Chambers 530

AUG 11 1997

Medical Officer's Review of NDA 20-841

Original

NDA #20-841 Submission: 3/ 7/97
M.O. Review #1 Review completed: 8/11/97

Generic name: Loteprednol Etabonate Ophthalmic Suspension, 0.5%
Proposed trade name: Lotemax
Chemical name: Chloromethyl-17α-[(ethoxycarbonyl-oxy]-11ß-hydroxy-3-oxoandrosta-1,4-diene-17 carboxylate

Sponsor: Pharmos Corporation
2 Innovation Drive, Suite A
Alachua, FL 32615

Pharmacologic Category: Steroid

Proposed Indication(s): Treatment of inflammation

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Related INDs:
Related NDAs: NDA 20-583 Loteprednol etabonate ophthalmic suspension, 0.5%
NDA 20-803 Loteprednol etabonate ophthalmic suspension, 0.2%

2 Table of Contents

3 **Material Reviewed**

NDA 20-841 Volume 1.1
NDA 20-583 Studies by reference - See Medical Officer's Review (MOR)

4 **Chemistry/Manufacturing Controls** - see Chemistry Review

Raw Material	Quantity mg/mL	% label excess	Range
Loteprednol etabonate	5		
Povidone			
Benzalkonium Chloride			
Edetate disodium			
Glycerin			
Tyloxapol			
Purified water			
Sodium Hydroxide	Adjust pH		
Hydrochloric acid	Adjust pH		

Additional Specifications:
pH
Osmolality 250-310
Particle size

Reviewer's Comments:

5 Animal Pharmacology/Toxicology - See Pharmacologist's Review

No additional issues identified.

6 Clinical Background

See MOR of NDA 20-583

7 Description of Clinical Data Sources

Review Number	Protocol	Indication	Location	Design	Treatment Arms	Number in each arm	Age Range	% (♂/♀) B/W/O	Duration of treatment
8	125	Inflammation following Cataract Surgery	US	Parallel Double masked	Loteprednol Vehicle	109 110	17-79	(25/75) 5/89/6	42 days
9	127	Inflammation following Cataract Surgery	US	Parallel Double masked	Loteprednol Vehicle	102 101	25-95	(42/58) 25/75/1	42 days

APPEARS THIS WAY
ON ORIGINAL

8 Clinical Studies

8.4 Indication # 4 Inflammation following Cataract Surgery

8.4.1 Reviewer's Trial # 8 Sponsor's Protocol # 125

Title: Comparison of Loteprednol Etabonate 0.5% Ophthalmic Suspension and Placebo in the Treatment of Inflammation Following Cataract Surgery with Intraocular Lens Implantation

Study Design: Randomized, double-masked, placebo-controlled, parallel group, multicenter study

Test Drug Schedule: All subjects received either loteprednol etabonate 0.5% ophthalmic suspension (LE) or placebo (vehicle), qid in the operated eye for up to 14 days following surgery.

Inclusion Criteria:

1. Adults, at least 18 years of age
2. Undergone a single procedure, uncomplicated extracapsular cataract extraction or phacoemulsification followed by implanation of a posterior chamber IOL
3. At 22 to 34 hours (Visit 1) following surgery, the post-operative eye was to have a combined anterior chamber rating of cell and flare ≥3.

Exclusion Criteria:

1. Monocular potential
2. Females of childbearing potential not using adequate birth control
3. Intraocular pressure that is greater than 30 mmHg in the post-operative treated eye or any type of glaucoma.

Primary Efficacy Criteria:

Reduction of anterior chamber inflammation (ACI, the sum of cell and flare=0) in the post-operative eye

Visit:	Screen	Surgery	1	2	3	4	5
Day:	-14 to -1	0	1	3	8	15	17
Procedure							
Informed Consent	X						
Inclusion/Exclusion	X		X				
Demographics, History	X						
Medication History	X						
Pregnancy Test	X					X	
Cataract Surgery		X					
Cell and Flare	X		X	X	X	X	X
Visual Acuity	X		X	X	X	X	X
Ocular Symptoms	X		X	X	X	X	X
Slit-Lamp Biomicroscopy	X		X	X	X	X	X
Intraocular Pressure (both eyes)	X		X	X	X	X	X
Funduscopic Exam	X					X	
Issue Masked Medication			X		X		
Recover Medication					X	X	X
Issue Tobramycin			X				
Recover Tobramycin					X		
Investigator's Global Assessment						X	
Complete End of Treatment Form							X
Dismiss Patient							X

Measurement scales: Primary and secondary outcomes

Cell: Determined using a slit beam at 1 mm height by 1 mm width with maximum luminance of the Haag-Streit (or equivalent) slit lamp. Pigment cells and red blood cells were to be ignored.

0	Less than or equal to 5 cells
1	6 to 10 cells
2	11 to 20 cells
3	21 to 40 cells
4	> 40 cells
5	Hypopyon

Flare: Determined using the widest slit beam at 1 mm height with maximum luminance of the Haag-Streit (or equivalent) slit lamp

0	None to trace
1	Mild (clearly noticeable, visible)
2	Moderate (without plastic aqueous)
3	Marked (with plastic aqueous)
4	Severe (with fibrin deposits and/or clots)

Anterior chamber inflammation (ACI): Sum of cell and flare score.

