table 12 and Table 13.

**Table 12: Pharmacokinetic Parameters of Radioactivity in Ocular Tissues After Repeated Instillations of 3H Difluprednate to the Right Eye of Male Dutch Rabbits (Cumulative Dose: 100 µg/200 µL per Eye per Day)**

| Tissue | $C_{max}$ | $T_{max}$ (h) | AUC 0-finite | SD (AUC 0-finite) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| Plasma (dry) | 10 | 0.5 | 745 | 10 | 79.1 (0.5–168*) |
| Plasma (wet) | 21 | 0.5 | 3577 | 92 | 161.7 (0.5–672*) |
| Blood | 10 | 0.5 | 718 | 41 | 47.8 (2–24)<br>172.4 (8–168*) |
| Aqueous humor | 217 | 0.5 | 1019 | 43 | 3.5 (0.5–24*) |
| Conjunctiva | 414 | 0.5 | 18808 | 3183 | 12.2 (0.5–24)<br>188.5 (24–672*) |
| Extraocular muscle | 44 | 2.0 | 2438 | 470 | 207.8 (8–672*) |
| Cornea | 2781 | 0.5 | 35994 | 5282 | 3.5 (0.5–8)<br>135.7 (24–672*) |
| Iris or ciliary body | 1063 | 0.5 | 23150 | 2742 | 6.3 (0.5–24)<br>230.6 (24–672*) |
| Lens | 51 | 8.0 | 2706 | 131 | 48.9 (8–168*) |
| Vitreous body | 1 | 0.5 | NC | NC | NC |
| Anterior retinal choroid | 339 | 0.5 | 9770 | 769 | 8.0 (0.5–24)<br>230.3 (24–672*) |
| Posterior retinal choroid | 35 | 0.5 | 800 | 31 | 8.0 (0.5–24) |
| Sclera | 198 | 0.5 | 4006 | 196 | 6.5 (0.5–24)<br>423.3 (24–672*) |
| Lacrimal gland | 14 | 8.0 | 743 | 108 | 104.9 (8–168*) |
| Sublacrimal gland | 18 | 0.5 | 788 | 45 | 12.3 (0.5–24) |

Figures in parentheses represent the time period of calculation in hours
*Finite. NC=Not calculated; SD=Standard deviation
AUC 0-finite: ng eq h/g or mL; Cmax: ng eq/g or mL

**Table 13: Radioactivity Levels in Ocular Tissues 24 h After Final Instillation of 3H Difluprednate to the Right Eye of Male Dutch Rabbits (Dose: 25 µg/50 µL per Eye per Unit Time)**

| Radioactivity Level (ng eq of difluprednate/g or mL) | | | |
|---|---|---|---|
| **Tissue** | **One Time*** | **12 Doses QID** | **28 Doses QID** |
| Plasma (dry) | 1 ± 1 | 3 ± 1 | 6 ± 1 |
| Plasma (wet) | 1 ± 1 | 9 ± 2 | 14 ± 2 |
| Blood | 0* | 3 ± 1 | 5 ± 1 |
| Aqueous humor | 0 ± 1 | 1 ± 1 | 2 ± 1 |
| Conjunctiva | 8 ± 5 | 46 ± 17 | 82 ± 38 |
| Extraocular muscle | 0 ± 0 | 6 ± 3 | 7 ± 4 |
| Cornea | 12 ± 7 | 74 ± 40 | 148 ± 91 |
| Iris or ciliary body | 3 ± 2 | 36 ± 12 | 55 ± 1 |
| Lens | 2 ± 1 | 15 ± 6 | 21 ± 2 |
| Vitreous body | 0 ± 0 | 0* | 0* |
| Anterior retinal choroid | 5 ± 5 | 21 ± 7 | 34 ± 12 |
| Posterior retinal choroid | 2 ± 3 | 4 ± 3 | 4 ± 1 |
| Sclera | 1 ± 1 | 7 ± 3 | 10 ± 3 |
| Lacrimal gland | 0 ± 1 | 2 ± 1 | 4 ± 2 |
| Sublacrimal gland | 0 ± 1 | 6 ± 2 | 4 ± 1 |

*Data from 24 hours in the single-dose experiment (Study D2005A0305). †Not detected. Data are expressed as the mean values ± SD of 4 animals
QID: 4 times a day

*Urinary and Fecal Excretion:*

In the single-dose study in rabbits (one 50-µL (25 µg/50 µL) dose of $^{3}$H-difluprednate was instilled into the right eye of 31 male Dutch rabbits; 28 of these rabbits were split into 7 groups of 4 rabbits each (Groups I to VII). In Group VII rabbits, samples of urine and feces were collected and analyzed for radioactivity at the end of the following time periods post-instillation: 24, 48, 72, and 168 hours. Table 14 summarizes these findings.

