Emergent or Worsening Ocular Symptoms

Experience	Combination (N=151) N %	Concomitant (N=148) N %
Any ocular symptoms	52 (34)	50 (34)
Blurred vision	10 (7)	10 (7)
Burning eye	19 (13)	13 (9)
Dryness of eye	2 (1)	1 (1)
Eye pain[a]	0 (0)	6 (4)
Foreign body sensation	3 (2)	5 (3)
Itching, eye	13 (9)	9 (6)
Pain/discomfort, eyelid	3 (2)	2 (1)
Photophobia	1 (1)	1 (1)
Stinging eye	13 (9)	13 (9)
Tearing eye	5 (3)	3 (2)
Vision cloudy	2 (1)	1 (1)
Taste, bitter	58 (38)	62 (42)
Taste, sour	4 (3)	5 (3)
Taste, sweet	0 (0)	1 (1)
Taste, unusual	0 (0)	1 (1)

a- p=0.014, significantly greater incidence in the concomitant group.

Emergent or Worsening Ocular Signs

Experience	Combination (N=151) N %	Concomitant (N=148) N %
Anterior Chamber sign	0 (0)	1 (1)
Conjunctival sign	19 (13)	19 (13)
Conjunctiva edema	5 (3)	3 (2)
Hyperemia, conjunctiva	14 (9)	13 (9)
Corneal sign[a]	8 (5)	21 (14)
Punctuate epithelial erosions or SPK[b]	1 (1)	10 (7)
Staining, fluorescein	5 (3)	11 (7)
Lens sign	7 (5)	6 (4)
Cataract, subcapsular, posterior	3 (2)	0 (0)
Lens, cortical opacity	2 (1)	5 (3)
Nuclear opacity, lens	0 (0)	2 (1)
Lids sign	16 (11)	9 (6)
Blepharitis	3 (2)	1 (1)
Erythema, eyelid	1 (1)	4 (3)
Exudate/scales, eyelid	4 (3)	1 (1)
Meibomitis	3 (2)	1 (1)
Optic Nerve	6 (4)	1 (1)
Glaucomatous cupping	6 (4)	1 (1)
Vitreous sign	2 (1)	1 (1)
Opacity, vitreous	2 (1)	0 (0)

a- p=0.011, significantly greater incidence in the concomitant group.
b- p=0.005, significantly greater incidence in the concomitant group.
All categories in which at least 1 patient had an emergent or worsening ocular sign are listed.

Study #6 Summary

1. The study demonstrates that the combination administered bid is equally effective to concomitant administration bid in lowering IOP (recognizing that bid administration is not the effective dosing regimen for dorzolamide.

2. The combination demonstrates a combination of adverse events equal to or greater than concomitant use of timolol and dorzolamide.

3. There is an unexplained increase in cup/disc ratios in the combination group.

9 Overview of Efficacy

The combination product is more effective than each of the individual ingredients administered alone, but less effective than the individual components given concomitantly as approved.

10 Overview of Safety

10.1.1 Deaths

Study 63, patient 8219 was a 60 year old white female with ocular hypertension, systemic hypertension and diabetes. On day 37 she experienced myalgia and on day 52, severe diplopia. The symptoms persisted and on day 79 she was hospitalized. A biopsy revealed the diagnosis of plasmacytoma and the patient died on Day 221.

Reviewer's Comments: *The applicant considers the relationship to drug therapy to be definitely not related, the reviewer considers it to be unknown.*

Study 44, patient 7346 was a 68 year old female who died following a myocardial infarction. She had been on treatment for 156 days.

Study 44, patient 7178 was a 66 year old male who died following a TIA and Heart failure. He had been on treatment for 210 days.

Study 43, patient 6143 was a 73 year old male who died following a malignant liver neoplasm. He had been on treatment for 264 days.

Study 44, patient 7024 was a 71 year old female who died following a CVA. She had been on treatment for 133 days.

Study 43, patient 6103 was a 66 year old female who died following a subarachnoid hemorrhage. She has been on treatment for 140 days.

Study 43, patient 6133 was a 73 year old female who died following an episode of pneumonia. She had been on treatment for 35 days.

Study 47, patient 7882 was a 81 year old diabetic female who died following an episode of bacterial pneumonia.