Investigator's Global Assessment (for entire study):

0	Fully Controlled: Inflammation is suppressed or cured, virtually no signs or symptoms
1	Reasonably Controlled: Inflammation is diminished, moderate decrease in signs or symptoms
2	Slightly controlled: Small decrease in signs and symptoms
3	Unchanged: No response or overall change in signs and symptoms
4	Worse: Overall increase in signs and symptoms

Supportive measures were:

ocular signs	(chemosis, erythema, palpebral injection, bulbar injection, corneal edema, hyphema, and ciliary flush) and
symptoms	(pain, photophobia, itching, tearing, dryness, discharge, and discomfort)

Visit Day Ranges

Visit	Nominal day	Accepted Range
1	Day 1	Day 1
2	Day 3	Days 2 to 6
3	Day 8	Days 7 to 12
4	Day 15	Days 13 to 20

Demographics		LE	Placebo	p-value
Age				
	Mean	71	70	.33
	Range	40-89	38-92	
Gender				
	Male	48 (44%)	39 (35%)	.15
	Female	61 (56%)	74 (65%)	
Race				
	Caucasian	98 (90%)	98 (87%)	.46
	Hispanic	5 (5%)	8 (7%)	
	Black	3 (3%)	7 (6%)	
	Other	3 (3%)	0 (0%)	
Iris Color				
	Light	64 (59%)	65 (58%)	.86
	Dark	45 (41%)	48 (42%)	
Surgery type				
	Phacoemulsification	99 (91%)	105 (93%)	.57
	ECCE	10 (9%)	8 (7%)	
Lens type				
	Foldable	48 (44%)	51 (45%)	.87
	Non-foldable	61 (56%)	62 (55%)	

Investigators

			Loteprednol	Vehicle
John Alpar, MD	Amarillo, TX	141	5	3
John Bokosky, M.D.	San Diego, CA	207	4	4
G. Richard Cohen, M.D.	Boca Raton, FL	187	12	11
Peter Donshik, M.D.	West Hartford, CT	202	3	2
Harold Helms, M.D.	Birmingham, AL	206	7	6
Barry Horwitz, M.D.	Houston, TX	122	10	10
Robert Lehman, M.D.	Nacogdoches, TX	208	10	10
Marian Macsai, M.D.	Morgantown, WV	203	2	2
Randall Olson, M.D.	Salt Lake City, UT	210	3	6
James Pickett, M.D.	San Marcos, TX	145	8	12
Michael Raizmann, M.D.	Boston, MA	163	1	1
John Stamler, M.D.	Iowa City, IA	204	5	5
Robert Stewart, M.D.	Houston, TX	132	12	16
James Syverud, M.D.	Appleton, WI	205	7	6
Joseph Tauber, M.D.	Kansas City, MO	168	6	6
Stefan Trocme, M.D.	Galveston, TX	169	5	7
Mitchell Wong, M.D.	Austin, TX	209	10	10

TERMINATED: ADVERSE EVENT:

132:5278	LOTEPREDNOL (77/F/CAUC)	15JUL96 DAY 4	INCREASED INFLAMMATION AND DISCOMFORT; EYE PAIN
169:5338	LOTEPREDNOL (66/M/BLACK)	27AUG96 DAY 15	CONGESTIVE HEART FAILURE
132:5274	PLACEBO (68/F/CAUC)	23JUN96 DAY 10	SWOLLEN LIDS; ITCHING RED EYE
132:5561	PLACEBO (73/F/CAUC)	05AUG96 DAY 4	EYE MATTED SHUT; EYE PAIN
205:5251	PLACEBO (79/F/CAUC)	05SEP96 DAY 9	EYE DRY ACHY AND BURNING

LOST TO FOLLOW-UP:

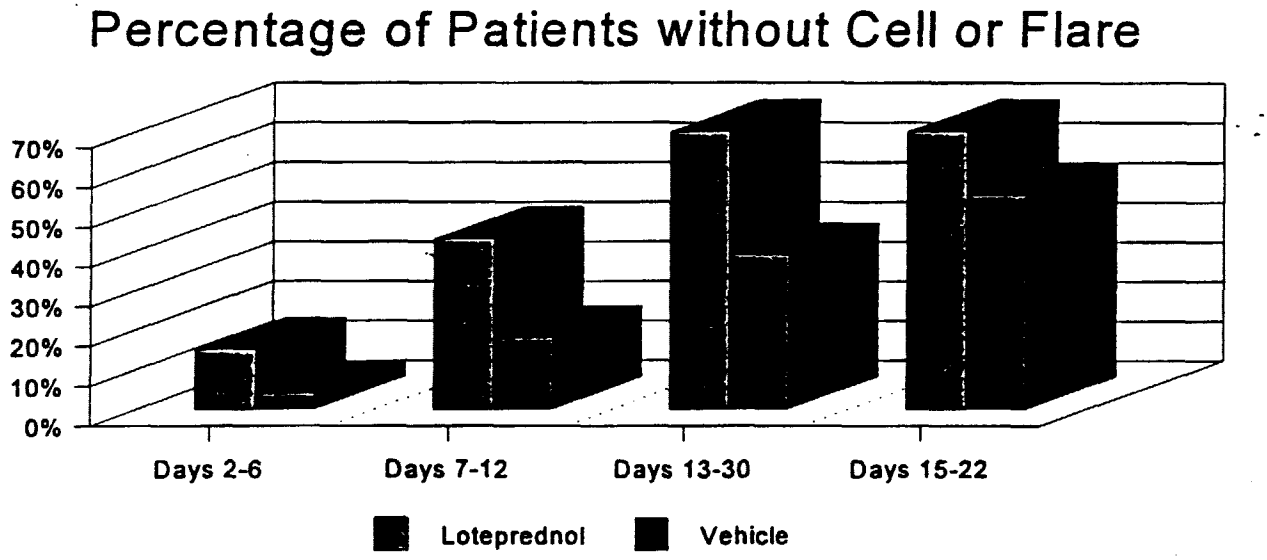
132:5272	PLACEBO (76/M/CAUC)	14JUN96 DAY 1	LOST TO FOLLOW-UP

DISCONTINUATION (ADMINISTRATIVE):

132:5281	LOTEPREDNOL (70/F/CAUC)	15JUL96 DAY 4	D/C PT DIDN'T WANT TO CONTINUE
202:5091	LOTEPREDNOL (73/F/CAUC)	03SEP96 DAY 8	D/C CORTICAL MATERIAL
204:5186	LOTEPREDNOL (70/F/CAUC)	13JUN96 DAY 8	D/C USE OF DISALLOWED MED (INFLAMASE FORTE GTT)
132:5280	PLACEBO (66/F/HISPN)	15JUL96 DAY 4	D/C PT DIDN'T RETURN FOR VISIT #3
145:5391	PLACEBO (76/M/CAUC)	23MAY96 DAY 3	D/C INADVERTENT TEAR IN POST CAP. NOT SEEN UNTIL THIS VISIT
145:5392	PLACEBO (67/M/HISPN)	23JUN96 DAY 32	D/C ACCIDENTALLY DISPENSED DRUG WHEN PT DID NOT QUALIFY
208:5424	PLACEBO (87/M/CAUC)	02JUL96 DAY 8	D/C FAMILY CONCERN OF PTS PHYSICAL EXERTION FOR OFFICE VISITS