**Table 14: Cumulative Excretion of Radioactivity in Urine and Feces After Single Instillation of 3H Difluprednate to the Right Eye of Male Dutch Rabbits (Dose: 25 µg/50 µL per Eye)**

| Excretion of Radioactivity (% of dose) | | | |
|---|---|---|---|
| **Time (h) Post-instillation** | **Urine** | **Feces** | **Total** |
| 0 - 24 | 30.0 ± 5.7 | 48.5 ± 5.7 | 78.5 ± 3.9 |
| 48 | 34.6 ± 5.4 | 56.7 ± 7.3 | 91.2 ± 2.4 |
| 72 | 35.8 ± 5.4 | 59.8 ± 8.0 | 95.6 ± 2.8 |
| 168 | 37.1 ± 5.4 | 62.4 ± 8.5 | 99.5 ± 3.6 |
| Cage washing (168) | 0 | | |

Data are expressed as mean values ± SD of 4 animals

When difluprednate 0.05% is instilled into the eye, the active molecule difluprednate is quickly metabolized into several major metabolites: DFB, DF (which is the breakdown product of DFB), and DF21C. DFB was the most prevalent metabolite.

Single-dose and multiple-dose studies of difluprednate in rabbits demonstrate that difluprednate is rapidly metabolized and distributed to the main ocular target tissues that are affected by inflammation (iris, ciliary body, choroids, and aqueous humor in the anterior chamber), difluprednate does not accumulate in the blood, and difluprednate seems to have a low affinity for melanin, which indicates that difluprednate should work effectively in patients regardless of their race and eye color (i.e., differing levels of melanin in the eye, brown eyes having higher levels of melanin than blue eyes). Single-dose studies also showed 99.5% of difluprednate and its metabolites were cumulatively excreted via the feces and urine, and after repeated doses, difluprednate levels increased without affecting the $C_{max}$, with clearance from most ocular tissues within 168 hours.

## MICROBIOLOGY

Not Applicable

## TOXICOLOGY

*Single-Dose Toxicity*

Not applicable.

*Repeated-Dose Toxicity*

The local and systemic effects of difluprednate 0.05% ophthalmic emulsion were evaluated in 4-week repeated dose topical ocular toxicity studies in rabbits and dogs. Macroscopic, intraocular pressure, and fluorescein tests revealed no abnormalities, and electroretinogram and fundus examinations showed that difluprednate had no adverse effects on the retina. In rabbits and dogs, small physiologic changes in relative and absolute organ weights, blood chemistry values, and histopathologic parameters were observed in the difluprednate treated groups. These changes are typically associated with glucocorticoid (GC) use. The results indicate that 0.05% difluprednate emulsion was not toxic and was well tolerated.

The no observed effect level (NOEL; the highest tested dose reported to have no effects) and the long-term local and systemic toxicity of difluprednate were evaluated after 6 months of subcutaneous administration in rats and of percutaneous administration in dogs.

In the first study 272 rats were split into 4 sets of 68 and then subdivided each group into 3 groups: Group I, 3 months; Group II, 6 months; and Group III, 6 months (followed by a 2-month drug withdrawal period to evaluate recovery from toxicity). Suppression of body weight gain was observed in males and females at 10.0 µg/kg per day, and food consumption increased after drug withdrawal. Increases in red blood cell count, hemoglobin, and hematocrit, and lowering of myeloid/erythroid rate owing to proliferation of erythroblasts were also observed at this dose in male rats, suggesting enhanced hematopoiesis. In addition, shortening of activated partial thromboplastin time occurred in females and males at the 10.0 µg/kg per day dose. These changes reversed after drug withdrawal.

