CLINICAL REVIEW of NDA 22-212/S-011

Application Type	SE5-011
Application Number(s)	22-212
Priority or Standard	Priority
Submit Date(s)	September 25, 2012
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PDUFA Goal Date	March 25, 2013
Division / Office	DTOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	March 11, 2013
Established Name	difluprednate ophthalmic emulsion, 0.05%
(Proposed) Trade Name	Durezol
Therapeutic Class	Corticosteroid
Applicant	Alcon Research, Ltd.
Formulation(s)	topical ophthalmic emulsion
Dosing Regimen	For the treatment of inflammation and pain associated with ocular surgery, one (1) drop in the affected eye 4 times daily in the evening throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then taper based on the clinical response For the treatment of endogenous anterior uveitis, one (1) in the affected eye(s) 4 times daily for 14 days followed by tapering as clinically indicated
Indication(s)	Treatment of inflammation and pain associated with ocular surgery Treatment of endogenous anterior uveitis
Intended Population(s)	All ages

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-212 SE5-011 be approved with the labeling revisions found in this review.

1.2 Risk Benefit Assessment

Alcon conducted Study C-10-004 in response to a Written Request to evaluate the use of Durezol in the treatment of post-operative inflammation following cataract surgery in pediatric patient ages 0 to 3 years. A total of 79 subjects were evaluated, of which 39 were exposed to Durezol and 40 to Prednisolone acetate suspension (Pred Forte) 1%. A similar safety profile was observed in both treatment groups.

There are no new safety concerns raised in this supplemental application concerning the use of Durezol in the treatment of post-operative inflammation following cataract surgery in pediatric subjects.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket clinical study requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name:	difluprednate ophthalmic emulsion 0.05%
Proposed Trade Name:	Durezol
Pharmacological Class:	corticosteroid
Indication(s)	treatment of inflammation and pain associated with ocular surgery treatment of endogenous anterior uveitis
Dosing Regimen:	For the treatment of inflammation and pain associated with ocular 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 postoperative period, followed by 2 times daily for a week and then a taper based on the response.

For the treatment of 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

Tables of Currently Available Treatments for Proposed Indications

Table of Currently Available Anterior Uveitis Treatments

Name of Drug	Indication
Durezol (difluprednate ophthalmic emulsion) 0.05%	Treatment of inflammation and pain associated with ocular surgery and treatment of endogenous anterior uveitis.
Vexol (rimexolone ophthalmic suspension) 1%	Indicated for the treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis
Maxidex (dexamethasone sodium phosphate suspension) 0.1%	Indicated for steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies
Maxidex (dexamethasone sodium phosphate ointment) 0.05%	Indicated for steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies
FML (fluorometholone suspension) 0.1%	Indicated for the treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe
FML Forte (fluorometholone suspension) 0.25%	Indicated for the treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe
FML (fluorometholone ointment) 0.1%	Indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
Flarex (fluorometholone acetate suspension) 0.1%	Indicated for use in the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye
Lotemax (loteprednol etabonate suspension) 0.5%	Indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation

	Also indicated for the treatment of post-operative inflammation following ocular surgery
Pred Forte (prednisolone acetate suspension) 1%	Indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL	Indicated for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids
Triesence (triamcinolone acetonide injectable suspension) 40 mg/mL	Indicated for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids Also indicated for visualization during vitrectomy
Kenalog 40 Injection ((triamcinolone acetonide injectable suspension)	Indicated for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids

Table of Currently Available Post-Operative Inflammation and Pain Treatments

Name of Drug	**Indication**
Durezol (difluprednate ophthalmic emulsion) 0.05%	Indicated for the treatment of inflammation and pain associated with ocular surgery and treatment of endogenous anterior uveitis
Vexol (rimexolone ophthalmic suspension) 1%	Indicated for the treatment of post-operative inflammation following ocular surgery and treatment of anterior uveitis
Lotemax (loteprednol etabonate gel) 0.5%	Indicated for the treatment of post-operative inflammation and pain following ocular surgery
Lotemax (loteprednol etabonate ointment) 0.5%	Indicated for the treatment of post-operative inflammation and pain following ocular surgery
Lotemax (loteprednol etabonate suspension) 0.5%	Indicated for the treatment of post-operative inflammation and pain following ocular surgery
Xibrom (bromfenac ophthalmic solution) 0.09%	Indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
Voltaren (diclofenac sodium ophthalmic solution) 0.1%	Indicated for the treatment of post-operative inflammation I patients who have undergone cataract extraction and temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%	Indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery
Acular (ketorolac tromethamine ophthalmic solution) 0.5%	Indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and treatment of post-operative inflammation in patients who have undergone cataract extraction.
Nevanac (nepafenac ophthalmic suspension) 0.1%	Indicated for the treatment of pain and inflammation associated with ocular surgery

2.3 Availability of Proposed Active Ingredient in the United States

Durezol (difluprednate ophthalmic emulsion) 0.05% was initially approved in the US on June 23, 2008, for the treatment of inflammation and pain following ocular surgery. On June 13, 2012 Durezol was approved to treat endogenous anterior uveitis.

2.4 Important Safety Issues with Consideration to Related Drugs

Difluprednate ophthalmic emulsion is a topical corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and 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. Other reactions include keratitis and corneal ulcers.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Agency issued a Written Request on February 18, 2009, in order to obtain pediatric information on Durezol. The original Applicant (Sirion) submitted a pediatric study protocol (Protocol ST-601-007) to IND 75,713 on August 4, 2009. Prior to initiating the study, Alcon acquired Durezol from Sirion. On June 1, 2010, Alcon submitted Protocol C-10-004 to the IND to study Durezol in pediatric patients 0 to 3 years of age for the treatment of post-operative inflammation following cataract surgery.

On 12 September 2011, the Agency granted an extension of the submission date of the study report from 01 October 2011 to 31 December 2012.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of sufficient quality to allow for a substantive review. A routine Division of Scientific Investigations (DSI) audit was requested. Refer to the DSI review for additional information.

3.2 Compliance with Good Clinical Practices

Study C-10-004 was conducted in accordance with the principles of Good Clinical Practice (ICH E6).

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There are financial interests or arrangements to disclose from one investigator that participated in the covered clinical trial (b) (6).

Description of Financial Interests and Arrangements - Reporting Period: C-10-004 (August 16, 2010 to June 8, 2012)

Investigator and Payment Description	Total monies by Investigator
(b) (6), **M.D.**	
Description	
Consulting	160,248.00
Honorarium	37,000.00
Total	197,248.00

Reviewer's Comments:

This investigator contributed (b) (6) patients to the study. Removal of the data from this site would have no significant impact on the final conclusions of either this study or the application as a whole.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no proposed changes to the Chemistry and Manufacturing Controls for Durezol in this supplemental application.

