

General Facts

- On June 23, 2008, after a six-month priority review, Durezol™ was approved by the US Food and Drug Administration for the treatment of inflammation and pain associated with ocular surgery.
- The recommended dosage and administration of Durezol is to instill one drop into the conjunctival sac of the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- Durezol is the first and only steroid with an approval for both inflammation and pain, making it the first innovation in the strong ophthalmic steroid class in more than 35 years.
- Difluprednate (the active ingredient in Durezol) is a difluorinated prednisolone derivative with potent anti-inflammatory activity. The molecule is fluorinated at the C6 and C9 positions, contributing to its potency.
- Durezol does not contain benzalkonium chloride (BAK), a preservative known to disrupt tear film stability, create toxic effects in the corneal and conjunctival epithelia, and cause immunoallergic reactions. Durezol is preserved with sorbic acid, which has been shown to cause little irritation or damage to ocular tissue and is recommended for sensitive eyes.
- Difluprednate has been evaluated in an extensive preclinical and clinical program in Japan.
 - In several preclinical studies conducted in Japan, difluprednate was:
 - Non-toxic to the eye and more bioavailable than a suspension formulation
 - Metabolized and then distributed to the cornea, conjunctiva, iris, ciliary body, aqueous humor, & retina/choroid; after a single dose, was barely detectable in the blood and after multiple doses, little accumulation in the blood.
 - Found to suppress uveitis and postoperative inflammation in animal models as well as betamethasone sodium phosphate, 0.1%, a strong steroid approved for use outside of the US.
 - Conclusions from clinical studies conducted in Japan
 - In one Phase 3 trial of 136 patients with anterior uveitis and panuveitis, those treated with difluprednate QID had a significantly greater improvement on Day 7 compared to those treated with betamethasone on the measures of anterior chamber cell score and total sign score.
 - In another trial of 18 patients with severe endogenous anterior uveitis and panuveitis (more than 50 anterior chamber cells) that did not respond to previous therapies, difluprednate QID was effective in reducing anterior chamber cell, flare, and total sign and symptom scores. After 14 days on difluprednate, 72% of patients had less than 10 cells and 11% had no cells in the anterior chamber.
 - In a 14 day non-inferiority trial for the treatment of inflammation following ocular surgery, difluprednate was comparable in efficacy to betamethasone on the measure of change from baseline in anterior chamber cell score.

Phase 3 (Pivotal) Clinical Trials

- Two phase 3 studies conducted at 26 sites from Jan 2007 through Sept 2007
- Durezol compared to placebo dosed BID and QID beginning 24 hours after intraocular surgery
- Patients had significant inflammation as evidenced by an anterior chamber cell grade 2 or higher (greater than 10 cells) the day after surgery
- Treatment occurred over 4 weeks and included tapering beginning at week 2 at investigators discretion
- The following grading system was used in this trial:

Anterior Chamber Cell		Anterior Chamber Flare		Signs of Inflammation*	
Grade	Cell Count	Grade	Flare	Grade	Scale
0	≤ 1 cell	0	None	0	Absent
1	2–10 cells	1	Mild (trace to clearly noticeable, visible)	1	Mild
2	11–20 cells	2	Moderate (without plastic aqueous humor)	2	Moderate
3	21–50 cells	3	Marked (with plastic aqueous humor)	3	Severe
4	> 50 cells	4	Severe (with fibrin deposits and/or clots)		

* Chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates were each graded on this scale.

Topline Results:

- 438 patients were included in the study: Durezol BID (N = 111); Durezol QID (N = 107); Placebo BID and QID (N = 220)

Outcome Measures: Inflammation

- Both regimens (BID and QID) had similar overall efficacy in the reduction of anterior chamber cells two weeks following surgery (87% in both arms) compared to placebo (30%).

MEASURE	Placebo	BID	QID
Percent reduction from baseline in anterior chamber cell count			
Mean baseline cell count (Day 0)	22.5 cells	24.1 cells	24.0 cells
Day 3/4	-5.5%	-47.6%	-39.4%
Day 8	-17.4%	-78.1%	-77.7%
Day 15	-30.4%	-86.8%	-87.0%
Day 29	-39.8%	-90.4%	-91.4%

- The percentage of patients with an anterior chamber cell grade of 0 increased over the study period in the BID- and QID-treated groups reaching 56% and 63%, respectively, on Day 15 compared with 16% in the placebo group ($P < 0.0001$). At Day 29, patients' scores in the BID and QID groups increased to 75% and 80%, respectively, compared with 29% in the placebo group ($P < 0.0001$).