Anterior chamber inflammation score: Percent response at each visit

Visit	Treatment Group	N at risk	Resolved N	%		95% C.I.	p value
2	LE	109	16	15%			
	Placebo	111	4	4%	11%	(-14%, 36%)	**0.003**
3	LE	102	44	43%			
	Placebo	92	17	18%	25%	(1%, 48%)	**<0.001**
4	LE	98	69	70%			
	Placebo	76	30	39%	31%	(10%, 51%)	**< 0.001**
5	LE	94	66	70%			
	Placebo	76	37	54%	17%	(-3%, 36%)	**0.02**



Reviewer's Comments: *Inflammation as measured by cell and flare cleared in a significantly larger percentage of patients in the loteprednol group.*

Treatment Failures – Patients who discontinued early for inadequate control or who had an increase of 3 or more in their ACI score.

LE	103	94%	6	6%			
Placebo	79	70%	34	30%	25%	(-34%,-15%)	<.001

Investigator's Global Assessment

	Fully Controlled	Reasonable Controlled	Slight Improvement	Unchanged	Worse
LE (n=109)	46	40	12	3	8
Placebo (n=111)	16	28	16	17	34

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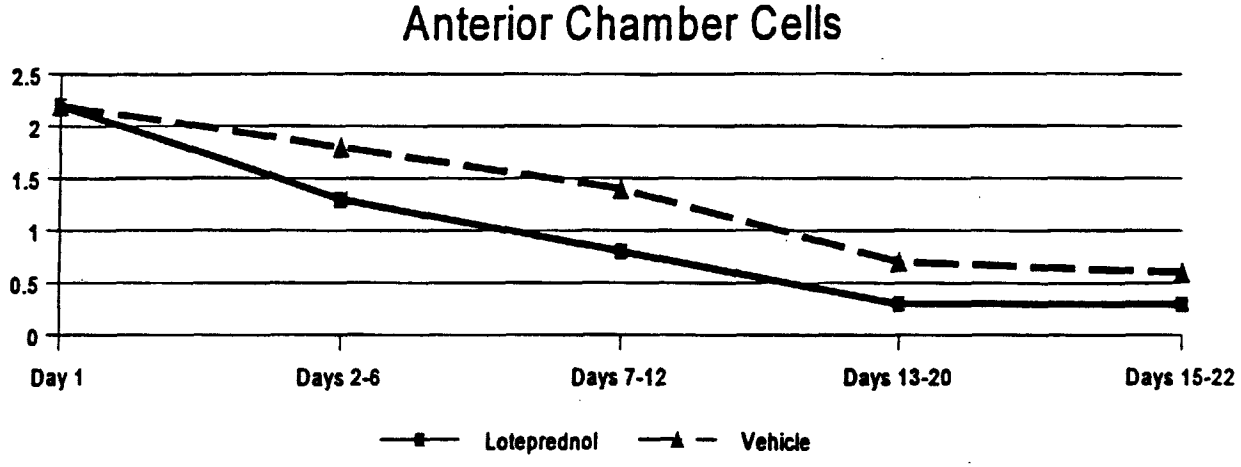
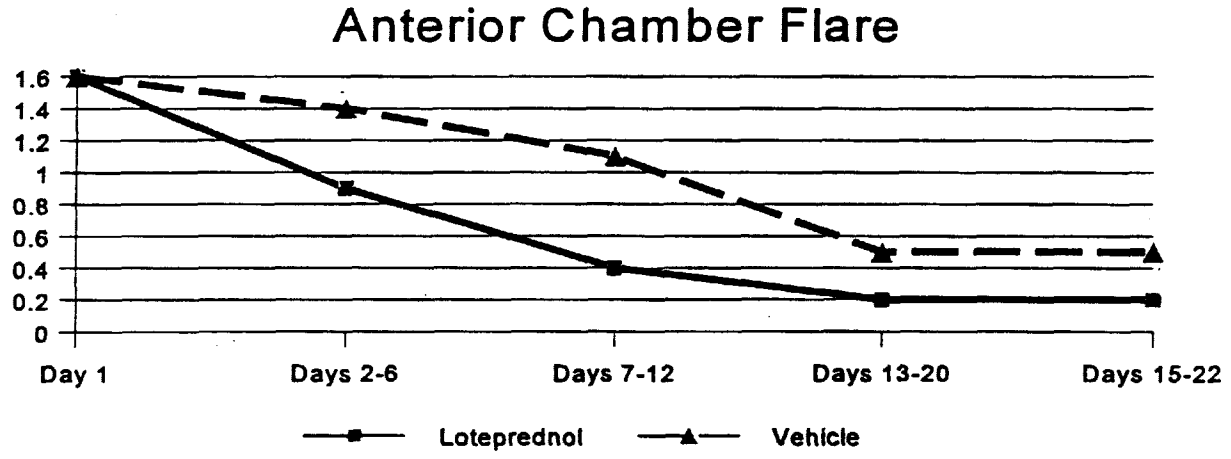


Loteprednol	2.2	1.3	0.8	0.3	0.3
Vehicle	2.2	1.8	1.4	0.7	0.6



Loteprednol	1.6	0.9	0.4	0.2	0.2
Vehicle	1.6	1.4	1.1	0.5	0.5

Reviewer's Comments:

There are reduced cell and flare scores in the loteprednol group, however, the difference between groups is small and not clinically significant.