See CMC review for the original application.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology studies submitted in this supplemental application. No changes were made to the sections of the label relevant to Pharmacology/ Toxicology.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were submitted to support the supplement. The applicant references the original NDA 22-212 for clinical pharmacology information to support administration of difluprednate ophthalmic emulsion 0.05% 4 times daily

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol #	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subject/Patients Enrolled
C-10-004 safety/ efficacy study	Prospective, multi-center randomized, double-masked, active-controlled,	Patients 0 to 3 years of age undergoing cataract surgery	Durezol Pred Forte	1 drop QID to study eye 1 drop QID to study eye	13 weeks	79 Patients Durezol: 39 Pred Forte: 40

5.2 Review Strategy

The sources of clinical data utilized in this review include the clinical trial listed above in Section 5.1.

5.3 Discussion of Individual Studies/Clinical Trials

Study C-10-004

Title: A Phase 3B, Multicenter, Randomized, Double-Masked, Parallel-Group, Active-Controlled Study of the Safety and Efficacy of Difluprednate Ophthalmic Emulsion, 0.05% (Durezol) 4 Times Daily (QID) and Prednisolone Acetate Ophthalmic Suspension, 1.0% (Pred Forte) QID for the Treatment of Inflammation Following Cataract Surgery in Children 0 to 3 Years of Age

Study Design

This study was prospective, multi-center, double-masked, parallel group, randomized, active-controlled trial designed to evaluate the safety and efficacy of Durezol compared to Pred Forte in the treatment of inflammation and pain following cataract surgery in patients ages 0-3 years. Post-operatively, patients were randomized in a 1:1 ratio to receive Durezol or Pred Forte.

During the screening phase (Day -14 to Day 0), patients were screened against the inclusion/exclusion criteria, and informed consent was obtained from the patient's parent or legal guardian. Patients who met all eligibility criteria were randomized to treatment on Day 0 (day of surgery). Study medication administration began on Day 0 immediately following surgery with 1 drop instilled in the affected eye. The parent or legal guardian of each patient was instructed to

instill the allocated study medication QID (1 drop in the affected eye 4 times daily) beginning on Day 1 for 14 days after surgery, followed by tapering for 14 days (dependent on the Investigator's determination of adequate response to treatment).

Safety and efficacy evaluations were conducted at study visits on Day 0 (day of surgery), Day 1, Day 8 ± 1 day, Day 15 ± 2 days, and for safety on Day 29 ± 2 days, 1 week after the last dose of study medication + 2 days, and 3 months + 1 week. A gross comparison of efficacy was made based upon the complete clearing of anterior chamber cells (grade = 0) at the end of the 14-day dosing period (Day 15 ± 2 days), and secondarily on a global assessment score and individual components based upon the clinical evidence of postoperative inflammation on Day 1, Day 8 ± 1 day, Day 15 ± 2 days, Day 29 ± 2 days, 1 week after the last dose of study medication + 2 days, and 3 months + 1 week. Safety was evaluated during the study through a review of adverse events (AEs), as well as safety parameter assessments including age appropriate estimation of visual acuity (VA), IOP measurements, fundoscopic exam, observations of postoperative bacterial or fungal infection, and ocular signs. Because the study population was pediatric (0 to 3 years of age), safety parameters were assessed when possible using age-appropriate methods.

Schedule of Visits and Measurements

Table 9.1.-2: Study Plan

Evaluation		Screening (Day -14 to -1) + 1 Day	Treatment				Follow-up		
			Day 0 (Day of Surgery)	Day 1	Day 8 (± 1 Day)	Days 15 (± 2 Days)	Day 29 (± 2 Days)	1 Week After the Last Study Drug Dose (+2 Days)	Month 3 (+1 Week)
Informed consent		X							
Inclusion/exclusion criteria		X							
Demographics		X							
Medical/ocular history		X							
Prior and current medication history		X							
Slit lamp/ophthalmoscopy/light examination (signs)	Anterior chamber cell grade	X		X	X	X	X	X	X
	Anterior chamber flare grade	X		X	X	X	X	X	X
	Corneal clarity	X		X	X	X	X	X	X
	Wound integrity			X	X	X	X	X	X
	Conjunctival injection	X		X	X	X	X	X	X
	Ciliary injection/limbal injection	X		X	X	X	X	X	X
	Chemosis	X		X	X	X	X	X	X
	Hypopyon	X		X	X	X	X	X	X
	Vitritis	X		X	X	X	X	X	X
	Cataract	X							
	External examination	X*		X*	X*	X*	X*	X*	X*
Symptoms	Photophobia	X		X	X	X	X	X	X
	Lacrimation	X		X	X	X	X	X	X
Global assessment of postoperative inflammation				X	X	X	X	X	X
Intraocular pressure		X*	X*	X	X	X	X	X	X
Visual acuity		X*		X	X	X	X	X	X
Fundoscopy		X*		X	X	X	X	X	X
Observation of postoperative bacterial or fungal infection			X	X	X	X	X	X	X
Dispense study medication			X						
Adverse event assessment			X	X	X	X	X	X	X
Concomitant medication documentation		X	X	X	X	X	X	X	X

* Both eyes

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Inclusion Criteria

1. 0 to 3 years of age.
2. Undergoing uncomplicated cataract extraction in 1 eye with or without IOL.
3. Informed consent signed by a parent or legal guardian.

Exclusion Criteria

1. Presence of any active or suspected viral, bacterial, or fungal disease in the study eye.
2. Use of any topical medication in the study within 7 days prior to surgery, except for drops that are needed to examine the eye or to prepare for surgery.
3. Patients with post-traumatic cataract.
4. Active uveitis in the study eye.
5. Ocular Neoplasm in the study eye.
6. Human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS).
7. Suspected permanent low vision or blindness in the fellow non-study eye. The study eye must not be the patient's only good eye.
8. Patients on systemic steroids or non-steroidal anti-inflammatory drugs.
9. History of steroid-induced IOP rise.
10. Currently on medication for ocular hypertension or glaucoma in the study eye.
11. Diabetes.

Primary Efficacy Variable

The primary efficacy endpoint was the number and percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days.

Secondary Efficacy Variables

The secondary efficacy endpoints were a global assessment score of postoperative inflammation and the corresponding individual components of the global assessment score at each postoperative visit (Day 1, Day 8 ± 1 day, Day 15 ± 2 days, Day 29 ± 2 days, 1 week after the last dose of study drug + 2 days, and 3 months + 1 week).

Table of Investigators

Investigator	**Investigator #**	**# of Patients Durezol N =40[a] n (%)**	**# of Patients Pred Forte N=40 n (%)**
Bothun, Erick, M.D. Minneapolis, MN 55454	5858	0 (0.0)	2 (5.0)
Council, Matthew, MD St. Louis, MO 63104	6306	0 (0.0)	0 (0.0)

Investigator	**Investigator #**	**# of Patients Durezol N =40[a] n (%)**	**# of Patients Pred Forte N=40 n (%)**
Facciani, John, MD Salem, VA 24153	5975	0 (0.0)	0 (0.0)
Gonzales, Carlos, MD Houston, TX 77025	5460	1 (2.5)	2 (5.0)
Kerr, Natalie, MD Memphis, TN 38163	5972	0 (0.0)	0 (0.0)
Lambert, Scott, MD Atlanta, GA 30322	4039	2 (2.5)	3 (7.5)
Lee, Dave, MD Colorado Springs, CO 80920	6171	0 (0.0)	1 (2.5)
Lustig, Marc, MD, PhD New York, NY 10023	6237	0 (0.0)	0 (0.0)
McGregor, Mary Lou, MD Columbus, OH 43205	6051	2 (5.0)	2 (5.0)
Morrison, David, MD Nashville, TN 37232	5900	0 (0.0)	1 (2.5)
O'Halloran, Henry, MD San Diego, CA 92123	4820	6 (15.0)	3 (7.5)
Orge, Faruk, MD Mayfield Heights, OH 44124	5971	4 (10.0)	1 (2.5)
Piccione, Richard, MD Opelousas, LA 70570	6033	4 (10.0)	0 (0.0)
Plager, David, MD. Indianapolis, IN 46202	3292	6 (15.0)	3 (7.5)
Reiser, Bibiana, MD. Los Angeles, CA 90027	5952	5 (12.5)	5 (12.5)
Roarty, John, MD Detroit, MI 48201	2911	2 (5.0)	2 (5.0)
Sala, Nicholas, DO Erie, PA 16501	6038	1 (2.5)	1 (2.5)
Struck, Michael, MD Madison, WI 53705	5969	0 (0.0)	0 (0.0)
VanderVeen, Deborah, MD Boston, MA 02115	5951/ 6259[b]	1 (2.5)	1 (2.5)
Wang, Serena, MD. Dallas, TX 75390	6008	2 (5.0)	8 (20.0)
Wilson, M. Edward, MD Charleston, SC 29425	3292	4 (10.0)	4 (10.0)

Investigator	Investigator #	# of Patients Durezol N =40[a] n (%)	# of Patients Pred Forte N=40 n (%)
Yoon, Hawke, MD Chicago, IL 60614	6023	0 (0.0)	1 (2.5)

[a] Patient 3008 was randomized to difluprednate 0.05% (Durezol) at site 6008 but withdrew consent prior to receiving study medication. This patient was not included in the safety, ITT, and PP analysis sets, but was included in the total number of patients enrolled and is accounted for in this table.
[b] Investigator was initially known by 2 site locations, 5951 and 6259. Site 5951 was closed and the Investigator enrolled patients at site 6259.

6 Review of Efficacy

6.1 Indication

The proposed indication is treatment of inflammation and pain associated with ocular surgery.

6.1.1 Methods

The sources of clinical data utilized in this review come from clinical trial C-10-004.

6.1.2 Demographics

Study C-10-004 - Demographic Statistics by Treatment (ITT Population)

	Durezol N=39 n (%)	Pred Forte N=40 (%)
Age		
0-27 Days	3 (7.7)	3 (7.5)
28 Days–23 Months	28 (71.8)	26 (65.0)
2-3 Years	8 (20.5)	11 (27.5)
Sex		
Male	17 (43.6)	20 (50.0)
Female	22 (56.4)	20 (50.0)
Ethnicity		
Hispanic, Latino, or Spanish	9 (23.1)	6 (20.0)
Not Hispanic, Latino, or Spanish	30 (76.9)	32 (80.0)
Race		
White	21 (53.8)	24 (60.0)
Black or African American	9 (23.1)	9 (22.5)
Asian	0 (0.0)	1 (2.5)

Multi-racial	3 (7.7)	2 (5.0)
Other	6 (15.4)	4 (10.0)
Iris Color		
Brown	22 (56.4)	22 (55.0)
Green	0 (0.0)	1 (2.5)
Blue	15 (38.5)	16 (40.0)
Grey	1 (2.6)	0 (0.0)
Other	1 (2.6)	1 (2.5)

Reviewer's Comments:

There were no remarkable differences between treatment groups regarding age, gender, ethnicity, race, or eye color.

6.1.3 Subject Disposition

Study C-10-004 - Subject Disposition and Primary Reason for Discontinuation

Disposition and Discontinuation	Durezol n (%)	Pred Forte n (%)
Total Randomized	40	40
Treated	39	40
As randomized	39 (97.5)	40 (100.0)
Not as randomized	0 (0.0)	0 (0.0)
Safety Population	39	40
Completed	39 (100.0)	37 (92.5)
Discontinued	0 (0.0)	3 (7.5)
ITT Population	39	40
Completed	39 (100.0)	37 (92.5)
Discontinued	0 (0.0)	3 (7.5)
Per Protocol (PP) Population	35	36
Completed	35 (100.0)	34 (94.4)
Discontinued	0(0.0)	2 (5.6)
Primary reason for Discontinuation		
Withdrawal by subject	1 (2.5)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (2.5)
Investigator decision	0 (0.0)	2 (5.0)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for study C-10-004 was the percentage of patients with an anterior cell grade of 0 (no cells) on Day 15 ± 2 days.

Primary Efficacy Analysis

The number and percentage of patients who had an anterior cell grade of 0 (no cells) on Day 15 ± 2 days was summarized by treatment group using descriptive statistics.

Analysis Population

Intent to Treat (ITT): All patients who received at least 1 administration of study medication.

Per Protocol (PP): All patients who received at least 1 administration of study drug, satisfied pre-randomization inclusion/exclusion criteria, and did not have major protocol deviations.

Table 11.4.1.1.1.-1:
Percentage of Patients with an Anterior Cell Grade of 0 at Day 15 ± 2 Days
(Intent-to-Treat)

		Durezol (N= 39)	Pred Forte (N= 40)
Visit	**Cell Count**	**n (%)**	**n(%)**
Day15	**Total**	38	40
	0 cells	30 (78.9)	31 (77.5)
	0 cells	8 (21.1)	9 (22.5)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
1 patient had missing Anterior Cell Grade assessment at all visits.

Reviewer's Comments:

The percentage of patients with complete clearing of anterior chamber cells (anterior cell grade = 0, no cells) on Day 15 ± 2 days, was similar for patients treated with Durezol and patients treated with Pred Forte (78.9% and 77.5%, respectively). The per protocol analysis is consistent with the ITT analysis.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints were a global assessment score of postoperative inflammation and the corresponding individual components of the global assessment score at each postoperative visit (Day 1, Day 8 ± 1 day, Day 15 ± 2 days, Day 29 ± 2 days, 1 week after the last dose of study drug + 2 days, and 3 months + 1 week).

A global assessment score was assigned by the Investigator based upon the clinical evidence of postoperative inflammation on Day 1, Day 8 ± 1 day, Day 15 ± 2 days, Day 29 ± 2 days, 1 week after the last dose of study medication + 2 days, and 3 months + 1 week. Results were reported according to the scale provided in Tables 9.5.1.1.-1 and 9.5.1.1.-2.

Table 9.5.1.1.-1:
Global Assessment of Inflammation – Individual Component Scoring Categories: Signs and Symptoms of Postoperative Inflammation

	Component	Measurement Scale
Signs	Anterior Chamber Cell Grade	0=0 cells, 1=1 to 10 cells, 2=11 to 20 cells, 3=21 to 50 cells, 4=> 50 cells
	Anterior Chamber Flare Grade	0=absent, 1=mild, 2=moderate, 3=severe
	Corneal Clarity	0=absent, 1=mild, 2=moderate, 3=severe*
	Conjunctival Injection	0=absent, 1=mild, 2=moderate, 3=severe*
	Ciliary/Limbal Injection	0=absent, 1=mild, 2=moderate, 3=severe*
	Chemosis	0=absent, 1=mild, 2=moderate, 3=severe*
	Hypopyon	0=absent, 1=mild, 2=moderate, 3=severe*
	Vitritis	0=absent, 1=mild, 2=moderate, 3=severe*
	Wound Integrity	0=absent, 1=mild, 2=moderate, 3=severe*
	Cataract	0=absent, 1=mild, 2=moderate, 3=severe*
Symptoms	Photophobia	0=absent, 1=mild, 2=moderate, 3=severe*
	Lacrimation	0=absent, 1=mild, 2=moderate, 3=severe*

*severe based upon the observations of the Investigator

Table 9.5.1.1.-2:
Global Assessment Score – Assessment Scale

Grade	Definition
0	Clear
1	Improving satisfactorily
2	Not improving or worsening; withdrawal from study indicated to allow appropriate alternative therapy to be instituted

Table 11.4.1.2.1.-1:
Global Assessment of Inflammation by Visit (Intent-to-Treat Population)

Visit	Assessment Score	Durezol (N= 39) n (%)	Pred Forte (N= 40) n (%)
Day 1	**Total**	39	40
	Clear	12 (30.8)	7 (17.5)
	Improving Satisfactorily	27 (69.2)	33 (82.5)
	Not Improving or Worsening	0 (0.0)	0 (0.0)
Day 8	**Total**	39	40
	Clear	19 (48.7)	10 (25.0)
	Improving Satisfactorily	19 (48.7)	28 (70.0)
	Not Improving or Worsening	1 (2.6)	2 (5.0)

Day 15	**Total**	39	40
	Clear	22 (56.4)	20 (50.0)
	Improving Satisfactorily	17 (43.6)	20 (50.0)
	Not Improving or Worsening	0 (0.0)	0 (0.0)
Day 29	**Total**	39	40
	Clear	31 (79.5)	29 (72.5)
	Improving Satisfactorily	8 (20.5)	10 (25.0)
	Not Improving or Worsening	0 (0.0)	1 (2.5)
1 Week After Last Dose	**Total**	39	40
	Clear	35 (89.7)	36 (90.0)
	Improving Satisfactorily	3 (7.7)	3 (7.5)
	Not Improving or Worsening	1 (2.6)	1 (2.5)
3 Months	**Total**	39	40
	Clear	36 (92.3)	37 (92.5)
	Improving Satisfactorily	2 (5.1)	3 (7.5)
	Not Improving or Worsening	1 (2.6)	0 (0.0)

Reviewer's Comments:

A higher percentage of patients treated with Durezol were completely clear of postoperative inflammation (global assessment score = 0) early in the dosing period at Day 1 and Day 8 compared to patients treated with Pred Forte (30.8% versus 17.5% and 48.7% versus 25%, respectively). Starting Day 15, the percentage of patients who were clear of postoperative inflammation between treatment groups was similar.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Study C-10-004 was designed to evaluate the safety and efficacy of Durezol in the treatment of inflammation following cataract surgery in children 0 to 3 years.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen was studied (QID for 14 days) in Study C-10-004.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated. The duration of treatment for the subjects in these trials was no longer than 14 days, followed by tapering for 14 days (dependent on the Investigator's determination of adequate response to treatment).

6.1.10 Additional Efficacy Issues/Analyses

Table 2: Descriptive Summary of Anterior Cell Grade by Visit (Intent-to-Treat Population)

Visit		Durezol (N= 39)	Pred Forte (N= 40)	Treatment Difference in Mean (95% CI)
Screening	m	38	40	
	Mean (SD)	0.0 (0.00)	0.0 (0.00)	NA
	Median	0	0	
	(Min, Max)	(0, 0)	(0, 0)	
Day 1	m	38	40	
	Mean (SD)	1.0 (0.72)	1.0 (0.96)	0.0 (-0.4, 0.4)
	Median	1	1	
	(Min, Max)	(0, 3)	(0, 4)	
Day 8	m	38	40	
	Mean (SD)	0.6 (0.72)	0.5 (0.68)	0.0 (-0.3, 0.3)
	Median	0	0	
	(Min, Max)	(0, 3)	(0, 2)	
Day 15	m	38	40	
	Mean (SD)	0.3 (0.60)	0.3 (0.55)	0.0 (-0.3, 0.2)
	Median	0	0	
	(Min, Max)	(0, 3)	(0, 2)	
Day 29	m	38	40	
	Mean (SD)	0.1 (0.31)	0.1 (0.35)	0.0 (-0.1, 0.2)
	Median	0	0	
	(Min, Max)	(0, 1)	(0, 2)	
1 Week After Last Dose	m	38	40	
	Mean (SD)	0.0 (0.16)	0.1 (0.35)	0.0 (-0.2, 0.1)
	Median	0	0	
	(Min, Max)	(0, 1)	(0, 2)	
3 Months	m	38	40	
	Mean (SD)	0.1 (0.23)	0.1 (0.32)	0.0 (-0.1, 0.1)

Median	0	0
(Min, Max)	(0, 1)	(0, 2)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
m = Number of patients with non-missing assessment
NA = Not Applicable (All patients had zero scores)
- 1 patient had missing Anterior Cell Grade assessment at all visits.

7 Review of Safety

7.1 Methods

Studies/Clinical Trials Used to Evaluate Safety

Protocol #	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subject/Patients Enrolled
C-10-004 safety/ efficacy study	Prospective, multi-center randomized, double-masked, active-controlled,	Patients 0 to 3 years of age undergoing cataract surgery	Durezol Pred Forte	1 drop QID to study eye 1 drop QID to study eye	13 weeks	79 Patients Durezol: 39 Pred Forte: 40

7.1.2 Categorization of Adverse Events

All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 13.0 and are presented within the Tables as Preferred Terms organized by System Organ Classification.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A - This supplement contain data from only one clinical trial (Protocol C-10-004).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 39 pediatric patients were exposed to Durezol during the conduct of Study C-10-004.

Table 12.1.-1:
Duration of Exposure to Study Medication (Days)
(Safety Population)

	Durezol (N = 39)		Pred Forte (N = 40)	
	N	(%)	N	(%)
1-2 Days	0	(0.0)	0	(0.0)
3-9 Days	0	(0.0)	1	(2.5)
10-17 Days	1	(2.6)	1	(2.5)
18-31 Days	27	(69.2)	32	(80.0)
> 31 Days	11	(28.2)	6	(15.0)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
Exposure = Date of the last instillation of study medication - date of the first instillation of study medication +1 (days)

Table 12.1.-2:
Mean Duration of Exposure to Study Medication (Days)
(Safety Population)

	Durezol (N = 39)	Pred Forte (N = 40)
Mean	30.6	29.2
SD	5.9	5.5
Median	30	30
(Min, Max)	(16, 49)	(8, 37)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
Exposure = Date of the last instillation of study medication - date of the first instillation of study medication +1 (days)
SD = Standard Deviation

7.2.2 Explorations for Dose Response

Only one dose of Durezol, the currently approved dose for adults, was studied in Study C-10-004.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

There were no clinical laboratory evaluations conducted for this study.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed in this supplement.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drugs (topical corticosteroids) are well known. Refer to Section 2.2 for currently approved products. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and 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.

See Section 7.4.5 for further detail.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in study C-10-004.

7.3.2 Nonfatal Serious Adverse Events

A total of 19 subjects experienced a serious adverse event, 8 treated with Durezol and 11 treated with Pred Forte.

Study C-10-004 – Nonfatal SAEs

Investigator/ Subject	Age	Sex	Treatment	Coded Adverse Event	Onset Day	Duration of Event	Outcome of Event	DC'D Due AE
5952/1908	2M	M	Durezol	IOP increased	17	N/A	Continuing w/Tx	No
5971/2404	1M	M	Durezol	Cataract cortical	39	53 Days	Resolved w/Tx	No

Investigator/ Subject	Age	Sex	Treatment	Coded Adverse Event	Onset Day	Duration of Event	Outcome of Event	DC'D Due AE
3296/1608	3M	F	Durezol	Medical observation	1	1 Days	Resolved wo/Tx	No
4820/1401	1M	F	Durezol	Medical observation	1	13 Hours	Resolved wo/Tx	No
4820/1403	10D	M	Durezol	Medical observation	1	1 Days	Resolved wo/Tx	No
4820/1404	1M	M	Durezol	Medical observation	1	24 Hours	Resolved wo/Tx	No
4820/1406	18D	F	Durezol	Medical observation	1	23 Hours	Resolved wo/Tx	No
4820/1409	19D	M	Durezol	Medical observation	1	1 Days	Resolved wo/Tx	No
3292/1207	1M	F	Pred Forte	Failure to thrive	18	N/A	Continuing w/Tx	No
3296/1602	1M	M	Pred Forte	Medical observation	1	1 Days	Resolved wo/Tx	No
4039/1305	1M	M	Pred Forte	Medical observation	1	1 Days	Resolved wo/Tx	No
4820/1402	15D	F	Pred Forte	Medical observation	1	24 Hours	Resolved wo/Tx	No
4820/1405	2Y	F	Pred Forte	Medical observation	1	23 Hours	Resolved wo/Tx	No
5858/1101	5M	M	Pred Forte	Medical observation	1	27 Hours	Resolved wo/Tx	No
5858/1102	1M	M	Pred Forte	Medical observation	1	29 Hours	Resolved wo/Tx	No
5952/1905	1M	M	Pred Forte	Medical observation	1	1 Days	Resolved wo/Tx	No
5952/1907	1M	F	Pred Forte	Medical observation	1	1 Days	Resolved wo/Tx	No
6051/3202	22D	M	Pred Forte	Medical observation	1	23 Hours	Resolved wo/Tx	No
6171/3401	1M	M	Pred Forte	Medical observation	1	1 Days	Resolved wo/Tx	No
6171/3401	1M	M	Pred Forte	Medical observation	8	1 Days	Resolved wo/Tx	No

Nonfatal SAE Narratives for Subjects Treated with Durezol

Patient 5952/1908, a 2-month old male infant with a medical history including bilateral cataracts was randomized into the study and received difluprednate 0.05% (Durezol). Patient 1908 had cataract surgery in study eye (OD) on Study Day 0 and received the first dose of Durezol the following day (Study Day 1). Sixteen days after receiving study medication (Study Day 17), the

patient demonstrated an increase in intraocular pressure (from 14 mmHg on Study Day 0 to 30 mmHg on Day 17) for the right eye (OD = study eye). Also, on Study Day 17, the patient had cataract surgery in the left eye (OS = non-study eye). This adverse event was assessed by the Investigator as possibly related to study medication, moderate in intensity, and continuing with treatment consisting of Cosopt. The Investigator also indicated that the Durezol was tapered for the patient. Participation in the study was not interrupted due to this serious adverse event. No systemic or ocular concomitant medications were ongoing at entry into the study (i.e., baseline). Following surgery on Day 0, the patient received ofloxacin, 1 drop 4 times daily in the study eye for 23 days.

Patient 5971/2404, a 4-month-old White male infant received difluprednate 0.05% (Durezol) while participating in clinical study C-10-004. On (b) (6), before the patient enrolled in the clinical trial, the patient underwent cataract surgery in his right eye (OD; non-study eye). On 19-SEP-2011, the patient was randomized to the study and received the first drop of Durezol immediately after cataract surgery in his left eye (OS; study eye). On 27-OCT-2011, the left eye of the patient was diagnosed with Cortical cataract (coded as Cataract cortical). On (b) (6), a vitrectomy surgery was performed to treat the cortical cataract. The investigator stated the event was serious, moderate in intensity and resolved with treatment. Participation in the study was not interrupted due to this serious adverse event.

Patient 4820/1401, a 1-month-old White male infant received difluprednate (Durezol) while participating in clinical study C-10-004. The Investigator reported that patient 1401 was admitted to the hospital for routine post operative observation. First exposure to Durezol was (b) (6). The patient was hospitalized from (b) (6). The Investigator classified the reported event was mild, resolved without treatment, and not related to the use of Durezol. Participation in the study was not interrupted due to this adverse event. In addition, the patient also experienced a single episode of post-anesthesia emesis (5 seconds), and this was reported as a non-serious adverse event. The Investigator stated the event was mild in intensity and resolved without treatment.

Patient 4820/1403, a 10-day-old White male neonate received difluprednate 0.05% (Durezol) while participating in clinical study C-10-004. On (b) (6), the patient had cataract surgery in the left eye and received the first drop of the test article immediately after surgery. Following the surgical procedure, the patient was admitted to the hospital for overnight observation as standard of care for neonatal patients. The patient was hospitalized from (b) (6). The Investigator classified the event as serious, mild in intensity, and resolved without treatment. Participation in the study was not interrupted due to this adverse event. In addition, the patient experienced an onset of photophobia on 09-APR-2011 and posterior capsule opacification on 09-MAY-2011 in the left eye (OS). The Investigator stated these two adverse events were non-serious, mild in intensity, resolved with treatment (posterior capsule opacification) and without treatment (photophobia).

Patient 4820/1404, a 1-month-old, White, male infant received difluprednate 0.05% (Durezol) while participating in clinical study C-10-004. On (b) (6), the patient had cataract

surgery in the left eye (OS) and received the first drop of the test article immediately after surgery. Following the surgical procedure, the patient was admitted to the hospital for overnight observation as standard of care for neonatal patients. The patient was hospitalized from (b) (6) . The investigator classified the reported event as serious, mild in intensity, and resolved without treatment. Participation in the study was not interrupted due to this adverse event.