Study Visit	Placebo	BID	QID	P value (same value for BID & QID unless indicated)
Percentage of patients with clearing (grade of "0" = ≤ 1 cell) of anterior chamber cells				
Day 3/4	1.9%	4.6%	6.6%	< 0.05 (QID only)
Day 8	9.2%	30.0%	34.6%	< 0.0001
Day 15	16.1%	55.5%	62.6%	< 0.0001
Day 29	29.4%	74.5%	80.4%	< 0.0001

- Differences in the percentage of patients with a clinical response (AC cell count ≤ 5 and flare grade = 0) were observed as early as Day 3. On Day 15, the percent of patients achieving a clinical response increased to 73% in the BID group and 71% in the QID group (both, $P < 0.0001$), compared with 27% in the placebo group. This treatment effect was sustained through Day 29, when clinical response was achieved in 79% and 82% of patients in the BID and QID groups, respectively ($P < 0.0001$), compared with 39% in the placebo group.

Study Visit	Placebo	BID	QID	P value (same value for BID & QID unless indicated)
Percentage of patients with clinical response (cell count ≤ 5 and flare grade of "0")				
Day 3/4	4.7%	13.8%	15.1%	< 0.05
Day 8	18.9%	46.4%	42.1%	< 0.0001
Day 15	27.1%	72.7%	71.0%	< 0.0001
Day 29	39.4%	79.1%	82.2%	< 0.0001

Outcome Measures: Pain

- Pain and discomfort, both symptoms associated with anterior ocular inflammation, were evaluated using the Visual Analog Scale (VAS). This was scored from 0 to 100 using a mark on a 100 mm line (0 = absent, 100 = maximal pain or discomfort)
- Compared to placebo, the percentage of patients who reported a VAS score of 0 (no pain at all) was higher in the BID and QID difluprednate groups. Differences were observed as early as Day 3/4, where the percentages of patients who were pain free were 38% and 45% in the BID and QID groups, respectively, compared to 25% in the placebo group. At Day 8, 42% and 58% of patients were pain free in the BID and QID groups, respectively, compared to 27% for placebo. This treatment effect continued at Day 15 and through Day 29.

Study Visit	Placebo	BID	QID	P value (same value for BID & QID unless indicated)
Percent of patients pain/discomfort free				
Day 3/4	24.8%	38.2%	45.3%	BID < 0.05; QID < 0.0001
Day 8	27.1%	41.8%	57.9%	BID < 0.05; QID < 0.0001
Day 15	34.9%	53.6%	62.6%	BID < 0.001; QID < 0.0001
Day 29	39.9%	63.6%	72.0%	< 0.0001
Mean pain/discomfort score				
Day 0	13.9	12.9	15.2	n/a
Day 3/4	17	9.1	7.2	n/a
Day 8	19.2	6.5	5.2	n/a
Day 15	16.6	4.9	4.3	n/a
Day 29	14.6	3.1	2.1	n/a

Safety Assessments

- A clinically significant IOP rise (≥ 10 mmHg from baseline and ≥ 21 mmHg at the same visit) was observed in only 3 patients (3%) in each of the Durezol treatment groups, and 2 patients (1%) in the placebo group. One patient in each Durezol group and both patients in the placebo group required IOP-lowering medication.

MEASURE	Placebo	BID	QID	P value (same value for BID & QID unless indicated)
Mean intraocular pressure (mmHg)				
Day 0	15.3	16.0	15.5	n/a
Day 3/4	12.6	14.6	14.8	n/a
Day 8	13.3	14.9	14.9	n/a
Day 15	13.4	14.9	14.9	n/a
Day 29	13.4	14.8	14.6	n/a

Important Safety Information

- Durezol, like other corticosteroids, is contraindicated in patients with viral diseases of the cornea and conjunctiva, and also in fungal infections or mycobacterial infections of the eye or ocular structures. Prolonged use of corticosteroids may increase the hazard of secondary ocular infections, exacerbate the severity of ocular viral infections, and increase the development of fungal infections of the cornea. It is important to monitor intraocular pressure when using ophthalmic steroids. The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.
- Adverse 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.
- Ocular adverse reactions occurring in 5–15% of subjects in clinical studies with Durezol included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1–5% of patients included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse events occurring in <1% of patients included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, scleral hyperemia, and uveitis. Most of these events may have been the consequence of the surgical procedure.

Please see full prescribing information by visiting www.durezol.com.