Supportive signs: Percent responding and change at final visit

	N with score >0	Resolved	Treatment effect	Baseline	Final	Change
Chemosis:						
LE	36	32 (89%)	19% (-2%, 41%)	1.3	0.2	-1.1
Placebo	36	25 (69%)	p = 0.065	1.3	0.6	-0.7
Erythema:						
LE	60	52 (87%)	28% (9%, 46%)	1.2	0.2	-1.0
Placebo	61	36 (59%)	p <0.001	1.2	0.5	-0.7
Palpebral injection						
LE	47	40 (85%)	26% (5%, 47%)	1.4	0.3	-1.1
Placebo	49	29 (59%)	p < 0.001	1.3	0.7	-0.7
Bulbar injection:						
LE	98	68 (69%)	42% (22%, 62%)	1.5	0.4	-1.1
Placebo	102	28 (27%)	p< 0.001	1.5	1.1	-0.4
Corneal edema:						
LE	55	46 (84%)	17% (-2%, 36%)	1.3	0.2	-1.1
Placebo	51	34 (67%)	p = 0.051	1.4	0.5	-0.9
Hyphema:						
LE	5	5 (100%)	50% (-19%,100%)	1.0	0.0	-1.0
Placebo	4	2 (50%)	p = 0.049	1.0	0.5	-0.5
Ciliary flush						
LE	52	47 (90%)	35% (15%, 55%)	1.0	0.1	-0.9
Placebo	54	30 (56%)	p < 0.001	1.0	0.4	-0.6

Reviewer's Comments:

The percentage of resolved signs all support the loteprednol group.

APPEARS THIS WAY
ON ORIGINAL

Supportive symptoms: Percent responding and change at final visit

Pain:						
LE	33	28 (85%)	31% (6,%, 56%)	1.3	0.2	-1.2
Placebo	41	22 (54%)	p = 0.003	1.2	0.8	-0.3
Photophobia:						
LE	43	28 (65%)	24% (-6, 53%)	1.2	0.4	-0.8
Placebo	41	17 (41%)	p = 0.020	1.3	1.0	-0.3
Itching:						
LE	25	19 (76%)	5% (-23%, 32%)	1.2	0.2	-1.0
Placebo	28	20 (71%)	p = 0.138	1.1	0.5	-0.6
Tearing:						
LE	32	27 (84%)	24% (-1%, 49%)	1.2	0.2	-0.9
Placebo	35	21 (60%)	p = 0.041	1.1	0.6	-0.5
Dryness:						
LE	5	5 (100%)	11% (-11, 33%)	1.0	0.0	-1.0
Placebo	9	8 (89%)	p = 0.317	1.0	0.1	-0.9
Discharge:						
LE	12	11 (92%)	8% (-20%. 37%)	1.2	0.1	-1.1
Placebo	12	10 (83%)	p = 0.705	1.1	0.2	-0.9
Discomfort:						
LE	43	33 (77%)	43% (16%, 69%)	1.2	0.3	-0.9
Placebo	50	17 (34%)	p < 0.001	1.1	1.0	-0.2

Reviewer's Comments:

The percentage of resolved symptoms all support the loteprednol group.

Intraocular Pressure –

Treatment	Elevation in IOP (mmHg)	Day 2-6	Days 7-12	Days 13+
LE	≥ 10	2	1	0
	6-9	1	5	1
	<6	107	97	97
Vehicle	≥ 10	0	0	0
	6-9	3	1	0
	<6	111	91	75

Reviewer's Comments:

There were more elevations in IOP in the loteprednol group.

8.4.2 Reviewer's Trial # 9 **Sponsor's Protocol # 127**

Title:	Comparison of Loteprednol Etabonate 0.5% Ophthalmic Suspension and Placebo in the Treatment of Inflammation following Cataract Surgery with Intraocular Lens Implantation
Study Design:	Randomized, double-masked, placebo controlled, parallel group, multicenter study (same as Study #8)
Test Drug Schedule:	All subjects received either loteprednol etabonate 0.5% ophthalmic suspension (LE) or placebo (vehicle), qid in the operated eye for up to 14 days following surgery (same as Study #8)
Inclusion Criteria:	Same as Study #8
Exclusion Criteria:	Same as Study #8
Primary Efficacy Criteria:	Same as Study #8
Schedule:	Same as Study #8
Measurement scales:	Same as Study #8
Visit Day Ranges	Same as Study #8

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Events > 2%	Loteprednol (n=110)	Vehicle (n=117)
Epiphora	14%	27%
Abnormal vision	14%	25%
Eye Discomfort	13%	26%
Photophobia	11%	26%
Eye Itching	10%	17%
Dry Eyes	6%	11%
Eye Pain	5%	32%
Headache	5%	7%
Anterior Chamber Cells	4%	12%
Ciliary flush	3%	9%
Eye discharge	3%	7%
Injection	3%	17%
Foreign body sensation	3%	6%
Iritis	3%	4%

Reviewer's Comments: *Evaluation of these reports is difficult because many are related to the surgical procedure and there is considerable overlap between the events. For example, anterior chamber cells, iritis and uveitis can all be the same event.*

Reviewer's Summary:

This study demonstrates that inflammation as measured by cell and flare cleared in a significantly larger percentage of patients in the loteprednol group than the vehicle group.

Demographics		LE	Placebo	p-value
Age				
	Mean	69	72	.10
	Range	25-95	47-99	
Gender				
	Male	43 (42%)	41 (41%)	.87
	Female	59 (58%)	59 (59%)	
Race				
	Caucasian	75 (74%)	70 (70%)	.58
	Hispanic	1 (1%)	4 (4%)	
	Black	25 (25%)	26 (26%)	
	Other	1 (1%)	0 (0%)	
Iris Color				
	Light	50 (49%)	49 (49%)	.99
	Dark	52 (51%)	51 (51%)	
Surgery type				
	Phacoemulsification	81 (79%)	79 (79%)	.94
	ECCE	21 (21%)	21 (21%)	
Lens type				
	Foldable	67 (66%)	68 (68%)	.73
	Non-foldable	35 (34%)	32 (32%)	