Reviewer's Comments: *These events have been considered unrelated to treatment.*

10.1.2 Other Significant/Potentially Significant Events

1. Visual acuity has not been reported in a manner which permits sufficient evaluation.

2. Too few patients have been studied to evaluate the potential for sulfonamide like hematologic events.

3. Cup to disc ratios appeared to trend worse in the combination group than in other groups in protocols 44, 43 and 58.

10.1.3 Overdose Experience *None*

10.2.1.1 Adverse Experiences Summary

	Combination (N=706) n (%)	2% Dorzolamide (N=327) n (%)	0.5% Timolol (N= 424) n (%)	Tim/Dorz (Concomitant) (N=269) n (%)	Open Label Combination (N=546) n (%)
Total Patients With AEs	365 (51.7)	178 (54.4)	201 (47.4)	108 (40.1)	282 (51.6)
Body as a Whole	30 (4.2)	17 (5.2)	18 (4.2)	6 (2.2)	37 (6.8)
Pain, abdominal	5 (0.7)	5 (1.5)	3 (0.7)	2 (0.7)	7 (1.3)
Cardiovascular System	12 (1.7)	12 (3.7)	10 (2.4)	6 (2.2)	45 (8.2)
Hypertension	4 (0.6)	4 (1.2)	3 (0.7)	2 (0.7)	9 (1.6)
Digestive System	35 (5.0)	14 (4.3)	21 (5.0)	7 (2.6)	40 (7.3)
Dyspepsia	5 (0.7)	1 (0.3)	2 (0.5)	0 (0)	6 (1.1)
Nausea	8 (1.1)	3 (0.9)	3 (0.7)	1 (0.4)	4 (0.7)
Endocrine System	5 (0.7)	3 (0.9)	3 (0.7)	3 (1.1)	9 (1.6)
Diabetes mellitus	3 (0.4)	2 (0.6)	3 (0.7)	2 (0.7)	6 (1.1)
Metabolic/Nutr/Immune	8 (1.1)	1 (0.3)	3 (0.7)	0 (0)	10 (1.8)
Hypercholesterolemia	1 (0.1)	0 (0)	0 (0)	0 (0)	7 (1.3)
Musculoskeletal System	23 (3.3)	15 (4.6)	22 (5.2)	3 (1.1)	49 (9.0)
Arthritis	1 (0.1)	0 (0)	2 (0.5)	0 (0)	6 (1.1)
Pain, back	4 (0.6)	7 (2.1)	2 (0.5)	1 (0.4)	8 (1.5)
Nervous Sys and Psychiatric	46 (6.5)	29 (8.9)	38 (9.0)	13 (4.8)	43 (7.9)
Dizziness	12 (1.7)	2 (0.6)	3 (0.7)	1 (0.4)	1 (0.2)
Headache	24 (3.4)	16 (4.9)	23 (5.4)	8 (3.0)	19 (3.5)
Paresthesia	1 (0.1)	4 (1.2)	2 (0.5)	2 (0.7)	2 (0.4)
Respiratory System	76 (10.8)	49 (15.0)	45 (10.6)	20 (7.4)	80 (14.7)
Bronchitis	9 (1.3)	3 (0.9)	1 (0.2)	3 (1.1)	13 (2.4)
Cough	10 (1.4)	6 (1.8)	4 (0.9)	3 (1.1)	4 (0.7)
Infection, upper respiratory	25 (3.5)	20 (6.1)	19 (4.5)	4 (1.5)	28 (5.1)
Influenza	12 (1.7)	5 (1.5)	4 (0.9)	4 (1.5)	15 (2.7)
Pharyngitis	6 (0.8)	7 (2.1)	2 (0.5)	4 (1.5)	8 (1.5)
Sinus disorder	4 (0.6)	4 (1.2)	3 (0.7)	0 (0)	3 (0.5)
Sinusitis	8 (1.1)	5 (1.5)	6 (1.4)	0 (0)	6 (1.1)
Skin and Skin Appendage	24 (3.4)	13 (4.0)	13 (3.1)	5 (1.9)	31 (5.7)
Special Senses	265 (37.5)	122 (37.3)	128 (30.2)	74 (27.5)	161 (29.5)
Blepharitis	5 (0.7)	3 (0.9)	1 (0.2)	1 (0.4)	7 (1.3)
Blurred vision	20 (2.8)	8 (2.4)	19 (4.5)	9 (3.3)	9 (1.6)
Burning and/or stinging, eye	109 (15.4)	50 (15.3)	31 (7.3)	14 (5.2)	12 (2.2)
Conjunctivitis	5 (0.7)	5 (1.5)	0 (0)	3 (1.1)	15 (2.7)
Conjunctivitis, follicular	2 (0.3)	2 (0.6)	4 (0.9)	1 (0.4)	6 (1.1)
Constriction, visual field	2 (0.3)	0 (0)	2 (0.5)	0 (0)	7 (1.3)
Defect, nasal step	0 (0)	1 (0.3)	2 (0.5)	0 (0)	8 (1.5)
Defect, visual field	8 (1.1)	4 (1.2)	6 (1.4)	5 (1.9)	28 (5.1)
Discharge, eye	10 (1.4)	3 (0.9)	8 (1.9)	3 (1.1)	1 (0.2)
Edema, conjunctival	6 (0.8)	1 (0.3)	1 (0.2)	4 (1.5)	2 (0.4)
Edema, eyelid	5 (0.7)	2 (0.6)	0 (0)	0 (0)	6 (1.1)
Erosion, corneal	15 (2.1)	9 (2.8)	17 (4.0)	2 (0.7)	7 (1.3)
Foreign body sensation	12 (1.7)	6 (1.8)	7 (1.7)	3 (1.1)	5 (0.9)
Injection, conjunctival	16 (2.3)	14 (4.3)	7 (1.7)	4 (1.5)	15 (2.7)
Injection, ocular	7 (1.0)	4 (1.2)	2 (0.5)	1 (0.4)	1 (0.2)
Irritation, eye	3 (0.4)	4 (1.2)	1 (0.2)	4 (1.5)	1 (0.2)
Itching, eye	15 (2.1)	6 (1.8)	9 (2.1)	4 (1.5)	6 (1.1)
Opacity, lens	3 (0.4)	6 (1.8)	2 (0.5)	3 (1.1)	21 (3.8)
Pain, eye	13 (1.8)	4 (1.2)	4 (0.9)	3 (1.1)	10 (1.8)
Perversion, taste	56 (7.9)	34 (10.4)	7 (1.7)	18 (6.7)	6 (1.1)
Staining, corneal	10 (1.4)	3 (0.9)	7 (1.7)	9 (3.3)	11 (2.0)
Tearing	13 (1.8)	8 (2.4)	4 (0.9)	1 (0.4)	4 (0.7)
Visual acuity decreased	4 (0.6)	0 (0)	2 (0.5)	3 (1.1)	1 (0.2)
Urogenital System	14 (2.0)	7 (2.1)	13 (3.1)	5 (1.9)	22 (4.0)
Urinary tract infection	4 (0.6)	3 (0.9)	3 (0.7)	3 (1.1)	6 (1.1)

Note: Patients with more than one adverse experience are counted only once in the body system totals and in the overall total.