The NOEL of difluprednate when subcutaneously administered in rats for up to 6 months was 1.0 μg/kg per day. Changes observed at 10.0 μg/kg per day were those typically associated with GC use. Long-term administration of difluprednate caused no serious toxicity in any vital organ (thymus, lung, spleen, brain, liver, kidney, heart, testes) and no deaths.

In a second study, 40 beagles (20 males, 20 females) were divided into 4 groups. The following 4 treatments were percutaneously applied once daily for 6 months: difluprednate at 125.0 (n = 12), 12.5 (n = 8), or 1.25 μg/kg per day (n = 8) or the drug's base (control; n=12). A 2-month drug withdrawal period was run on 4 dogs from the control group and 4 dogs from the 125.0 μg/kg dose group.

At the application site, thinning of the skin was accompanied by scales, redness, and suppressed hair growth. Atrophy of the epidermis and cutaneous appendage and decreased subcutaneous adipose tissue were observed on histologic examination. These changes reversed after drug withdrawal.

At 125.0 μg/kg per day (equivalent to 15.0 g of ointment/60.0 kg person per day or 7.5 mg of difluprednate/60 kg person per day), the following findings were observed: atrophy of lymphatic tissues (thymus and adrenal glands); increases in neutrophils, hepatic glycogen, water intake, urine volume, and sodium (Na); decreases in lymphocytes, eosinophils, and potassium (K); slight renal disorder; elevation of alkaline phosphatase and γ-glutamyl transpeptidase; thinning of the abdominal skin and bone (sternum); and delayed sexual maturation. No deaths or serious symptoms occurred, and all changes were reversible once treatments ended. These various systemic effects were deemed attributable to activation of the GC receptors, a pharmacologic effect, and not considered to be effects caused directly by difluprednate. At 12.5 μg/kg per day, slight changes in the thymus, adrenal cortex, and abdominal epidermis were found in both males and females, but the degree of change was milder than for the changes exhibited at the higher dose. Therefore, 12.5 μg/kg per day of difluprednate showed some mild effects attributed to GC use. At 1.25 μg/kg per day, no changes attributable to difluprednate were observed, and this dose was considered to be an accurate NOEL.

The NOEL of difluprednate when percutaneously administered in dogs for 6 months was 1.25 μg/kg per day; the changes observed at 125.0 μg/kg per day were attributed to GC activation effects; and the clinical, pathologic, and histologic effects reflect the excessive physiologic inhibitory activity associated with GC use. Long-term administration of difluprednate caused no serious toxicity in any vital organ (thymus, lung, spleen, brain, liver, kidney, heart, testes, ovaries, uterus) and no deaths.

In addition to having the same changes observed with difluprednate 25.0 μg/kg per day, difluprednate 125.0 μg/kg per day also was associated with an increase in water intake, decreases in lymphocyte and eosinophil ratios, increases in γ-glutamyl transpeptidase and alkaline phosphatase, decreases in creatinine and K, hypertrophy of hepatocytes, and an increase in periodic acid-Schiff–positive substances. No serious symptoms or deaths occurred. Decreases in lymphocyte and eosinophil ratios and atrophy of the lymphatic organs and adrenal gland were also noted with betamethasone 125.0 μg/kg per day.

There were no gender differences in the degree of difluprednate toxicity seen, and all changes in the difluprednate-treated groups were considered to be due to the pharmacologic actions of GCs. In addition, when comparing the effects of difluprednate with those of betamethasone, although difluprednate exerted slightly stronger effects on a dose basis, it was considered that the findings were similar for both drugs and that difluprednate exerted no specific effects.

**Genotoxicity**

Difluprednate was not genotoxic in vitro in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). Difluprednate, DF17C, DF21B, and DFB did not show chromosomal aberration–inducing ability under the conditions of their respective studies.

An *in vivo* micronucleus test of difluprednate in mice was also negative, which found no increase in the number of micronuclear erythrocytes occurring under the conditions of the study, corroborating that difluprednate had no chromosomal aberration-inducing ability.