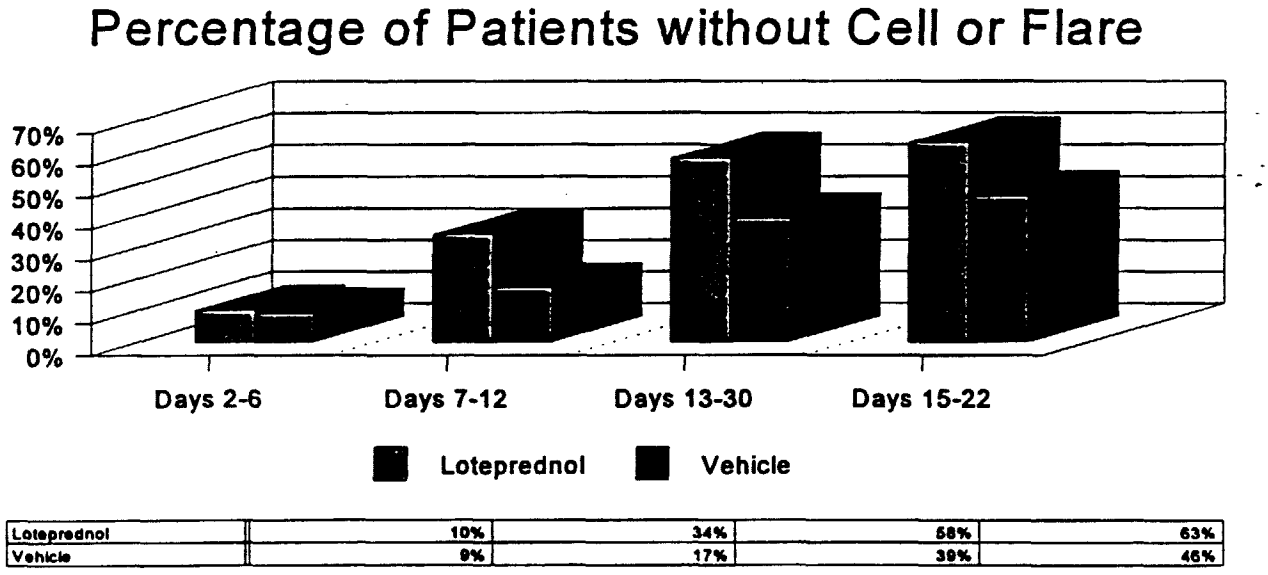
Investigators

		Inv #	Loteprednol	Vehicle
Cecil Beehler, MD	Fort Meyers, FL	211	5	6
Bruce Bodner, M.D.	Norfolk, VA	197	2	2
Bradley Bowman, M.D.	Dallas, TX	194	3	3
David Cooke, M.D.	St. Joseph, MI	212	4	4
J. Luther Crabb, M.D.	Memphis, TN	201	18	18
L. Raymond DeBarge,M.D.	Fort Oglethorpe, GA	183	8	7
Eric Donnenfeld, M.D.	Rockville Centre, NY	220	4	4
Marcel Estopinal, M.D.	Nashville, TN	193	7	9
Kenneth Fox, M.D.	Fredericksburg, VA	151	3	4
Peter Kastl, M.D., Ph.D.	New Orleans, LA	199	2	3
Kenneth Olander, M.D., Ph.D.	Milwaukee, WI	184	10	10
Elizabeth, Sharpe, M.D.	Mt. Pleasant, SC	213	3	2
Robert Shofner, M.D.	Nashville, TN	192	4	4
Janis Stahl, M.D.	Golden, CO	196	3	2
Dara Stevenson, M.D.	New Orleans, LA	214	11	10
William Stewart, M.D.	Charleston, SC	109	4	3
Tom Walters, M.D.	Austin, TX	107	11	10

INV:PAT TREATMENT - AGE/SEX/RACE	DATE	========= DISCONTINUED ========= REASON
TERMINATED: ADVERSE EVENT:		
199:7243 PLACEBO (69/F/BLACK)	28AUG96 DAY 8	CORNEAL EDEMA
211:7310 PLACEBO (68/M/CAUC)	12SEP96 DAY 2	TOXIC KERATITIS
212:7332 PLACEBO (68/F/CAUC)	16AUG96 DAY 11	ELEVATED IOP
214:7392 PLACEBO (86/M/CAUC)	14JUN96 DAY 2	TEARING, BLURRED VISION, PAIN, PHOTOPHOBIA
LOST TO FOLLOW-UP:		
220:7587 PLACEBO (83/M/CAUC)	25SEP96 DAY 5	
DISCONTINUATION (ADMINISTRATIVE):		
107:7428 LOTEPREDNOL (60/F/CAUC)	17JUL96 DAY 15	PT STARTED CORTICOSTEROID THERAPY PRIOR TO V4
213:7364 LOTEPREDNOL (83/M/CAUC)	20CT96 DAY 19	MISSED VISIT 3 & LATE FOR VISIT 4
211:7311 PLACEBO (69/F/CAUC)	13SEP96 DAY 3	CATARACT SURGERY OS SCHEDULED WHILE PT STILL ON STUDY GTTS
220:7584 PLACEBO (89/F/CAUC)	16SEP96 DAY 3	PT ENROLLED WITH EXCLUSION CRITERIA #9, BY ERROR.

Anterior chamber inflammation score: Percent response at each visit

Visit	Treatment Group	N at risk	Resolved N	%		95% C.I.	p value
2	LE	102	10	10%			
	Placebo	100	9	9%	1%	(-25%, 27%)	**0.83**
3	LE	96	33	34%			
	Placebo	83	14	17%	18%	(-8%,43%)	**0.005**
4	LE	93	54	58%			
	Placebo	70	27	39%	19%	(-3%, 42%)	**0.008**
5	LE	93	59	63%			
	Placebo	63	29	46%	17%	(-5%, 39%)	**0.028**



Reviewer's Comments: *Inflammation as measured by cell and flare cleared in a significantly larger percentage of patients in the loteprednol group.*