Patient 4820/1406, an 18-day-old, White, female infant received difluprednate 0.05% (Durezol) while participating in the clinical study C-10-004. On (b) (6), the patient had a cataract surgery in the right eye (OD) and received the first drop of Durezol immediately after surgery. Following the surgical procedure, the patient was admitted to the hospital for overnight observation as standard of care for neonatal patients. The patient was hospitalized from (b) (6) . The Investigator stated the reported event was serious, mild in intensity, and resolved without treatment. Participation in the study was not interrupted due to this adverse event.

Patient 4820/1409, a 19-day-old, non-White, male infant received difluprednate 0.05% (Durezol) while participating in clinical study C-10-004. On (b) (6), the patient had cataract surgery in the right eye (OD) and received the first drop of Durezol immediately after surgery. Following the surgical procedure, the patient was admitted to the hospital for overnight observation as standard of care for neonatal patients. The patient was hospitalized from (b) (6) . The Investigator stated the reported event was serious, mild in intensity, and resolved without treatment. Participation in the study was not interrupted due to this adverse event.

Reviewer's Comments:

These adverse events are consistent with the age and general findings in the population of subjects undergoing cataract extraction and were seen in both treatment groups.

7.3.3 Dropouts and/or Discontinuations

Table 10.1.-5:
Reasons for Discontinuation
(All Patient Population)

	Total (N=80) n (%)	**Durezol (N=40) n (%)**	**Pred Forte (N=40) n (%)**
Total	**4 (5.0)**	**1 (2.5)**	**3 (7.5)**
Lost to Follow-Up	1 (1.3)	0 (0.0)	1 (2.5)
Subject's Parent or Legal Guardian Withdraws Consent	1 (1.3)	1 (2.5)	0 (0.0)
Investigator Believes That Continuation is Not in the Subject's Best Interest	2 (2.5)	0 (0.0)	2 (5.0)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension

Table 10.1.-8:
Reasons for Discontinuation
(Safety Population)

	Total (N=79) n (%)	**Durezol (N=39) n (%)**	**Pred Forte (N=40) n (%)**
Total	**3 (3.8)**	**0 (0.0)**	**3 (7.5)**
Lost to Follow-Up	1 (1.3)	0 (0.0)	1 (2.5)
Investigator Believes That Continuation is Not in the Subject's Best Interest	2 (2.5)	0 (0.0)	2 (5.0)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension

Table 10.1.-6:
Reasons for Discontinuation
(Intent-to-Treat Population)

	Total (N=79) n (%)	**Durezol (N=39) n (%)**	**Pred Forte (N=40) n (%)**
Total	**3 (3.8)**	**0 (0.0)**	**3 (7.5)**
Lost to Follow-Up	1 (1.3)	0 (0.0)	1 (2.5)
Investigator Believes That Continuation is Not in the Subject's Best Interest	2 (2.5)	0 (0.0)	2 (5.0)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension

Patients Discontinued from Study

Investigator/ Subject	Age	Sex	Treatment	Visit DC'D	Reason for Discontinuation
6008/3008	47M	M	Durezol	Missing	Subject's parent or legal guardian withdraws consent
3296/1606	47M	F	Pred Forte	Missing	Lost to follow-up
5900/1801	40M	M	Pred Forte	Missing	Investigator believes that continuation is not in the subject's best interest
				Day 8	Investigator believes that continuation is not in the subject's best interest
5971/2402	2M	F	Pred Forte	Missing	Investigator believes that continuation is not in the subject's best interest
				Day 15	Investigator believes that continuation is not in the subject's best interest

Reviewer's Comments:

Four subjects discontinued C-10-004. A review of the submitted case report forms revealed:

1) *6008/3008 – consent withdrawn prior to surgery and did not receive test article (i.e. Durezol).*

2) *3296/1606 – missed Day 8 visit; made Day 15 visit, missed Day 29 Visit and considered lost to follow-up.*

3) *5900/1801 – Investigator and Medical Monitor recommended withdrawal six days after post-op Day 1 Visit because of anterior chamber inflammation. Test article (i.e. Pred Forte) discontinued, and patient placed on Pred Forte, atropine, and Tobradex.*

4) *5971/2402 – non-compliance with test article noted at Day 8 Visit; Investigator and Medical Monitor recommended withdrawal nine days after Day 8 Visit because of anterior chamber inflammation. Test article (i.e. Pred Forte) discontinued, and patient placed on Pred Forte, homatropine, and oral prednisolone.*

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-Emergent Adverse Events Occurring at an Incidence 1% or Greater

Coded Adverse Event	Durezol N=39 n (%)	Pred Forte N=40 n (%)
Eye Disorders		
Conjunctivitis	3 (7.7)	
Posterior capsule opacification	3 (7.7)	
Corneal oedema	1 (2.6)	1 (2.5)
Corneal opacity	1 (2.6)	1 (2.5)
Eye inflammation		2 (5.0)
Angle closure glaucoma		1 (2.5)
Anterior capsule contraction		1 (2.5)
Anterior chamber fibrin		1 (2.5)
Cataract cortical	1 (2.6)	
Conjunctival haemorrhage		1 (2.5)
Conjunctival hyperaemia		1 (2.5)
Corectopia		1 (2.5)
Dacryostenosis acquired	1 (2.6)	
Eye irritation		1 (2.5)
Eyelid cyst	1 (2.6)	
Eyelid oedema	1 (2.6)	
Hyphaema		1 (2.5)
Lacrimation increased		1 (2.5)
Ocukar hypertension		1 (2.5)
Photophobia	1 (2.6)	
Pupillary disorder		1 (2.5)
Retinal haemorrhage		1 (2.5)
Vitreous haemorrhage		1 (2.5)
Vitritis		1 (2.5)
Gastrointestinal Disorders		
Diarrhoea		1 (2.5)
Teething	1 (2.6)	
General Disorders and Administration Site Conditions		
Pyrexia		2 (5.0)
Eye complication associated with device		1 (2.5)
Immune System Disorders		
Seasonal allergy	1 (2.6)	1 (2.5)
Infections and Infestations		
Nasopharyngitis	5 (12.8)	2 (5.0)
Ear infection	3 (7.7)	1 (2.5)

Coded Adverse Event	**Durezol N=39 n (%)**	**Pred Forte N=40 n (%)**
Bronchiolitis	1 (2.6)	1 (2.5)
Otitis media	1 (2.6)	1 (2.5)
Sinusitis	2 (5.1)	
Bronchitis	1 (2.6)	
Candidiasis		1 (2.5)
Croup infectious		1 (2.5)
Laryngitis		1 (2.5)
Oral candidiasis	1 (2.6)	
Otitis media acute	1 (2.6)	
Pharyngitis streptococcal	1 (2.6)	
Respiratory syncytial virus bronchiolitis		1 (2.5)
Respiratory syncytial virus infection		1 (2.5)
Tonsillitis		1 (2.5)
Urinary tract infection	1 (2.6)	
Viral infection		1 (2.5)
Viral upper respiratory tract infection	1 (2.6)	
Injury, Poisoning and Procedural Complications		
Corneal abrasion	1 (2.6)	
Procedural vomiting	1 (2.6)	
Skin laceration		1 (2.5)
Investigations		
Medical observation	6 (15.4)	10 (25.0)
Intraocular pressure increased	3 (7.7)	1 (2.5)
Oxygen saturation decreased		1 (2.5)
Metabolism and Nutrition Disorders		
Failure to thrive		1 (2.5)
Musculoskeletal and Connective Tissue Disorders		
Joint stiffness		1 (2.5)
Nervous System Disorders		
Hyptonia		2 (5.0)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1 (2.6)	1 (2.5)
Asthma		1 (2.5)
Laryngiospasm	1 (2.6)	
Nasal congestion		1 (2.5)
Rhinorrhoea		1 (2.5)
Skin and Subcutaneous Tissue Disorders		
Rash	1 (2.6)	2 (5.0)
Dermatitis		2 (5.0)
Surgical and Medical Procedures		
Cataract operation	3 (7.7)	6 (15.0)
Dental operation	1 (2.6)	
Strabismus correction		1 (2.5)

Coded Adverse Event	Durezol N=39 n (%)	Pred Forte N=40 n (%)
Vitrectomy	1 (2.6)	

Reviewer's Comments:

The most common adverse drug reactions were medical observation (15.4%), nasopharyngitis (12.8%), conjunctivitis (7.7%), posterior capsule opacification (7.7%), ear infection (7.7%), increased intraocular pressure (7.7%), and cataract operation (7.7%)

7.4.2 Laboratory Findings

Not performed.

7.4.3 Vital Signs

Not performed.

7.4.4 Electrocardiograms (ECGs)

Not performed.

7.4.5 Special Safety Studies/Clinical Trials

Corticosteroids have a known risk of increasing IOP and therefore IOP was monitored.

Table 12.5.3.2.-1:
Intraocular Pressure (IOP) Change from Baseline (mmHg) to Any Visit (Safety Population)

			Durezol (N= 39)		Pred Forte (N= 40)	
			N	(%)	N	(%)
All Patients		**Total**	**17**		**15**	
		> 40 mmHg	0	(0.0)	0	(0.0)
	Increase	**31-40 mmHg**	0	(0.0)	1	(6.7)
		21-30 mmHg	2	(11.8)	1	(6.7)
		11-20 mmHg	3	(17.6)	3	(20.0)
	No Change	**± 10 mmHg**	12	(70.6)	8	(53.3)
		11-20 mmHg	0	(0.0)	2	(13.3)
		21-30 mmHg	0	(0.0)	0	(0.0)
	Decrease	**31-40 mmHg**	0	(0.0)	0	(0.0)
		> 40 mmHg	0	(0.0)	0	(0.0)

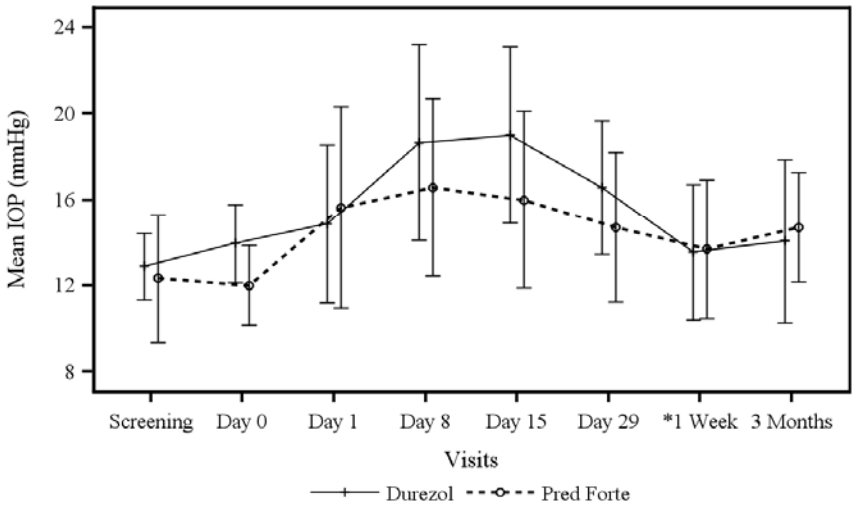
Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
mmHg = millimeters of mercury; Baseline = Screening Visit
Change from baseline = post-baseline visit - baseline
Any visit is representative of the worst case scenario and is defined as the visit with maximum change in IOP in absolute value from baseline to any scheduled or unscheduled visit for the study eye.

Table 12.5.3.2.-2:
Intraocular Pressure (IOP) Change from Baseline (mmHg) to Exit Visit (Safety Population)

		Durezol (N= 39)		Pred Forte (N= 40)	
		N	(%)	N	(%)
All Patients	**Total**	**12**		**12**	
	> 40 mmHg	0	(0.0)	0	(0.0)
Increase	**31-40 mmHg**	0	(0.0)	0	(0.0)
	21-30 mmHg	0	(0.0)	0	(0.0)
	11-20 mmHg	2	(16.7)	2	(16.7)
No Change	**± 10 mmHg**	10	(83.3)	10	(83.3)
	11-20 mmHg	0	(0.0)	0	(0.0)
	21-30 mmHg	0	(0.0)	0	(0.0)
Decrease	**31-40 mmHg**	0	(0.0)	0	(0.0)
	> 40 mmHg	0	(0.0)	0	(0.0)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
mmHg = millimeters of mercury; Baseline = Screening Visit
Change from baseline = post-baseline visit - baseline

Figure 12.3.5.2.-1:
Mean Intraocular Pressure (IOP) (mmHg) with 95% Confidence Interval by Visit – Study Eye
(Safety Population)



* 1 week after last dose

Table 12.5.3.2.-4:
Patients with Intraocular Pressure (IOP) Greater Than or Equal to 40 mmHg at Any Visit
(Safety Population)

	Durezol (N= 39)			Pred Forte (N= 40)		
	Total	N	(%)	Total	N	(%)
All Patients	**29**	1	(3.4)	**33**	1	(3.0)

Durezol = Difluprednate 0.05% Ophthalmic Emulsion
Pred Forte = Prednisolone Acetate 1% Ophthalmic Suspension
mmHg = millimeters of mercury
Any visit is representative of the worst case scenario and is defined as the visit with maximum IOP at any scheduled or unscheduled visit for the study eye.

Reviewer's Comments:

These IOP findings are consistent with the age and general findings in the population of subjects undergoing cataract extraction and were seen in both treatment groups.

7.4.6 Immunogenicity

N/A – Immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

N/A – Durezol does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

Adverse events were analyzed by demographic parameters (age, sex, race/ethnicity, and iris color). Based on these analyses, the events are consistent with the overall safety population.

7.5.4 Drug-Disease Interactions

No drug-disease interaction analyses were performed.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between Durezol and any of the concomitant medications allowed in those studies. Drug interactions, if any, are expected to be similar to those for other corticosteroids. The extremely limited systemic absorption of Durezol would limit the potential for drug interaction.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted

7.6.2 Human Reproduction and Pregnancy Data

No information was obtained on the use of Durezol in these populations.

7.6.3 Pediatrics and Assessment of Effects on Growth

This submission is a pediatric supplement. Study C-10-004 was conducted in response to a Written Request to evaluate the use of Durezol in the treatment of post-operative inflammation following cataract surgery in pediatric patient ages 0 to 3 years. A similar safety profile was observed in pediatric subjects comparing Durezol to Pred Forte.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Durezol is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions / Safety Issues

There was no new information to report.

8 Postmarket Experience

Durezol has been approved in the US only. During the reporting period, there were no marketing authorizations withdrawn or suspended. No marketing authorization was refused, nor was any marketing authorization sought, in any country during the reporting period.

Durezol was launched in the US by Sirion on October 1, 2008, after receiving US FDA marketing approval on June 23, 2008. Alcon subsequently acquired Durezol from Sirion on April 5, 2010. Since that time, an estimate of the number of patients exposed to Durezol has been calculated from prescriptions filled and from physician samples and summarized below.

Table 5.3.6.4–1 Durezol Sales Volume April 5, 2010 to June 30, 2012

Description	Sales and Sample Volume
Total patients exposed to Durezol (estimated)	(b) (4)

Table 5.3.6.5–1 Postmarketing Adverse Drug Experiences Summary

SOC Name	PT Name	AE Count
Cardiac disorders	Cardiac flutter	1
	Palpitations	1
	Tachycardia	1
Cardiac disorders		**3**
Ear and labyrinth disorders	Ear discomfort	1
	Tinnitus	1
Ear and labyrinth disorders		**2**
Eye disorders	Abnormal sensation in eye	2

	Cataract	6
	Cataract cortical	1
	Cataract subcapsular	2
	Conjunctival erosion	2
	Conjunctivitis	1
	Corneal deposits	1
	Corneal disorder	2
	Corneal epithelium defect	1
	Corneal opacity	3
	Corneal perforation	2
	Cyanopsia	1
	Dry eye	2
	Eye discharge	4
	Eye inflammation	1
	Eye irritation	21
	Eye oedema	1
	Eye pain	28
	Eye pruritus	4
	Eye swelling	3
	Eyelid margin crusting	2
	Eyelid oedema	2
	Eyelid ptosis	1
SOC Name	**PT Name**	**AE Count**
	Eyelids pruritus	1
	Foreign body sensation in eyes	8
	Iris disorder	1
	Iris hypopigmentation	1
	Iritis	7
	Keratitis	2
	Keratitis interstitial	1
	Lacrimation increased	7
	Macular oedema	1
	Mydriasis	1
	Necrotising retinitis	1
	Ocular hyperaemia	5
	Photophobia	6
	Punctate keratitis	4
	Pupils unequal	1
	Retinal pigment epitheliopathy	2
	Scleral thinning	1
	Ulcerative keratitis	8
	Vision blurred	17
	Visual acuity reduced	5

	Visual acuity reduced transiently	1
	Visual impairment	3
Eye disorders		**177**
Gastrointestinal disorders	Abdominal discomfort	4
	Diarrhoea	3
	Dry mouth	1
	Dyspepsia	1
	Glossodynia	1
	Hypoaesthesia oral	1
	Lip swelling	1
	Nausea	3
	Oral discomfort	1
	Swollen tongue	1
	Toothache	1
	Vomiting	1
Gastrointestinal disorders		**19**
General disorders and administration site conditions	Condition aggravated	5
	Drug effect prolonged	1
	Drug ineffective	8
	Fatigue	2
	Feeling hot	1
	Influenza like illness	1
	Irritability	1
	Malaise	1
	Medication residue	1
	No adverse event	2
	Oedema peripheral	1
SOC Name	**PT Name**	**AE Count**
	Pyrexia	1
	Rebound effect	3
	Therapeutic product ineffective for unapproved indication	1
	Thirst	2
	Unevaluable event	1
General disorders and administration site conditions		**32**
Immune system disorders	Hypersensitivity	1
Immune system disorders		**1**
Infections and infestations	Endophthalmitis	3
	Enteritis infectious	1
	Keratitis bacterial	1
	Pneumonia	1
Infections and infestations		**6**

Injury, poisoning and procedural complications	Circumstance or information capable of leading to medication error	1
	Corneal abrasion	2
	Drug dispensing error	4
	Expired drug administered	1
	Eye injury	1
	Incorrect dose administered	1
	Injury	1
	Medication error	1
	Suture related complication	1
	Toxic anterior segment syndrome	2
Injury, poisoning and procedural complications		**15**
Investigations	Blood glucose increased	1
	Blood pressure increased	2
	Heart rate increased	5
	International normalised ratio decreased	1
	Intraocular pressure increased	52
	Medical observation	6
	Oxygen saturation decreased	1
	Weight decreased	1
Investigations		**69**
Metabolism and nutrition disorders	Abnormal loss of weight	1
	Dehydration	1
Metabolism and nutrition disorders		**2**
Musculoskeletal and connective tissue disorders	Arthralgia	2
	Back pain	1
	Muscle spasms	1
	Musculoskeletal stiffness	1
	Pain in extremity	1
Musculoskeletal and connective tissue disorders		**6**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung adenocarcinoma	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		**1**
Nervous system disorders Ataxia		1
SOC Name	**PT Name**	**AE Count**
	Cerebrovascular accident	1
	Dizziness	6
	Dysgeusia	2
	Headache	14
	Paraesthesia	1
	Parosmia	1
	Retinal migraine	1
	Sinus headache	1

	Somnolence	2
	Trigeminal neuralgia	1
	Visual field defect	1
Nervous system disorders		**32**
Psychiatric disorders	Anger	1
	Anxiety	1
	Depression	1
	Hallucination	1
	Mood swings	1
Psychiatric disorders		**5**
Renal and urinary disorders	Nocturia	1
Renal and urinary disorders		**1**
Respiratory, thoracic and mediastinal disorders	Cough	1
	Dyspnoea	4
	Epistaxis	3
	Nasal congestion	1
	Nasal septum disorder	1
	Oropharyngeal pain	1
	Throat irritation	1
	Throat tightness	1
	Wheezing	1
Respiratory, thoracic and mediastinal disorders		**14**
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	2
	Blister	1
	Dry skin	1
	Erythema	4
	Hair texture abnormal	2
	Nail discolouration	1
	Pain of skin	1
	Pruritus	4
	Psoriasis	1
	Rash	8
	Rash macular	1
	Skin depigmentation	4
	Skin discolouration	1
	Skin disorder	1
	Skin exfoliation	1
	Skin hyperpigmentation	1
	Skin hypopigmentation	1
SOC Name	**PT Name**	**AE Count**
	Skin wrinkling	2
	Swelling face	4

Skin and subcutaneous tissue disorders		**42**
Surgical and medical procedures	Eye excision	1
	Off label use	2
Surgical and medical procedures		**3**
Vascular disorders	Blood pressure fluctuation	1
	Hot flush	1
	Hypertension	1
Vascular disorders		**3**
Summary		**433**

9 Appendices

9.1 Literature Review/References

An independent literature review did not reveal any additional information relevant to this application.

9.2 Advisory Committee Meeting

An advisory committee meeting was not required for this application.

9.3 Labeling Recommendations

See labeling recommendations which follow in the attached package insert.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LUCIOUS LIM
03/19/2013

WILLIAM M BOYD
03/20/2013