**Reproductive Toxicity**

*Fertility and Embryonic Development*

The effect of subcutaneous administration of difluprednate during the reproductive and early embryonic development period in rats was examined (Fertility and Early Embryonic Development). No effects on the reproductive potential and embryonic development were noted in the rats at 0.1 μg/kg, but at 10.0 μg/kg suppression of body weight gain, a decrease in food intake, and a decrease in thymus weight were noted in both male and female rats before mating; these changes were accompanied by a decrease in embryonic body weights and a delay in embryonic ossification. There were no observed abnormalities in the estrous cycle or copulation and fertility rates, and there were no differences in the number of corpora lutea, weight of the placenta, number of implantations, and number of dead embryos (zero in all groups) between the 3 treatment groups and the control group. Also, no embryonic abnormalities in the viscera, bones, or general appearance occurred as a result of difluprednate exposure.

*Embryo-Fetal Development*

The effect of difluprednate on the embryo and fetus during the organogenic developmental period in rats, with observations of the effect on maternal functions such as delivery, lactation, and nursing, was studied (Embryo-Fetal Development in Rats). No effects on the embryos and fetuses that could be attributed to difluprednate were observed at the 0.1- and 1.0-μg/kg doses. At 10.0 μg/kg there were decreases in placental weight. At 100 μg/kg decreases in the weight of the fetus and delays in fetal ossification were noted. There were no differences in the number of implantations and dead fetuses in any of the treatment groups as compared with the control group. Additionally, no fetal abnormalities in the viscera, bones, or general appearance occurred as a result of difluprednate exposure. No effects on dam rats attributed to difluprednate were observed at doses of 0.1, 1.0, and 10.0 μg/kg. At 100.0 μg/kg suppression of body weight gain and decreases in food intake and thymus weights were observed in the dams. There were also no observed effects on pup delivery, lactation, nursing, or postnatal development, which included neonatal morphologic growth and differentiation, various kinds of behavioral development, and reproductive potential.

The toxic effects of difluprednate on adult female rabbits and their embryos during the organogenic developmental period were studied (Embryo-Fetal Development in Rabbits). In the difluprednate 10.0 μg/kg group, 1 abortion was attributed to difluprednate. Body weight and food intake were observed during the late stage of gestation. Abnormal clinical signs and necropsy findings were not traceable to difluprednate use. Difluprednate 10.0 μg/kg exhibited fetolethal, fetal growth inhibitory, and teratogenic activity. Cleft palate, hypogenesis of the first digit of the forelegs, cerebral hernia, and club hand are anomalies previously reported to occur with the use of GCs. The NOEL of difluprednate in this study was 1.0 μg/kg, and 10.0 μg/kg was considered teratogenic.

**Studies in Juvenile Animals**

The effect of difluprednate on the morphology, functional development, and reproductive performance of neonates was studied (Perinatal and Lactation Periods in Rats).

Nursing period (Days 0 to 21 after birth): Survival rates in all difluprednate groups up to Day 21 after birth were not significantly different from the survival rate in the control group, and there were no significant differences in neonate body weight during the nursing and weaning periods between the difluprednate groups and the control group. In regard to organ weights, both male and females at 10 weeks after birth, there were no changes in absolute weights, and only males in the difluprednate 0.1 and 1.0 μg/kg groups show a non-dose-relationship increase in testicular weight.

Differentiation, emotional, and reproductive effects on juveniles: No abnormalities were observed at the times of differentiation (ie, appearance of hair and opening of eyelids). At 4 weeks of age emotional tests of males showed a decrease in rearing behavior in the difluprednate 1.0 μg/kg group, but no correlation with the drug was noted; in the water multiple T-maze test at 5 weeks of age, males and females showed no significant differences in the learning curve in association with the accumulation of trials when compared with the control group. Vision, auditory, sensation, and muscle strength tests at 3 months of age revealed no abnormalities in the difluprednate-treated or control groups. There were no significant differences between the difluprednate and control groups in development and differentiation times for testicular descent and vaginal opening or in their respective copulation and pregnancy indexes.

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## PART III: CONSUMER INFORMATION

**PrDUREZOL®**
Difluprednate Ophthalmic Emulsion
0.05% w/v

**This leaflet is part III of a three-part "Product Monograph" published when DUREZOL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DUREZOL®. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
DUREZOL® (difluprednate) ophthalmic emulsion is used to treat:

- inflammation and pain associated with cataract surgery
- -endogenous anterior uveitis (inflammation of the uvea i.e. the middle part of the eye)

**What it does:**
DUREZOL® ophthalmic emulsion is believed to stimulate the production of certain proteins that help prevent the production of other substances that are part of the inflammatory process (e.g. prostaglandins, leukotrienes). This helps to reduce the pain and inflammation of cataract surgery and uveitis.