10.2.1.2 Emergent or Worsening Symptoms Summary

	Combination (N=706) n (%)	2% Dorzolamide (N=327) n (%)	0.5% Timolol (N= 424) n (%)	Tim/Dorz (Concomitant) (N=269) n (%)	Open Label Combination (N=546) n (%)
Any ocular symptoms	245 (34.9)	134 (41.0)	106 (25.1)	96 (35.7)	142 (26.3)
Blurred vision	63 (9.0)	31 (9.5)	26 (6.1)	25 (9.3)	38 (7.0)
Burning eye	104 (14.8)	58 (17.7)	38 (9.0)	25 (9.3)	57 (10.6)
Dryness of eye	11 (1.6)	8 (2.4)	15 (3.5)	5 (1.9)	8 (1.5)
Eye pain	10 (1.4)	3 (0.9)	4 (0.9)	8 (3.0)	9 (1.7)
Foreign body sensation	18 (2.6)	4 (1.2)	11 (2.6)	8 (3.0)	12 (2.2)
Eyelid pain or discomfort	15 (2.1)	5 (1.5)	4 (0.9)	3 (1.1)	13 (2.4)
Itching eye	44 (6.3)	17 (5.2)	15 (3.5)	17 (6.3)	25 (4.6)
Stinging eye	63 (9.0)	38 (11.6)	15 (3.5)	28 (10.4)	23 (4.3)
Tearing eye	32 (4.6)	16 (4.9)	4 (0.9)	7 (2.6)	22 (4.1)
Vision cloudy	12 (1.7)	9 (2.8)	7 (1.7)	3 (1.1)	5 (0.9)
Bitter taste	175 (24.9)	84 (25.7)	17 (4.0)	104 (38.7)	100 (18.5)
Sour taste	32 (4.6)	14 (4.3)	2 (0.5)	11 (4.1)	17 (3.1)
Sweet taste	9 (1.3)	11 (3.4)	2 (0.5)	3 (1.1)	5 (0.9)
Unusual taste	7 (1.0)	0	1 (0.2)	1 (0.4)	0

10.2.1.3 Emergent or Worsening Signs Summary

	Combination (N=706) n (%)	2% Dorzolamide (N=327) n (%)	0.5% Timolol (N= 424) n (%)	Tim/Dorz (Concomitant) (N=269) n (%)	Open Label Combination (N=546) n (%)
Lids sign	61 (8.7)	19 (5.8)	25 (5.9)	19 (7.1)	41 (7.6)
Blepharitis	14 (2.0)	4 (1.2)	4 (0.9)	4 (1.5)	12 (2.2)
Erythema, eyelid	12 (1.7)	6 (1.8)	5 (1.2)	4 (1.5)	7 (1.3)
Debris, eye	8 (1.1)	3 (0.9)	3 (0.7)	6 (2.2)	7 (1.3)
Exudate/scales, eyelid	8 (1.1)	1 (0.3)	4 (0.9)	1 (0.4)	4 (0.7)
Edema, eyelid	3 (0.4)	3 (0.9)	3 (0.7)	0	7 (1.3)
Anterior Chamber sign	8 (1.1)	1 (0.3)	0	8 (3.0)	2 (0.4)
Anterior chamber cells	3 (0.4)	1 (0.3)	0	7 (2.6)	2 (0.4)
Conjunctiva sign	91 (12.9)	45 (13.8)	50 (11.8)	42 (15.6)	92 (17.0)
Hyperemia, conjunctiva	70 (10.0)	36 (11.0)	37 (8.7)	30 (11.2)	64 (11.9)
Conjunctival follicles	5 (0.7)	1 (0.3)	2 (0.5)	4 (1.5)	9 (1.7)
Conjunctival edema	10 (1.4)	5 (1.5)	6 (1.4)	4 (1.5)	4 (0.7)
Conjunctivitis, follicular	2 (0.3)	4 (1.2)	3 (0.7)	2 (0.7)	11 (2.0)
Conjunctival discharge	5 (0.7)	0	2 (0.5)	1 (0.4)	6 (1.1)
Cornea signs	83 (11.8)	33 (10.1)	53 (12.5)	42 (15.6)	75 (13.9)
SPK	51 (7.3)	23 (7.0)	34 (8.0)	26 (9.7)	45 (8.3)
Staining, fluorescein	32 (4.6)	13 (4.0)	25 (5.9)	17 (6.3)	35 (6.5)
Arcus Senilis	1 (0.1)	0	0	0	6 (1.1)
Lens signs	28 (4.0)	12 (3.7)	12 (2.9)	8 (3.0)	57 (10.8)
Lens, cortical opacity	11 (1.6)	3 (0.9)	2 (0.5)	5 (1.9)	23 (4.3)
Nuclear opacity, lens	6 (0.9)	4 (1.2)	6 (1.4)	3 (1.1)	18 (3.4)
Coloration, lens nucleus	4 (0.6)	4 (1.2)	5 (1.2)	2 (0.7)	17 (3.2)
Cataract, subcapsular, posterior	6 (0.9)	3 (0.9)	2 (0.5)	0	7 (1.3)
Optic Nerve signs	18 (2.6)	8 (2.5)	5 (1.2)	2 (0.7)	26 (4.9)
Glaucomatous cupping	13 (1.9)	6 (1.9)	2 (0.5)	1 (0.4)	19 (3.6)
Retina signs	9 (1.3)	4 (1.2)	7 (1.7)	0	26 (4.9)
Hemorrhage, retina	2 (0.3)	2 (0.6)	3 (0.7)	0	6 (1.1)
Vitreous signs	11 (1.6)	5 (1.5)	10 (2.4)	1 (0.4)	22 (4.2)
Detachment, vitreous	7 (1.0)	3 (0.9)	5 (1.2)	0	15 (2.8)
Degeneration, vitreous	0	2 (0.6)	2 (0.5)	1 (0.4)	6 (1.1)