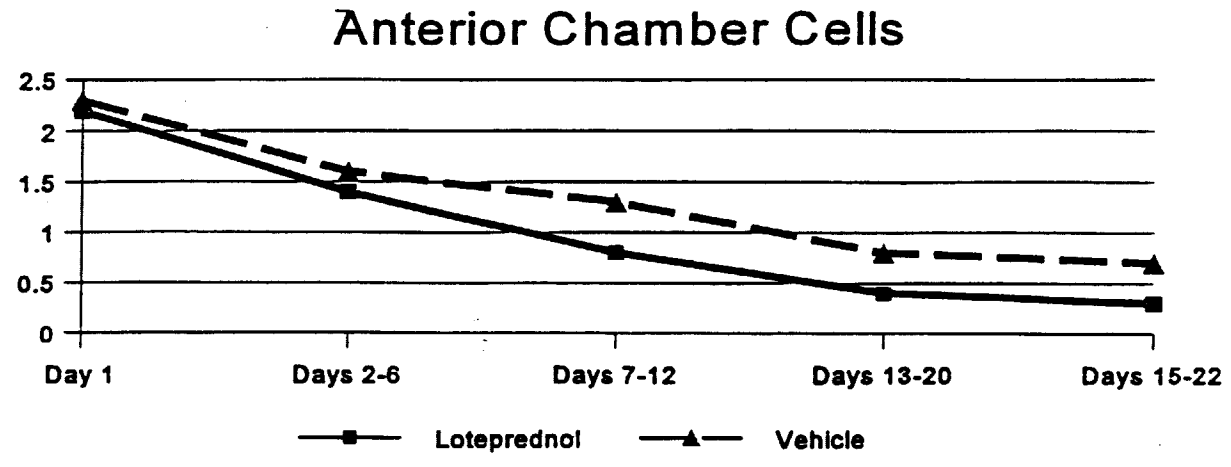
Treatment Failures Patients who discontinued early for inadequate control or who had an increase of 3 or more in their ACI score.

	No		Yes			
LE	97	95%	5	5%		
Placebo	75	75%	25	25%	20%	(-30%,-11%) <.001

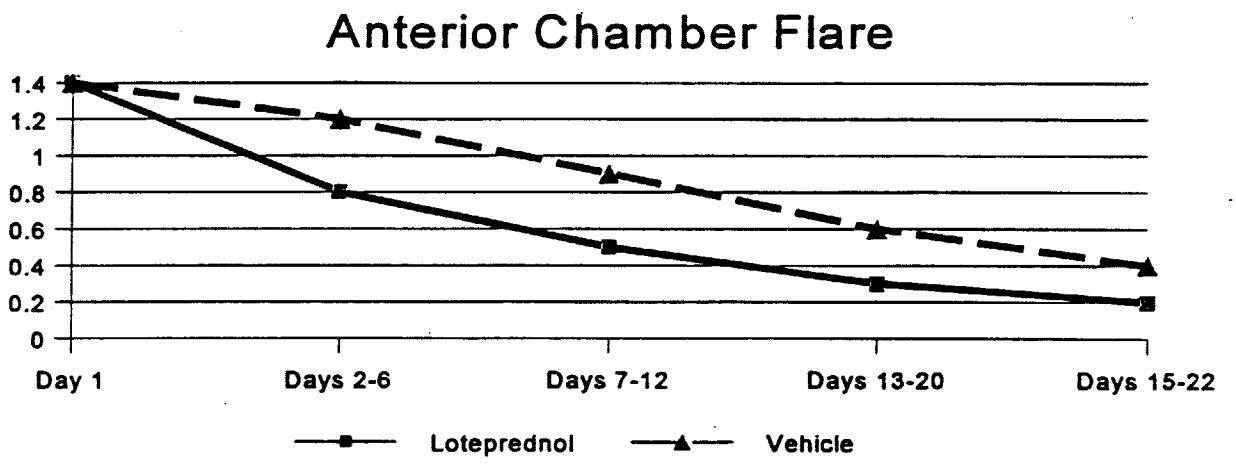
Investigator's Global Assessment

	Fully Controlled	Reasonable Controlled	Slight Improvement	Unchanged	Worse
LE (n=102)	49	42	2	3	6
Placebo (n=98)	19	29	12	8	30

Mean LE	0.8	
Mean Placebo	2.0	p<.001



Loteprednol	2.2	1.4	0.8	0.4	0.3
Vehicle	2.3	1.6	1.3	0.8	0.7



Loteprednol	1.4	0.8	0.5	0.3	0.2
Vehicle	1.4	1.2	0.9	0.6	0.4

Reviewer's Comments:

There are reduced cell and flare scores in the loteprednol group, however, the difference between groups is small and not clinically significant.

Supportive signs: Percent responding and change at final visit

	N with score >0	Resolved	Treatment effect	Baseline	Final	Change
Chemosis:						
LE	20	17 (85%)	26% (-9%, 61%),	1.1	0.2	-0.9
Placebo	17	10 (59%)	p = 0.017	1.1	0.5	-0.5
Erythema:						
LE	29	21 (72%)	26% (-6%, 57%),	1.1	0.3	-0.7
Placebo	32	15 (47%)	p= 0.018	1.2	0.6	-0.5
Palpebral injection						
LE	21	15 (71%)	12% (-21%, 45%),	1.1	0.3	-0.8
Placebo	27	16 (59%)	p = 0.338	1.3	0.6	-0.6
Bulbar injection:						
LE	77	53 (69%)	36%(14%, 58%),	1.2	0.4	-0.8
Placebo	76	25 (33%)	p <.001	1.2	1.0	-0.2
Corneal edema:						
LE	26	20 (77%)	15% (-11%, 42%),	1.3	0.3	-1.0
Placebo	39	24 (62%)	p = 0.592	1.2	0.4	-0.7
Hyphema:						
LE	0	N/A	N/A	N/A	N/A	N/A
Placebo	2	1 (50%)		1.0	0.5	-0.5
Ciliary flush						
LE	29	27 (93%)	43% (14%, 72%).	1.0	0.1	-0.9
Placebo	26	13 (50%)	p = 0.001	1.0	0.5	-0.5

Reviewer's Comments:

The percentage of resolved signs all support the loteprednol group.