**When it should not be used:**
DUREZOL® ophthalmic emulsion should not be used if you:

- are allergic to difluprednate or any ingredients contained in DUREZOL® ophthalmic emulsion (see What the important nonmedicinal ingredients are)
- are allergic to other corticosteroids
- have eye diseases caused by viruses (such as herpes simplex, vaccinia, and varicella) or caused by bacteria or a fungus
- think you have any other eye infection

**What the medicinal ingredient is:**
Difluprednate, 0.05% w/v.

**What the important nonmedicinal ingredients are:**
INACTIVE: boric acid, castor oil, glycerin, sodium acetate, sodium EDTA, sodium hydroxide (to adjust the pH to 5.2 to 5.8), polysorbate 80 and water for injection.
PRESERVATIVE: sorbic acid 0.1%.

**What dosage forms it comes in:**
DUREZOL® ophthalmic emulsion is a sterile preserved ophthalmic emulsion for topical ophthalmic use only.

## WARNINGS AND PRECAUTIONS

**BEFORE you use DUREZOL®** ophthalmic emulsion, talk to your doctor or pharmacist**:**

- if you have or have ever had glaucoma (increased pressure in the eye that can lead to gradual loss of vision). DUREZOL® ophthalmic emulsion may increase the risk of developing glaucoma when it is used for a long period of time. If you use DUREZOL® for 7 days of longer, your doctor will probably monitor the pressure in your eyes.
- if you have or have ever had herpes simplex virus (a virus that causes sores on the face, lips, genitals, and rectum and can also cause eye infections.)
- if you currently have an any type of eye infection. Your doctor will probably tell you not to use DUREZOL® ophthalmic emulsion.
- if you have diabetes. You may be at a higher risk of developing glaucoma or cataracts (clouding of the lens) if DUREZOL® is used for long periods of time.
- if you are allergic to difluprednate, other steroid medications, any other medications or any of the ingredients in DUREZOL® ophthalmic emulsion.
- if you are taking any other prescription and nonprescription medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), vitamins, nutritional supplements, and herbal products. Your doctor may need to change the doses of your medications or monitor you carefully for side effects.
- if you are pregnant, plan to become pregnant, are breast-feeding, or planning to breastfeed. If you become pregnant while using DUREZOL® ophthalmic emulsion, call your doctor.
- if you are using another eye drop medication. Use the eye medications at least 10 minutes apart.

**While taking DUREZOL® ophthalmic emulsions**
Tell your doctor if your symptoms do not improve after 2 days of treatment with DUREZOL® ophthalmic emulsion. Do not stop using DUREZOL® ophthalmic emulsion suddenly without first talking to your doctor.

**Slowed healing after surgery**
DUREZOL® ophthalmic emulsion may slow healing after surgery and increase the risk of certain complications, such as eye infection or worsening an infection. Call your doctor right away if your pain and swelling do not improve or if you experience any of the following: eye redness, itching, tearing or discharge; feeling that something is in your eye; seeing floating spots; sensitivity to light; or red, swollen or crusty eyelids.

**If you wear contact lenses**
Do not wear any contact lens that has not been approved by your doctor.

Do not use DUREZOL® ophthalmic emulsion while you are wearing regular contact lenses. DUREZOL® ophthalmic emulsion contains sorbic acid, a preservative that can be absorbed by soft contact lenses and cause discoloration. Wait at least 10 minutes after using DUREZOL® ophthalmic emulsion before putting your contact lenses in.

**Driving and using machines**
DUREZOL® ophthalmic emulsion can cause side effects that may impair your vision. Do not drive or use machines until your vision is clear.

## INTERACTIONS WITH THIS MEDICATION

No specific drug interaction studies have been done with DUREZOL® ophthalmic emulsion.

Tell your doctor or pharmacist if you are taking (or recently took) any topical NSAIDs. Taking DUREZOL® ophthalmic emulsion and NSAIDS at the same time may delay healing after surgery.

Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines (including with or without prescription, over the counter, vitamins, minerals, and herbals).

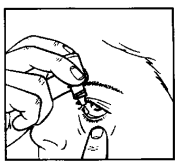
## PROPER USE OF THIS MEDICATION

Always use DUREZOL® ophthalmic emulsion exactly as your doctor has told you.

**Usual dose:**
Treatment of inflammation and pain after cataract surgery
Apply one drop of DUREZOL® ophthalmic emulsion into the pocket between the eyelid and affected eye 4 times daily beginning 24 hours after surgery and continuing for 2 weeks. Then change your dose as directed by your doctor.

Treatment of endogenous anterior uveitis
Apply one drop into the pocket between the eyelid and the affected eye 4 times daily for 14 days. Then change your dose as directed by your doctor.

**How to Use:**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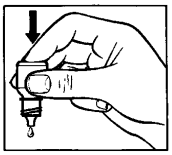
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- Wash your hands thoroughly with soap and water.
- Check the dropper tip to make sure that it is not chipped or cracked.
- Avoid touching the dropper tip against your eye or anything else to avoid contamination. Eye drops and eye dropper must be kept clean.
- Pull down your lower eyelid with a clean finger until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Gently press on the base of the bottle to release one drop of DUREZOL® emulsion at a time
- Do not squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).
- After using DUREZOL® emulsion, press a finger into the corner of your eye, by the nose (picture 3). This helps to stop DUREZOL® emulsion getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use. Do not wipe or rinse the dropper tip.
- If a drop misses your eye, try again.
- Wipe any excess liquid from your face with a tissue.
- If you are to use more than one drop in the same eye, wait at least 5 minutes before applying the next drop.
- Wash your hands to remove any medication.

When you use DUREZOL® ophthalmic emulsion, be careful not to let the tip of the bottle touch your eyes, fingers, face, or any surface. If the tip does touch another surface, bacteria may get into the eye drops. Using eye drops that are contaminated with bacteria may cause serious damage to the eye or loss of vision. If you think your eye drops have become contaminated, call your doctor or pharmacist.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
Use the medication as soon as you remember the missed dose. If it is almost time for your next dose, skip the missed dose and use the medicine at your next regularly scheduled time. Do not use extra medicine to make up the missed dose. Do not double dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DUREZOL® ophthalmic emulsion can cause side effects, although not everybody gets them.

Side effects in the eye observed with DUREZOL® ophthalmic emulsion include: increase in eye pressure; slowed or impaired healing of the eye; reduced vision; clouding of the lens; eye inflammation with or without surface damage; floating particles that appear as spots; problems with the iris, including inflammation; separation of vitreous gel from the retina, which may result in retinal detachment; bloodshot eyes; eyelid inflammation or swelling; eyelashes that curve towards the eye; problems with the cornea, including damage, tiny tears and ulcers; dry eye; flashes of light in vision; damage to the eye surface; and complications following cataract surgery, including contraction of the lens capsule, displacement of the pupil, dislocation of the lens and removal of blebs from the eye.

Side effects in the rest of the body observed with DUREZOL® ophthalmic emulsion include: dizziness, diarrhea, skin discoloration and increased heart rate.

Some side effects can be serious. If you experience any of the following symptoms, call your doctor immediately:

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|
| | Only if severe | In all cases | |
| **Allergic (hypersensitivity) reactions / with symptoms such as** hives, difficulty breathing; swelling of the face, lips, tongue, or throat | | | √ |
| **Vision changes/** with symptoms such as sudden vision loss, blurred vision, tunnel vision, eye pain, eye itching, irritation or redness, severe headache, sensitivity to light, foreign body sensation in eye | | √ | |
| **New infection**- with symptoms such as eye swelling, weeping, drainage, crusting | | √ | |

***This is not a complete list of side effects. For any unexpected effects while taking DUREZOL® ophthalmic emulsion, contact your doctor or pharmacist.***

## HOW TO STORE IT

Store at 15 -25°C (59 -77°F). Do not freeze. Protect from light. When not in use keep the bottles in the protective carton.

**Keep DUREZOL® ophthalmic emulsion out of sight and reach of children.**

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    **Health Canada**
    **Postal Locator 0701E**
    **Ottawa, Ontario**
    **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.novartis.ca or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.



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