Summary of Events	% of Patients in Study(ies)
Abdominal pain	3, 2, 1
Allergic conjunctivitis	1
Anterior chamber cells	2
Anxiety	2
Arthralgia	1
Arthritis	1, 0
Av nicking	1
Back pain	2, 2, 1
Bitter taste	38, 32, 25, 19, 16, 13
Blepharitis	4, 3, 2, 2, 2, 1, 0
Blood pressure increased	2
Blurred vision	20, 12, 9, 7, 5, 4, 4, 4, 2, 2, 1, 1
Bronchitis	3, 2, 2, 0
Cataract	2, 2, 1, 1, 1
Chalazion	2, 2, 1, 1
Chemosis	1
Chest pain	3, 1, 0
Conjunctiva edema	3, 3, 2, 2, 1
Conjunctival follicles	3, 1, 0
Conjunctival discharge	3, 1
Conjunctival injection	6, 3, 3, 2
Conjunctival hyperemia	15, 12, 10, 9, 9, 5, 2, 1
Conjunctivitis	2, 1, 1
Corneal guttata	1
Corneal erosion	13, 2, 1, 0
Corneal staining	4, 3
Corneal epithelial defect	3, 1
Cortical lens opacity	3, 2, 2, 1, 1, 1
Cough	2, 2, 2, 1
Cystitis	0
Depression	2, 0
Diabetes loss of control	1
Diabetic retinopathy	2, 2
Diarrhea	3, 1, 0
Dilated episcleral vessels	2
Dizziness	4, 2, 2, 2
Dry eyes	3, 3, 2, 2, 1, 0, 0
Dry cornea	1
Dry mouth	2, 1
Dyspepsia	2, 2, 1
Dyspnea	2
Eczema	2, 1
Episcleritis	1
Eye discharge	3, 2, 1, 1
Eye irritation	1
Eye debris	5, 1
Eye stickiness	4, 0

Eye itching	9, 8, 7, 7, 4, 4, 3, 3, 2, 2, 2, 0
Eye heaviness	3, 1, 0
Eye redness	2, 1, 0
Eye aching	2
Eye discomfort	1, 0
Eye pain	4, 4, 3, 3, 1, 1, 1, 0
Eye burning and/or stinging	31, 30, 26, 20, 18, 14, 13, 12, 10, 6, 5, 1
Eyelid exudate/scales	3, 2, 1
Eyelid edema	2, 2, 1, 1, 0
Eyelid erythema	4, 4, 1, 1
Eyelid irritation	1, 1, 0
Eyelid inflammation	3
Eyelid papillae	1
Eyelid pain or discomfort	6, 3, 2, 1, 1
Eyelids puffy	1
Flu-like illness	2, 1, 0
Fluorescein staining	10, 6, 4, 4, 3, 0
Follicular conjunctivitis	2, 2, 1, 0
Foreign body sensation	4, 4, 4, 3, 3, 3, 2, 2, 2, 1, 0
Gastritis	1
Glaucomatous cupping	4, 3, 2, 1
Headache	7, 3, 3, 3, 3, 1
Herpes zoster	2
Hordeolum	1
Hypercholesterolemia	2
Hypertension	1, 1, 0, 0
Impacted meibomian glands	1
Influenza	4, 3, 2, 2, 0
Lens opacity	2, 1, 0, 0
Macular degeneration	1
Meibomitis	2
Muscle cramp	1, 0
Mucus discharge	1
Musculoskeletal system	7, 6, 3, 3, 2, 1
Myalgia	1, 1
Nasal congestion	3
Nausea	2, 2, 2, 1, 1
Neck pain	2
Nuclear lens opacity	5, 4, 3, 2, 0
Ocular injection	3
Optic disc hemorrhage	2, 2
Optic disc cupping	2
Optic atrophy	1
Optic nerve abnormality	4, 4, 4, 1
Paresthesia	1, 0, 0
Pharyngeal discomfort	2
Pharyngitis	2, 1, 1
Photophobia	2, 1, 1

Photopsia	2
Posterior subcapsular lens opacity	2
Pseudoexfoliation, lens capsule	1
Punct. epith. erosions or spk	16, 13, 7, 5, 4, 1
Rash	1
Respiratory difficulty	14, 13, 12, 11, 8, 7
Retinal hemorrhage	1, 1, 1
Rhinorrhea	1
Saucerized optic nerve	1
Scotoma	2, 0
Scurf	2
Sinus disorder	2, 1, 1
Sinusitis	2, 2, 1, 1
Skin malignant neoplasm	1
Sour taste	11, 4, 4, 3, 3, 2
Special senses	65, 45, 36, 33, 32, 19
Stinging eye	22, 12, 9, 6, 3, 1
Subconjunctival hemorrhage	3, 3, 1
Sweet taste	6, 1, 1, 0, 0, 0
Taste perversion	22, 11, 8, 8, 1
Tearing	10, 6, 4, 3, 3, 3, 3, 3, 3, 1, 0
Tendinitis	1
Unusual taste	5, 2, 0
Upper respiratory tract infection	7, 5, 3, 3, 2, 2, 1
Urinary tract infection	2, 1, 0
Urolithiasis	2
Vertigo	1
Vision cloudy	5, 3, 1, 0, 0
Visual field defect	3, 2, 2, 0
Visual discomfort	2
Visual acuity decreased	3
Visual disturbance	2, 1
Visual field constriction	2
Vitreous opacity	2, 2, 1, 1, 1, 0, 0
Vitreous detachment	3, 2
Vitreous degeneration	2, 2
Vomiting	2, 1