Supportive symptoms: Percent responding and change at final visit

Pain:						
LE	24	20 (83%)	24% (-2,%, 50%)	1.4	0.4	-1.0
Placebo	37	22 (59%)	p = 0.018	1.1	0.6	-0.5
Photophobia:						
LE	33	22 (67%)	22% (-9, 54%)	1.4	0.6	-0.8
Placebo	36	16 (44%)	p = 0.031	1.3	1.0	-0.3
Itching:						
LE	22	16 (73%)	10% (-25%, 45%)	1.1	0.4	-0.8
Placebo	19	12 (63%)	p = 0.603 ✓	1.0	0.4	-0.6
Tearing:						
LE	35	28 (84%)	25% (-3%, 53%)	1.4	0.3	-1.0
Placebo	31	17 (60%)	p = 0.028	1.4	0.7	-0.6
Dryness:						
LE	7	6 (86%)	-14% (-42, 14%)	1.0	0.1	-0.9
Placebo	3	3 (100%)	p =N/A	1.0	0.0	-1.0
Discharge:						
LE	15	14 (93%)	2% (-19%. 23%),	1.0	0.1	-0.9 ✓
Placebo	12	11 (92%)	p = 0.414	1.0	0.1	-0.9
Discomfort:						
LE	34	28 (82%)	30% (4%, 56%),	1.3	0.3	-1.0
Placebo	38	20 (53%)	p = 0.006	1.1	0.7	-0.4

Reviewer's Comments:

The percentage of resolved signs all support the loteprednol group.

Intraocular Pressure –

Treatment	Elevation in IOP (mmHg)	Day 2-6	Days 7-12	Days 13+
LE	≥ 10	0	0	0
	6-9	0	2	1
	<6	102	94	93
Vehicle	≥ 10	0	1	0
	6-9	2	1	1
	<6	98	82	69

Reviewer's Comments:

The number of elevations in IOP is approximately equal in each group.

Events > 2%	Loteprednol (n=102)	Vehicle (n=101)
Eye Discomfort	14%	19%
Eye Itching	13%	13%
Eye Pain	12%	15%
Photophobia	11%	29%
Epiphora	10%	17%
Injection	8%	30%
Dry Eyes	6%	5%
Anterior Chamber Cells	4%	6%
Eyelid Erythema	4%	9%
Ciliary flush	3%	6%
Corneal Edema	3%	8%
Eye discharge	2%	6%

Reviewer's Comments: *Evaluation of these reports is difficult because many are related to the surgical procedure and there is considerable overlap between the events. For example, anterior chamber cells, iritis and uveitis can all be the same event.*

Reviewer's Summary:

This study demonstrates that inflammation as measured by cell and flare cleared in a significantly larger percentage of patients in the loteprednol group than the vehicle group.

Summary of Efficacy: -

These studies demonstrate that patients treated with loteprednol had their inflammation, as measured by cell and flare, cleared more frequently than patients treated with vehicle.

Summary of Safety:

Intraocular pressure was more frequently elevated in patients treated with loteprednol.

Evaluation of adverse reaction reports are difficult because many are related to the surgical procedure and there is considerable overlap between the events. For example, anterior chamber cells, iritis and uveitis can all be the same event.

11 Labeling Review

Reviewer recommended additions are identified by [redacted] *Reviewer recommended deletions are identified by* ~~*single strikeout lines.*~~ *This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.*

Two different package inserts have been proposed. One utilizes the class labeling for steroids together with a clear notation that the product is not as effective as prednisolone acetate. The second insert does not include the uveitis indication and therefore does not include the comparative statements to prednisolone.

16 pages
REDACTED
DRAFT
LABELING

12 Conclusions

a. [redacted]

b. [redacted]

c. The submitted studies in NDA 20-841 demonstrate safety and effectiveness for the treatment of post-cataract inflammation.

13 Recommendations

1. Following resolution of the chemistry/manufacturing issues and labeling issues, NDA 20-841 is recommended for approval for the treatment of giant papillary conjunctivitis and post-operative inflammation following cataract surgery. Approval for the steroid class indication is **not recommended**, unless it is accompanied by clear statements that the product is not as effective as other steroids (prednisolone acetate suspension, 1%) and that patients in whom a stronger steroid is needed should not use this product.

2. The applicant should submit revised labeling consistent with the recommendations in this review.

3. [redacted]

4.

/S/
Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-841
NDA 20-583
HFD-550
HFD-340/Carreras
HFD-550/PM/Holmes
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

550
Loteprednol

FEB 5 1998

Medical Officer's Review of NDA 20-583
Amendment

NDA #20-583
NDA #20-841
M.O. Review #4

Submit Date: 1/21/98
Review completed: 2/ 5/98

Generic name:	Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trade name:	Lotemax
Chemical name:	Chloromethyl-17α-[(ethoxycarbonyl-oxy]-11ß-hydroxy-3-oxoandrosta-1,4-diene-17 carboxylate
Sponsor:	Pharmos Corporation 33 Wood Ave, South, Suite 466 Iselin, NJ 08830
Agent:	Bausch & Lomb Pharmaceuticals 8500 Hidden River Parkway Tampa, FL 33637 (813) 975-7727
Pharmacologic Category:	Steroid
Proposed Indication(s):	Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.
Dosage Form and Route of Administration:	Ophthalmic suspension for topical ocular administration
NDA Drug Classification:	1S

Labeling Review

Reviewer recommended additions are identified by shading. Reviewer recommended additions are identified by redlining and deletions are identified by ~~a strikeout line.~~ This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

This review is based on discussions with the applicant, with the understanding that the Office of Drug Evaluation V has not yet commented on the labeling and will have the final authority over the labeling.