10.2.2 Laboratory Findings, Vital Signs, ECGs

Reviewer's Comments: *The number of patients studied is not sufficient to rule out the possibility of blood dyscrasias due to the product, however, the frequency is not expected to be greater than currently observed with currently approved ophthalmic sulfonamides or with oral carbonic anhydrase inhibitors.*

Electrolyte changes observed were considered minimal.

Blood pressure and pulse changes observed were considered minimal.

10.2.3 Special Studies

Reviewer's Comments: *The corneal endothelial study is being reviewed as part of a submission to NDA 20-408.*

10.2.4 Drug-Demographic Interactions

Reviewer's Comments: *The drug product appears to be more effective in patients with higher baseline intraocular pressure and light colored irides.*

The differences with respect to the demographic factors of age, gender and nationality are not completely understood at this time. Further evaluation will be needed for clarification. No additional labeling in this regard is merited at this time.

10.2.5 Drug-Disease Interactions *No significant new findings*

10.2.6 Drug-Drug Interactions *No significant new findings*

10.2.7 Withdrawal Phenomena/Abuse Potential *No significant new findings*

10.2.8 Human Reproduction Data *No significant new findings.*

11 Labeling Review

Reviewer's Comments: *Labeling recommendations are identified below. Recommended deletions are identified by ~~single lines~~. Recommended additions are identified in red. Comments from other review disciplines have not yet been incorporated into this review.*

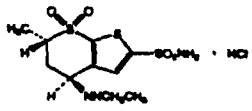
COSOPT

(~~D~~dorzolamide ~~H~~hydrochloride/~~T~~timolol ~~M~~maleate ~~O~~ophthalmic ~~S~~solution)
Sterile Ophthalmic Solution

DESCRIPTION
COSOPT (dorzolamide hydrochloride/timolol maleate ophthalmic solution) is the combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

Dorzolamide hydrochloride is described chemically as: (4 S-trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4 H-thieno[2,3- b]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active. The specific rotation is:

$[\alpha]$ 25°C 405 nm (C=1, water) = ~17°.



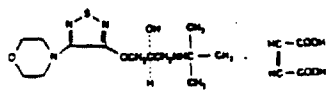
Its empirical formula is $C_{10}H_{16}N_2O_4S_3 \cdot HCl$ and its structural formula is:

Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Timolol maleate is described chemically as: (-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided primarily as the levo-isomer. The nominal optical rotation of timolol maleate is:

$[\alpha]$ 25°C 405 nm in 1N HCl (C = 5) = -12.2°.

Its molecular formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ and its structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate is stable at room temperature.

COSOPT is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution. The pH of the solution is approximately 5.65. Each mL of COSOPT contains 20.00 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5.00 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action

COSOPT is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a beta$_1$ and beta$_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as administering each product individually as labeled.

Pharmacokinetics/Pharmacodynamics

Dorzolamide Hydrochloride

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the

parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to plasma proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 2 mg b.i.d. closely approximates the amount of drug delivered by topical ocular administration of dorzolamide 2% t.i.d. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

Timolol Maleate

In a study of plasma drug concentrations in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL.

Clinical Studies

Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect of COSOPT b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% timolol (b.i.d.) and 2.0% dorzolamide (b.i.d. and t.i.d.).

The IOP-lowering effect of COSOPT b.i.d. was greater (1-3 mmHg) than that of monotherapy with either 2.0% dorzolamide t.i.d. or 0.5% timolol but less than that of concomitant therapy with dorzolamide t.i.d. and timolol b.i.d.

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Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of COSOPT b.i.d was consistent during the 12 month follow-up period..

INDICATIONS AND USAGE
COSOPT is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to Timoptic (failed to achieve target IOP determined after multiple measurements over time).

Cosopt provides less IOP lowering efficacy than the administration of Timoptic 0.5% and Trusopt dosed separately as labeled.

CONTRAINDICATIONS
COSOPT is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

Systemic Exposure
COSOPT contains dorzolamide, a sulfonamide, and timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS). Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Cardiac Failure
Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, COSOPT should be discontinued.

Obstructive Pulmonary Disease
Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which COSOPT is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blocking agents, including COSOPT.

Major Surgery
The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus
Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis
Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General

Dorzolamide has not been studied in patients with severe renal impairment (CrCl < 30 mL/min). Because dorzolamide and its metabolite are excreted predominantly by the kidney, COSOPT is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of COSOPT. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, COSOPT should be discontinued and the patient evaluated before considering restarting the drug. (See ADVERSE REACTIONS.)

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. COSOPT has not been studied in patients with acute angle-closure glaucoma.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See PRECAUTIONS, Information for Patients.)

Information for Patients

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

COSOPT contains dorzolamide (which is a sulfonamide) and although administered topically is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product (see WARNINGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See PRECAUTIONS, General.)

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

Patients should be advised that COSOPT contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of COSOPT.

Drug Interactions

Carbonic anhydrase inhibitors: There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and COSOPT. The concomitant administration of COSOPT and oral carbonic anhydrase inhibitors is not recommended.

Acid-base disturbances: Although acid-base and electrolyte disturbances were not reported in the clinical trials with dorzolamide hydrochloride ophthalmic solution, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving COSOPT.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and COSOPT should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as COSOPT, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Injectable Epinephrine: (See PRECAUTIONS, General, Anaphylaxis.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Dorzolamide Hydrochloride~~

In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately 12 times the recommended human ophthalmic dose. No treatment-related tumors were seen in a 21-month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide hydrochloride for one year at 2 mg/kg/day (25 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye at 0.4 mg/kg/day (~5 times the recommended human ophthalmic dose) for one year.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats with either timolol maleate or dorzolamide hydrochloride demonstrated no adverse effect on male or female fertility at doses up to ~~21,000~~ approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy
Teratogenic Effects: Pregnancy Category C

Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of ≥ 2.5 mg/kg/day (31 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased fetal weights. No treatment-related

malformations were seen at 1.0 mg/kg/day (13 times the recommended human ophthalmic dose).

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. COSOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether dorzolamide is excreted in human milk. Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from COSOPT in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

During clinical studies. of approximately 700 patients treated with COSOPT, approximately 5% of all patients discontinued therapy with COSOPT because of adverse reactions.

The most frequently reported adverse experiences were ocular burning, stinging and foreign body sensation, taste perversion (bitter, sour or unusual taste) and blurred vision. These were reported in up to 38% of patients.

Corneal erosions, corneal fluorescein staining, conjunctival hyperemia, ocular itching, superficial punctate keratitis and tearing were reported in up to 15% of patients. Other events were reported in generally less than 5% of patients included: Abdominal pain, allergic conjunctivitis, anterior chamber cells, anxiety, arthralgia, arthritis, av nicking, back pain, blepharitis, blood pressure increased, bradycardia, bronchitis, cardiac arrest, cardiac failure, cataract progression, cerebral vascular accident, chalazion, chemosis, chest pain, conjunctiva edema, conjunctival follicles, conjunctival injection, conjunctival discharge, conjunctivitis, corneal guttata, corneal epithelial defect, cortical lens opacity, cough, depression, diabetes loss of control, diabetic retinopathy, diarrhea, dilated episcleral vessels, dizziness, dry cornea, dry eyes, dry mouth, dyspepsia, dyspnea, eczema, episcleritis, eye discharge, eye heaviness, eye discomfort, eye pain, eye stickiness, eye irritation, eye redness, eye debris, eye aching, eyelid pain or discomfort, eyelid irritation, eyelid exudate/scales, eyelid papillae, eyelid erythema, eyelid edema, eyelid inflammation, eyelids puffy, flu-like illness, follicular conjunctivitis, foreign body sensation, gastritis, glaucomatous cupping, headache, herpes zoster, hordeolum, hypercholesterolemia, hypersensitivity skin reactions, hypertension, hypotension, impacted meibomian glands, influenza, lens opacity, macular degeneration, meibomitis, muscle cramps, mucus discharge (crusting), myalgia, nasal congestion, nausea, neck pain, nuclear lens opacity, ocular injection, optic atrophy, optic disc cupping, optic nerve abnormality, optic disc hemorrhage, paresthesia, pharyngeal discomfort, pharyngitis, photophobia, photopsia, posterior subcapsular lens opacity, pseudoexfoliation, lens capsule, rash,

retinal hemorrhage, rhinorrhea, saucerized optic nerve, scotoma, scurf, sinus disorder, sinusitis, skin malignant neoplasm, subconjunctival hemorrhage, sweet taste, tendinitis, upper respiratory tract infection, urinary tract infection, urolithiasis, vertigo, vision cloudy, visual field defect, visual acuity decreased, visual disturbance, visual field constriction, visual discomfort, vitreous opacity, vitreous degeneration, vitreous detachment, and vomiting.

Other adverse reactions that have been reported with the individual components are listed below:

Dorzolamide - Allergic/Hypersensitivity: Signs and symptoms of systemic allergic reactions including angioedema, bronchospasm, pruritus, urticaria; Body as a Whole: Asthenia/fatigue; Nervous System: Paresthesia; Special Senses:

Iridocyclitis and transient myopia

Timolol (ocular administration) - Body as a Whole: Asthenia/fatigue; Cardiovascular: Arrhythmia, syncope, heart block, cerebral ischemia, worsening of angina pectoris, palpitation and pulmonary edema; Digestive: Anorexia; Immunologic: Systemic lupus erythematosus; Nervous System/Psychiatric: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; Skin: Urticaria and alopecia; Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), and respiratory failure; Endocrine: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS); Special Senses: Ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; and choroidal detachment following filtration surgery (see PRECAUTIONS, General); Urogenital: Retroperitoneal fibrosis and impotence.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss; Cardiovascular: Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; Digestive: Gastrointestinal pain, hepatomegaly mesenteric arterial thrombosis, ischemic colitis; Hematologic: Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; Endocrine: Hyperglycemia, hypoglycemia; Skin: Skin irritation, increased pigmentation, sweating, cold hands and feet; Musculoskeletal: Arthralgia, claudication; Nervous System/Psychiatric: Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; Respiratory: Rales, bronchial obstruction; Special Senses: Tinnitus; Urogenital: Urination difficulties, Peyronie's disease.

OVERDOSAGE

There are no human data available on overdosage with COSOPT.

Electrolyte imbalance, development of an acidotic state, dizziness, headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest and possible central nervous system effects consistent with systemic administration of beta-blockers or carbonic anhydrase inhibitors may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored (see also ADVERSE REACTIONS). A study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION
The dose is one drop of COSOPT in the affected eye(s) two times daily.

COSOPT
(Dorzolamide Hydrochloride/Timolol Maleate Ophthalmic Solution)

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart (see also PRECAUTIONS, Drug Interactions).

HOW SUPPLIED
COSOPT Ophthalmic Solution is a clear, colorless to nearly colorless, slightly viscous solution.

No. 3628 COSOPT Ophthalmic Solution is supplied in an OCUMETER*, a white, opaque, plastic ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3628-03, 5 mL
NDC 0006-3628-10, 10 mL.

Storage
Store COSOPT between 15 and 25°C (59-77°F).
Protect from light.

MERCK & CO., INC., West Point, PA 19486, USA

Issue Date _____
Printed in USA

12 Conclusions

1. The submission was not well put together making it more difficult than the average NDA to review. Specifically:
    a. Study reports were split into different volumes.
    b. References for data sources referred to appendices which were blank and further referred to Case Report Tabulations which were not initially included.
    c. Adverse events were listed on tables just as "Adverse events" without specifying the particular event and it was often necessary to trace back two or more references to find the actual event.
    d. Some of the specific recommendations from the "Pre-NDA meeting" were not followed (IOP confidence intervals).

2. The combination product is more effective than each of the individual ingredients administered alone, but less effective than the individual components given concomitantly as approved.

3. The adverse experiences reported with the combination product are consistent with the sum of the adverse experiences from each of the two individual components.

4. The number of patients studied is not sufficient to rule out the possibility of blood dyscrasias due to the product, however, the frequency is not expected to be greater than currently observed with currently approved ophthalmic sulfonamides or with oral carbonic anhydrase inhibitors.

5. The percentage of patients discontinued for Adverse Reactions is potentially misleading because it fails to include patients who discontinued for multiple reasons (i.e., elevated IOP and an adverse event).

13 Recommendations

Cosopt (NDA 20-869) as submitted is not recommended for approval at this time because the studies fail to support the proposed labeling. The applicant should be encouraged to amend the application for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to Timoptic (failed to achieve target IOP determined after multiple measurements over time), and address the deficiencies outlined below:

The following should be submitted:

1. Major labeling revisions consistent with this review.

2. A table for each of the Studies 1-6 (Protocols 44, 47, 63, 64, 43 and 58) showing the number and percentage of patients with a 0, 1, 2 and >2 lines increase in visual acuity from baseline and a 1, 2, and >2 line decrease in visual acuity.

3. Revised particular matter specifications.

4. Revised stability conditions such that the relative humidity is ≤40% when the temperature is at 25°C.

5. A revised analysis of pupil measurements using consistent sources for the pupil measurements (either all measurements from a perimeter or none from a perimeter).

6. An explanation for the apparent imbalance in Cup to Disc ratios observed in several studies should be submitted.

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

cc: HFD-550
HFD-340
HFD-550/PM/Gorski
HFD-830/CHEM/Ho
HFD-550/PHARM/Weir
HFD-550/MO/Chambers
NDA 20-369

Medical Officer's Review of NDA 20-869

NDA 20-869
M.O. Review #2

Submission date: 2/12/98
Review completed: 2/12/98

Proposed trade name: Cosopt

Established name: Dorzolamide hydrochloride/timolol maleate ophthalmic solution

Chemical name: (4S-*trans*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride, (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol maleate (1:1) (salt)

Active ingredients: Dorzolamide hydrochloride
Timolol maleate

Inactive ingredients: Sodium citrate dihydrate USP hydroxyethyl cellulose mannitol sodium hydroxide to adjust to pH 5.65.

Preservative: benzalkonium chloride (BAK)

Applicant: Merck Research Laboratories
Merck & Co., Inc.
West Point, PA 19486
(215) 397-2905

Pharmacologic Category: Combination carbonic anhydrase inhibitor (CAI) and β-blocker

Proposed Indication(s): COSOPT is indicated in the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time). The IOP-lowering of COSOPT b.i.d. was slightly less than that seen with the concomitant administration of 0.5% timolol b.i.d. and 2.0% dorzolamide t.i.d. (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

11 Labeling Review

Reviewer's Comments: *Labeling recommendations after receiving comments from the applicant are identified below. Recommended deletions are identified by ~~a strikeout line~~. Recommended additions are identified in [redacted].*

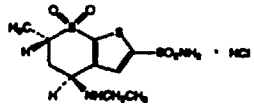
COSOPT

(dorzolamide hydrochloride/timolol maleate ophthalmic solution)
Sterile Ophthalmic Solution

DESCRIPTION
COSOPT (dorzolamide hydrochloride/timolol maleate ophthalmic solution) is the combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

Dorzolamide hydrochloride is described chemically as: (4 S-trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4 H-thieno[2,3- b]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active. The specific rotation is:

$[\alpha]$ 25°C 405 nm (C=1, water) = ~17°.

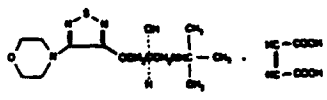


Its empirical formula is $C_{10}H_{16}N_2O_4S_3 \cdot HCl$ and its structural formula is:
Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Timolol maleate is described chemically as: (-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided primarily as the levo-isomer. The nominal optical rotation of timolol maleate is:

$[\alpha]$ 25°C 405 nm in 1N HCl (C = 5) = -12.2°.

Its molecular formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ and its structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate is stable at room temperature.

COSOPT is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution. The pH of the solution is approximately 5.65 and the osmolality is approximately xxx. Each mL of COSOPT contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action

COSOPT is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a beta$_1$ and beta$_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents administered as COSOPT b.i.d. results in additional intraocular pressure reduction compared to either component administered alone; but the reduction is not as much as when dorzolamide t.i.d. and timolol b.i.d. are administered concomitantly (see *Clinical Studies).*

Pharmacokinetics/Pharmacodynamics

Dorzolamide Hydrochloride

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to plasma proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 2 mg b.i.d. closely approximates the amount of drug delivered by topical ocular administration of dorzolamide 2% t.i.d. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

Timolol Maleate
In a study of plasma drug concentrations in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL.

Clinical Studies
Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect of COSOPT b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% timolol (b.i.d.) and 2.0% dorzolamide (b.i.d. and t.i.d.). The IOP-lowering effect of COSOPT b.i.d. was greater (1-4 mmHg) than that of monotherapy with either 2.0% dorzolamide t.i.d. or 0.5% timolol b.i.d. The IOP-lowering effect of COSOPT b.i.d. was mmHg less than that of concomitant therapy with 2.0% dorzolamide t.id. and 0.5% timolol b.i.d.

Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of COSOPT b.i.d was consistent during the 12 month follow-up period.

INDICATIONS AND USAGE
COSOPT is indicated [redacted] of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time). The IOP-lowering of COSOPT b.i.d. was slightly less than that seen with the concomitant administration of 0.5% timolol b.i.d. and 2.0% dorzolamide t.i.d. (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

CONTRAINDICATIONS

COSOPT is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

Systemic Exposure

COSOPT contains dorzolamide, a sulfonamide, and timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, COSOPT should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which COSOPT is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blocking agents, including COSOPT.

Major Surgery
The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus
Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis
Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS
General
Dorzolamide has not been studied in patients with severe renal impairment (CrCl < 30 mL/min). Because dorzolamide and its metabolite are excreted predominantly by the kidney, COSOPT is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of COSOPT. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, COSOPT should be discontinued and the patient evaluated before considering restarting the drug. (See ADVERSE REACTIONS.)

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. COSOPT has not been studied in patients with acute angle-closure glaucoma.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See PRECAUTIONS, *Information for Patients*.)

Information for Patients

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

COSOPT contains dorzolamide (which is a sulfonamide) and although administered topically is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product (see WARNINGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See PRECAUTIONS, *General.*)

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

Patients should be advised that COSOPT contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of COSOPT.

Drug Interactions

Carbonic anhydrase inhibitors: There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and COSOPT. The concomitant administration of COSOPT and oral carbonic anhydrase inhibitors is not recommended.

Acid-base disturbances: Although acid-base and electrolyte disturbances were not reported in the clinical trials with dorzolamide hydrochloride ophthalmic solution, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving COSOPT.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and COSOPT should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as COSOPT, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockage (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Injectable Epinephrine: (See PRECAUTIONS, General, Anaphylaxis.)

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately 12 times the recommended human ophthalmic dose. No treatment-related tumors were seen in a 21-month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide hydrochloride for one year at 2 mg/kg/day (25 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye at 0.4 mg/kg/day (~5 times the recommended human ophthalmic dose) for one year.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

The following tests for mutagenic potential were negative for dorzolamide: (1) *in vivo* (mouse) cytogenetic assay; (2) *in vitro* chromosomal aberration assay; (3) alkaline elution assay; (4) V-79 assay; and (5) Ames test.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats with either timolol maleate or dorzolamide hydrochloride demonstrated no adverse effect on male or female fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy
Teratogenic Effects: Pregnancy Category C.

Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of ≥ 2.5 mg/kg/day (31 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased fetal weights. No treatment-related malformations were seen at 1.0 mg/kg/day (13 times the recommended human ophthalmic dose).

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

[redacted]

Nursing Mothers
It is not known whether dorzolamide is excreted in human milk. Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from COSOPT in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

During clinical studies of approximately 700 patients treated with COSOPT, approximately 5% of all patients discontinued therapy with COSOPT because of adverse reactions.

The most frequently reported adverse experiences were ocular burning, stinging and foreign body sensation, taste perversion (bitter, sour, or unusual taste) and blurred vision. These were reported in up to 38% of patients.

Corneal erosions, corneal fluorescein staining, conjunctival hyperemia, ocular itching, superficial punctate keratitis and tearing were reported in up to 5% of patients. Other events were reported in generally less than 5% of patients, included: Abdominal pain, allergic conjunctivitis, anterior chamber cells, anxiety, arthralgia, arthritis, eye irritation, back pain, blepharitis, blood pressure increased, bradycardia, bronchitis, cardiac arrest, cardiac failure, cataract progression, cerebral vascular accident, chalazion, chemosis, chest pain, conjunctival edema, conjunctival follicles, conjunctival injection, conjunctival discharge, conjunctivitis, corneal guttata, corneal epithelial defect, cortical lens opacity, cough, depression, diabetes loss of control, diabetic retinopathy, diarrhea, dilated episcleral vessels, dizziness, dry cornea, dry eyes, dry mouth, dyspepsia, dyspnea, eczema, episcleritis, eye discharge, eye heaviness, eye discomfort, eye pain, eye stickiness, eye irritation, eye redness, eyelid debris, eye aching, eyelid pain or discomfort, eyelid irritation, eyelid exudate/scales, eyelid papillae, eyelid erythema, eyelid edema, eyelid inflammation, eyelids puffy, flu-like illness, follicular conjunctivitis, gastritis, glaucomatous cupping, headache, herpes zoster, hordeolum, hypercholesterolemia, hypersensitivity, skin reactions, hypertension, hypotension, impacted meibomian glands, influenza, lens opacity,