6 pages
REDACTED

DRAFT
LABELING

13 Recommendations

NDAs 20-583 and 20-841 are recommended for approval for the treatment of steroid responsive disease and inflammation following cataract surgery with the labeling identified in this review. Approval for the steroid class indication is **recommended**, only with the language included in the above proposed labeling that the product is not as effective as prednisolone acetate suspension, 1% and that patients in whom a stronger steroid is needed should not use this product.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-550/PM/LoBianco
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

Medical Officer's Review of NDA 20-583 & 20-841
Amendment

NDA #20-583
NDA #20-841
M.O. Review #5

Submit Dates: 12/10&11/97, 1/14&21/98
Review completed: 2/23/98

Generic name: Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trademark: Lotemax

Sponsor: Pharmos Corporation
33 Wood Ave, South, Suite 466
Iselin, NJ 08830

Agent: Bausch & Lomb Pharmaceuticals
8500 Hidden River Parkway
Tampa, FL 33637
(813) 975-7727

Pharmacologic Category: Steroid

Proposed Indication(s): Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Labeling Review

Reviewer recommended additions are identified by shading. Reviewer recommended additions are identified by redlining and deletions are identified by ~~a strikeout line.~~ This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

This review is based on discussions with the applicant, with the understanding that the Office of Drug Evaluation V has not yet commented on the labeling and will have the final authority over the labeling.

Related Reviews: Pharm/Tox Review dated 4/25/97
Chemistry/Manufacturing Review dated 2/98

11 pages
REDACTED

DRAFT
LABELING

Medical Officer's Review of NDA 20-583 & 20-841
Amendment & Safety Update

NDA #20-583
NDA #20-841
M.O. Review #6

Submit Date: 2/24/98
Review completed: 2/25/98

Generic name: Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trademark: Lotemax

Sponsor: Pharmos Corporation
33 Wood Ave, South, Suite 466
Iselin, NJ 08830

Agent: Bausch & Lomb Pharmaceuticals
8500 Hidden River Parkway
Tampa, FL 33637
(813) 975-7727

Pharmacologic Category: Steroid

Proposed Indication(s):

LOTEMAX is 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.

LOTEMAX was less effective than prednisolone acetate 1% in two 28-day controlled clinical studies in acute anterior uveitis, where 72% of patients with LOTEMAX experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%. LOTEMAX should not be used in patients who require a more potent corticosteroid for this indication.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

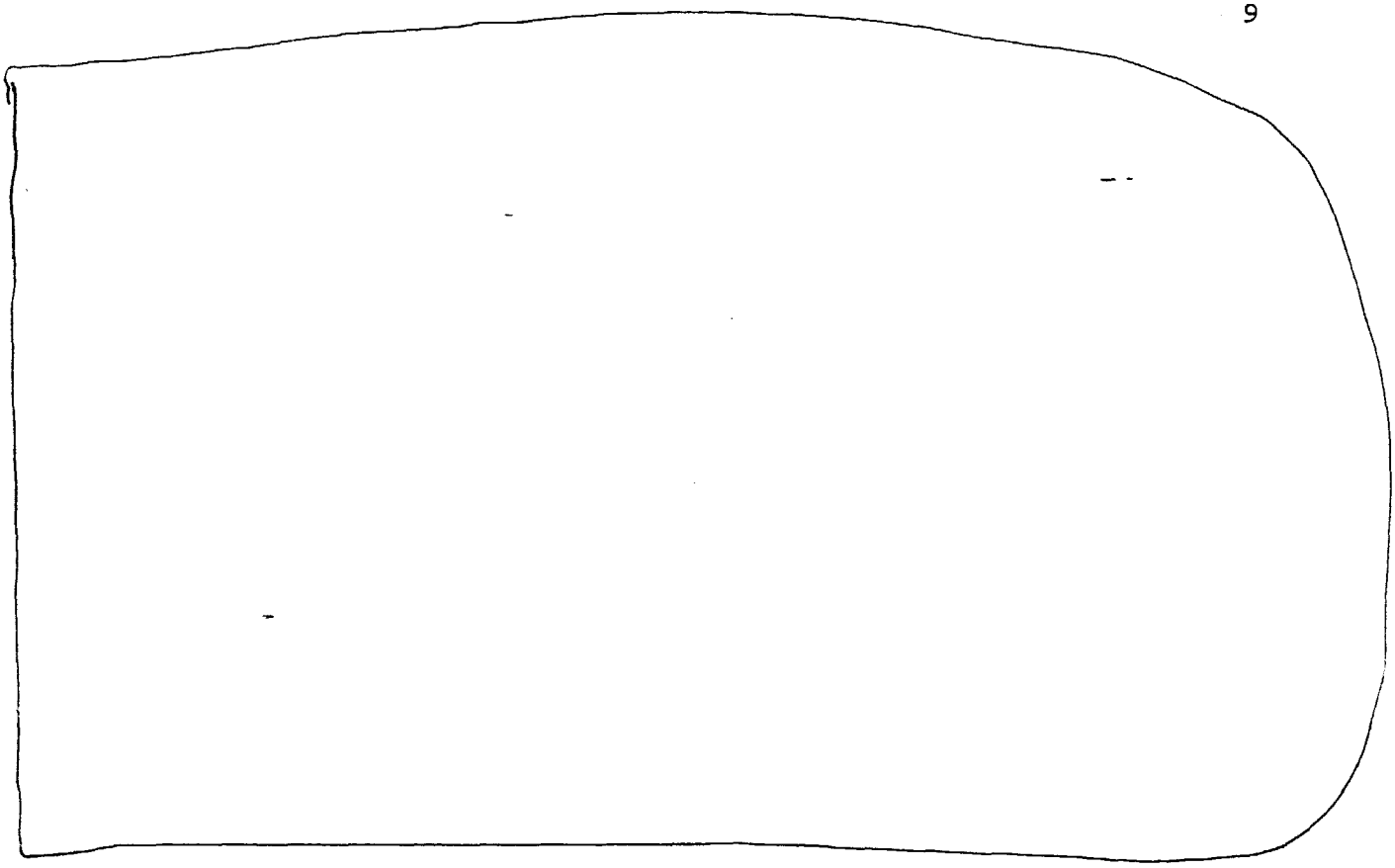
Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Submitted: Revised labeling, safety update and Phase 4 commitments.

10 pages redacted

DRAFT LABELING



Reviewer's Comments: *Acceptable.*

Safety update: No new safety information is available for this product.

Reviewer's Comments: *Acceptable.*

APPEARS THIS WAY
ON ORIGINAL

Recommendation:

NDA 20-583 and NDA 20-841, Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% is recommended for approval.

/S/
Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-550/PM/LoBianco
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers