DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 22 2000

TRANSMITTED BY FACSIMILE

David Garbe
Director, Scientific Information and Medical Compliance
Allergan, Inc.
2525 DuPont Drive TL-1L
PO Box 19534
Irvine, CA 92623-9534

RE: NDA 20-613
Alphagan (brimonidine tartrate ophthalmic solution) 0.2%
MACMIS ID # 8412

Dear Mr. Garbe:

This letter is in reference to Allergan, Inc.'s (Allergan) promotional campaign for Alphagan. We refer to your dissemination of promotional materials[1] that suggest or imply that Alphagan is safer than beta-blockers for lowering intraocular pressure. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials and has concluded that they are false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. We have identified many examples in your promotional campaign in footnote #1. However, this is not an exhaustive listing. Our specific objections follow:

Misleading Claims of Superior Safety

1. In the headline of the sales aid (RX9478) and journal ad (SIMC99-369), you claim that one can "steer clear of first-line risks" by "mak[ing] ALPHAGAN your first line choice." On the second page of the sales aid, you similarly claim that one can "**minimize** first-line **concerns**" by "mak[ing] Alphagan your first-line choice" (emphasis added).

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1. Patient brochure titled "For glaucoma patients using intraocular pressure-reducing eye drops Are you feeling your best?"
Fold-out brochure and diskette titled, "Have you asked your glaucoma patients Are you feeling your best?"
Sales aid RX9478
Mailer 7831X
Cup to disk ratio card RX9414
Advertisement titled "Steer clear of first-line risks" SIMC99-369
Exhibit poster titled "Steer clear of beta-blocker risks" SIMC99-371
Clipboard titled, "Are your patients feeling their best?"
Telephone message pad RX9246

2. Further, in your brochure titled "Steer clear of first-line risks" identified as RX9478, you also claim one may "**minimize** first-line **concerns** by making Alphagan your first-line choice" (emphasis added). Additionally, many of your promotional materials have the tagline, "**The** safe course to long-term efficacy" (emphasis added).

3. Also in your brochure titled "Have you asked your glaucoma patients Are you feeling your best?" you make numerous inferences that Alphagan does not have risks like topical beta-blockers, and that Alphagan is a "safer alternative."

4. On the clipboard, you list numerous physical limitations a patient may have: 1. "irregular heartbeat," 2. "Difficulty breathing, consistent coughing, recent difficulty in smoking cigarettes," 3. "Not able to exercise," 4. "Depression, weepiness, lability," 5. "Generally not feeling well," 6. "Tired, yawning," 7. "Balance problems or dizziness," 8. "Confusion," 9. "Falling," 10. "Changes in sexual desire or performance," and 11. "Having a problem with other medications." You imply these limitations related to beta-blockers can be avoided with Alphagan.

5. Similarly, in your brochure titled "Avoid the risks of topical beta-blocker side effects" identified as 7831X, you suggest that because 19% of patients with glaucoma take systemic anti-hypertensive beta-blockers, topical beta-blockers should typically be avoided in these patients. You follow this claim with the statement that the efficacy of timolol was significantly reduced by concomitant systemic beta-blocker administration, but that systemic beta-blocker therapy had no influence on the efficacy of Alphagan. Again, you imply that Alphagan is safer and more effective than timolol.

6. In the patient brochure titled "For glaucoma patients using intraocular pressure-lowering eye drops Are you feeling your best?" you make the following statements:

> Your intraocular pressure (IOP) lowering eyedrops "may also be the cause of some unwanted side effects—especially if you're using a topical beta-blocker.'
>
> "You may be experiencing breathing difficulties, an irregular heartbeat, or a reduction in exercise tolerance."
>
> "You may have fallen recently, felt dizzy or faint, and at times seemed confused, even depressed, or unusually sad."
>
> "You may also have noticed a recent change in sexual desire or performance."

> Again, you imply that Alphagan is the safer alternative; because not only does it not cause any of the above side effects, but Alphagan's side effects "are usually not severe enough to cause you to stop using Alphagan."

All of these promotional materials are misleading because they state or suggest that Alphagan is a safer alternative to topical beta-blockers. However, none of these claims are supported by substantial evidence. Your multi-center head-to-head comparative trials with timolol 0.5% conducted to demonstrate the safety and efficacy of Alphagan identified the safety concerns discussed below.

Fair Balance

> Further, these materials are also misleading because they lack fair balance because you have not adequately presented the **safety concerns associated with the use of Alphagan** (emphasis added). For instance, you fail to present with similar prominence as your claims for Alphagan that "patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness," and that "Alphagan may cause fatigue and/or drowsiness in some patients." Further, the PI for Alphagan includes the side effects of dizziness, depression, hypertension, anxiety, palpitations, and syncope. These side effects are not prominently conveyed.

Misleading Data

> In the sales aid RX9535, you claim that in clinical studies[2], the "First-line mean peak IOP reduction (26.3%) comparable to timolol (24.4%) at the end of year 1 (N=837)." Your claim is misleading because you omitted material facts. You claim that Alphagan is as effective as timolol at lowering IOP at the end of one year, but fail to present that in this extended study, 44% of the patients treated with Alphagan dropped out of the study (59 patients withdrew because of ocular allergy experienced with brimonidine therapy versus 1 patient with timolol) while only 22% of the timolol patients dropped out.
>
> Further, you claim that new 4-year data in 31 patients demonstrate that Alphagan has sustained first-line IOP reduction comparable to timolol. This claim is misleading because it lacks adequate substantiation. It is also inconsistent with the precautions section of the PI that states "during the studies there was a loss of effect in some patients" and "the IOP lowering efficacy observed with Alphagan Ophthalmic Solution during the

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2. L. Jay Katz and the Brimonidine Study Group. "Brimonidine Tartrate 0.2% Twice Daily vs Timolol 0,5% Twice Daily: 1-Year Results in Glaucoma Patients. *American Journal of Ophthalmology.* January 1999.

first month of therapy may not always reflect the long-term level of IOP reduction."

Requested Actions

In order to address these objections, we request that you immediately cease the dissemination of these violative promotional materials and all similar promotional materials that contain the same or similar messages.

You should respond in writing to us regarding this issue by October 6, 2000. Your response should include Allergan's intent to comply with the above request, the date that it ceased disseminating these and any other violative promotional materials with the same or similar messages, and a list of the discontinued materials.

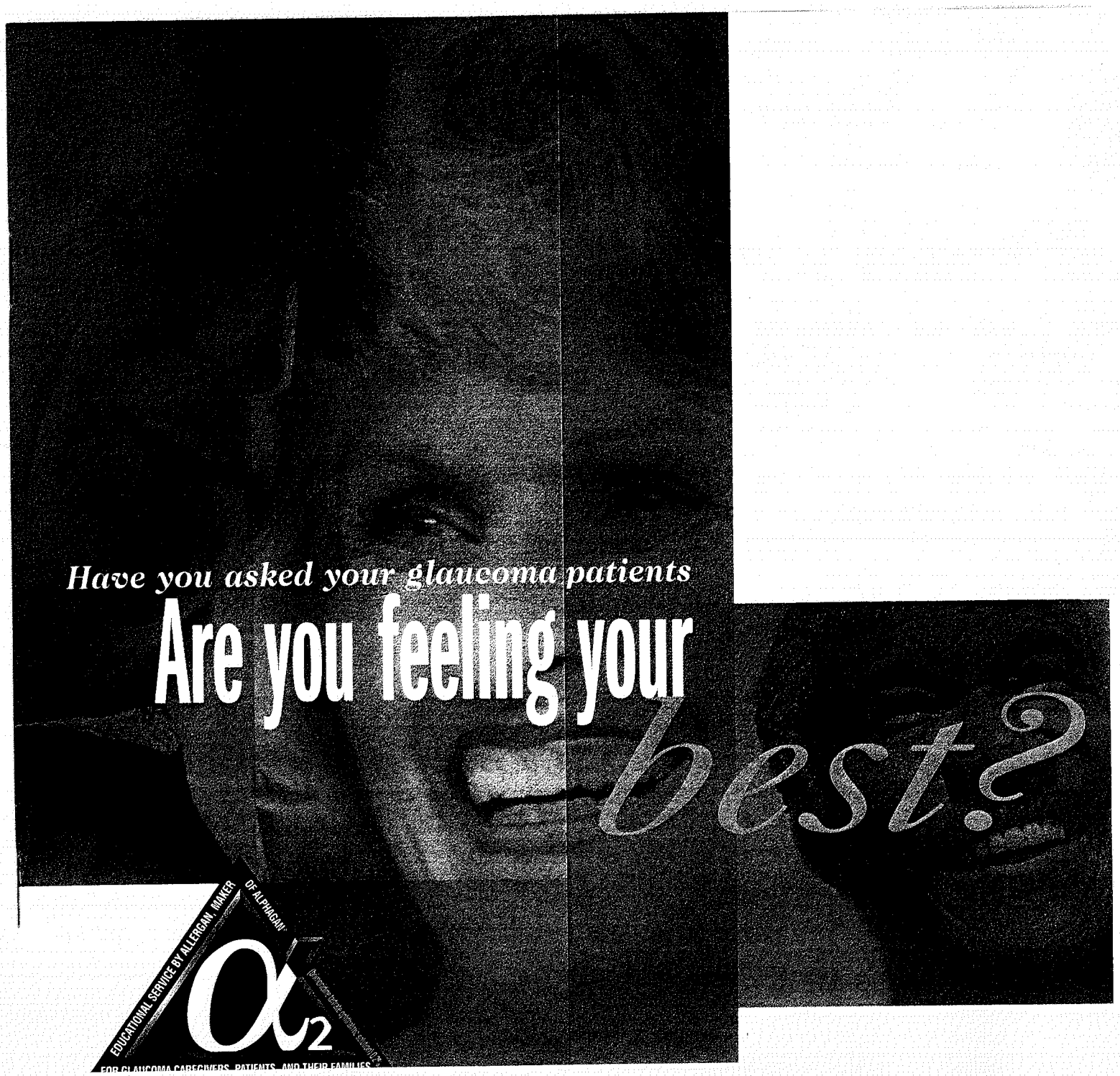
If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 8412 and NDA 20-613.

Sincerely,

/S/

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications


Have you asked your glaucoma patients
Are you feeling your best?
EDUCATIONAL SERVICE BY ALLERGAN, MAKER OF ALPHAGAN
FOR GLAUCOMA CAREGIVERS, PATIENTS, AND THEIR FAMILIES

For existing patients on beta-blocker therapy

Topically applied beta-blockers are easily absorbed into the bloodstream and can cause systemic side effects. As a result, patients using long-term therapy often develop conditions that were not apparent or were undiagnosed at the time you initiated therapy.[8] For example, patients may develop congestive heart failure or a slowed heart rate that is only clinically apparent with the use of a topical beta-blocker.[8]

Also of particular concern are patients taking other medications for a variety of coexisting systemic disorders. A systemically absorbed topical beta-blocker added to a patient's existing regimen can magnify or decrease the effects of their systemic medication.

This brochure will help you and your clinical staff identify and correlate patient symptoms with conditions associated with the use of topical beta-blockers. Once a potential risk is identified and you consider switching your patient to another agent, you may want to prescribe ALPHAGAN®—a safer alternative with proven first-line efficacy.[1-7] ALPHAGAN® ophthalmic solution is an ideal replacement therapy choice that can keep your existing glaucoma patients feeling their best.

In some patients IOP lowering diminishes over time and at varying times of onset. Patients should be monitored closely.

For newly diagnosed glaucoma patients

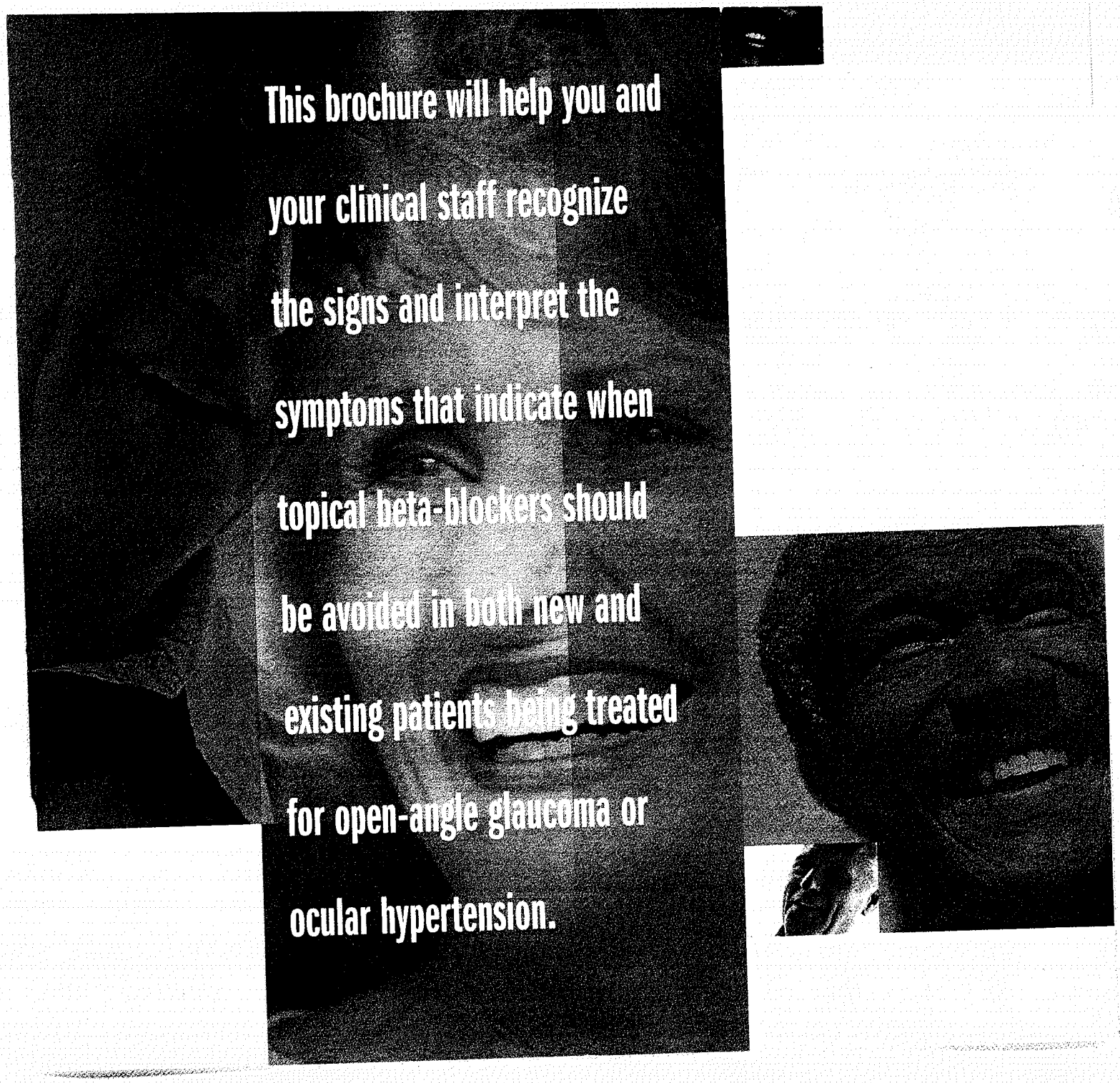
For more than 20 years, topical beta-blockers have been the most commonly prescribed drugs for the treatment of open-angle glaucoma or ocular hypertension. However, many limitations associated with their long-term use have emerged including systemic safety risks.

The risk for systemic side effects should be of real concern to ophthalmologists and clinical staff who are considering starting newly diagnosed glaucoma patients on one of these agents—especially given the availability of safer agents such as ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%.

This brochure will help you and your clinical staff carefully screen new patients who may be at risk for topical beta-blocker systemic side effects. To avoid such risks, you may want to consider prescribing an alternative IOP-lowering agent such as ALPHAGAN® ophthalmic solution.

Proven long-term efficacy comparable to timolol[1-6] combined with a favorable ocular and systemic safety profile[1-7] has made ALPHAGAN® a first-line choice that can keep your newly diagnosed glaucoma patients feeling their best.

Caution should be exercised in treating patients with severe cardiovascular disease. Patients should be monitored carefully.


This brochure will help you and your clinical staff recognize the signs and interpret the symptoms that indicate when topical beta-blockers should be avoided in both new and existing patients being treated for open-angle glaucoma or ocular hypertension.

Are your patients feeling their best?

Understanding Your Patients'

Ask your patients if they have a history of, or are taking medication for, any of the following conditions:

Cardiovascular effects[9-16] **such as:** ▶ Arrhythmia ▶ Bradycardia ▶ Congestive heart failure ▶ Hypotension	**Pulmonary effects**[9-11, 13, 14, 16] **such as:** ▶ Asthma ▶ Bronchial constriction ▶ Dyspnea	**Hyperlipidemia**[9-16]	**Diabetes**[9-11, 16]	**Central nervous system effects**[9-14, 16] **such as:** ▶ Depression ▶ Impotence
Commonly prescribed systemic beta-blockers: ▶ Atenolol ▶ Betapace® ▶ Blocadren® ▶ Corgard® ▶ Inderal® ▶ Inderal® LA ▶ Inderide® ▶ Inderide® LA ▶ Kerlone® ▶ Lopressor® ▶ Lopressor HCT® ▶ Normodyne® ▶ Propranolol® ▶ Sectral® ▶ Tenoretic® ▶ Tenormin® ▶ Timolide® ▶ Toprol-XL® ▶ Visken® ▶ Zebeta® ▶ Ziac®	Commonly prescribed respiratory agents: ▶ Aerobid® ▶ Atrovent® ▶ Azmacort® ▶ Beclovent® ▶ Brethine® ▶ Combivent® ▶ Flovent® ▶ Flovent® Rotadisk® ▶ Maxair® Autohaler® ▶ Maxair® Inhaler ▶ Proventil® ▶ Proventil® HFA ▶ Proventil® Repetabs® ▶ Pulmicort Turbuhaler® ▶ Serevent® ▶ Serevent® Diskus® ▶ Slo-Bid® Gyrocaps ▶ Theo-Dur® Extended Release Tablets ▶ Theo-24® Extended Release Capsules ▶ Uniphyl® ▶ Vanceril® ▶ Vanceril® Double Strength ▶ Ventolin® ▶ Volmax® Extended Release	Commonly prescribed cholesterol-reducing agents: ▶ Baycol® ▶ Colestid® ▶ Flavored Colestid® ▶ Lescol® ▶ Lipitor® ▶ Mevacor® ▶ Niaspan® ▶ Pravachol® ▶ Questran® ▶ Tricor® ▶ Zocor®	Commonly prescribed antidiabetic agents: ▶ Amaryl® ▶ Diaßeta® ▶ Glucophage® ▶ Glucotrol® ▶ Glucotrol XL® ▶ Glynase® Pres Tab® ▶ Humalog® Cartridge ▶ Humulin® ▶ Novolin® ▶ Novolin® PenFill® ▶ Novolin Prefilled® ▶ Prandin® ▶ Precose® ▶ Rezulin®	Commonly prescribed antidepressants: ▶ Desyrel® ▶ Effexor® ▶ Effexor® XR ▶ Paxil® ▶ Prozac® ▶ Remeron® ▶ Serzone® ▶ Wellbutrin® ▶ Wellbutrin SR® ▶ Zoloft® Commonly prescribed erectile dysfunction agent: ▶ Viagra®

This list is representative. Some medications may not be listed.

Conditions and Symptoms

The prevalence of coexisting systemic conditions and systemic beta-blocker use in glaucoma patients is an important consideration for making appropriate clinical management decisions, particularly when selecting first-line treatment. For example, because of the potential for adverse effects, patients taking antihypertensive beta-blockers are unlikely candidates for concomitant topical beta-blocker therapy. The prevalence of such patients taking systemic beta-blockers, or with concomitant conditions in which topical beta-blockers should be avoided, suggests careful evaluation of safer alternatives such as ALPHAGAN®.

Caution should be exercised in treating patients with severe cardiovascular disease.

Did you know ...

There is a high prevalence of systemic beta-blocker use and coexisting systemic conditions in glaucoma patients[16]

SYSTEMIC AGENT	
19%	Systemic antihypertensive beta-blocker
SYSTEMIC DISORDER	
17%	Diabetes mellitus
8%	Anxiety/depression
7%	Asthma
6%	Hyperlipidemia

The records of 100 consecutive patients with chronic open-angle glaucoma (IOP greater than 21 mm Hg before therapy) were studied to determine the most common systemic medications prescribed in this population. Data were assessed to determine interactions of glaucoma and systemic medications, influence of glaucoma medications on general health, and influence of systemic medications on the ocular status.

Literature suggests that topical beta-blockers should typically be avoided or used with caution in these patients.[8,11,16-18]

Understanding Your Patients'

For existing patients on topical beta-blocker therapy

Topically applied beta-blockers have historically been the most commonly prescribed IOP-lowering medication. From this extensive experience, however, many clinical limitations associated with their use have emerged. Due to systemic side effects, a significant percentage of patients cannot use topical beta-blockers or have subtle cumulative side effects. As a result, many ophthalmologists are turning to safer agents, such as ALPHAGAN®, as their preferred first-line IOP-lowering medication.

As with all agents, caution should be exercised in treating patients with severe cardiovascular disease.

Did you know ...

Many glaucoma patients are unable to use nonselective topical beta-blockers[9]

12%	had systemic contraindications
10%	discontinued treatment due to side effects
22%	**total percentage unable to use beta-blockers**

Patients with systemic contraindications to starting beta-blocker therapy and those without contraindications who discontinued treatment due to side effects.

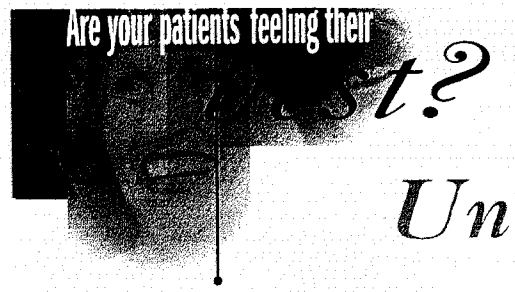
Study was conducted as a retrospective chart review of 310 consecutive patients with glaucoma or severe ocular hypertension requiring medical therapy for elevated IOP.

Conditions and Symptoms

It is important for you to be able to identify symptoms that may be compromising the health and well-being of your glaucoma patients.

When speaking with your patients, be sure to observe their general state of health, listen for complaints, and specifically ask about topical beta-blocker side effects. Follow up with questions to get more information about their symptoms if you notice any of the following:

Look and listen for the following symptoms:
▶ Irregular heartbeat (too fast or too slow)
▶ Difficulty breathing or constant coughing
▶ Exercise intolerance
▶ Feeling tired, depressed, or sad
▶ Generally not feeling well
▶ Tired, yawning
▶ Feeling dizzy or light-headed
▶ Confusion
▶ Recently fallen down
▶ Reduction in sexual desire or performance
▶ Having a problem with other medications



Understanding Your Patients'

Because of the potential for systemic adverse events with the use of topical beta-blockers, these agents have more contraindications to therapy with respect to both comorbidities and drug interactions than the newer IOP-lowering medications.[19] The systemic adverse effects seen with topical beta-blockers are particularly worrisome in the treatment of elderly patients, many of whom are receiving multiple medications for coexisting disease states.[19] Conditions such as impaired respiratory function and depression may go unnoticed in this patient population but can be exacerbated by topically applied beta-blockers.[19] The table on the next page will help you correlate patient symptoms with conditions associated with topical nonselective beta-blockers.

Upon reviewing the table on the next page, you may consider evaluating other IOP-lowering agents and, for some patients, prescribe a safer alternative, such as ALPHAGAN®, for long-term IOP control.

SYMPTOMS	POTENTIAL ASSOCIATION WITH BETA-BLOCKERS
Irregular heartbeat, heart beating differently	Arrhythmia, bradycardia, and hypotension—a result of lowered blood pressure—are well-known cardiovascular effects of ocular administration of beta-blockers. If you hear symptoms that may be related to profound bradycardia, take your patient's pulse. A patient with a very slow pulse should be referred to an internist.[9,16-19]
Difficulty breathing or constant coughing	Pulmonary effects seen with beta-blockers include asthma, bronchial constriction, bronchospasm, and dyspnea. Patients with asthma are at particular risk. Beta-blockers can cause and aggravate pulmonary edema and aggravate existing COPD.[9,10,16,17]

Conditions and Symptoms

SYMPTOMS	POTENTIAL ASSOCIATION WITH BETA-BLOCKERS
Exercise intolerance	Topical beta-blockers have a significant effect on both maximal heart rate and time exhaustion, reducing exercise tolerance and performance.[15,17,19]
Feeling tired, depressed, or sad	Clinical depression is one of the most commonly unrecognized side effects of beta-blocker therapy. A change in medication may benefit a patient's mental health.[14,19]
Generally not feeling well	Because beta-blockers are systemic drugs, they can cause your patients to not feel their best overall. Inquire about specific events or complaints.[16,18,19]
Tired, yawning	Fatigue is common with beta-blocker treatment and may be a sign of depression.[11,17,19]
Balance problems or dizziness, confusion, falling	Dizziness and confusion are common CNS effects seen with beta-blocker treatment. Fainting and/or numbness in limbs may also be associated.[9,14,17]
Changes or a reduction in sexual desire or performance	Impotence may result from the use of beta-blockers. However, many patients may be uncomfortable and unwilling to talk about this condition. Discussion with a healthcare professional of the same sex or discussion including your patient's spouse or sexual partner may help ease conversation.[14,19]
Having a problem with other medications	There is a real potential for adverse drug interactions when topical beta-blockers are combined with other systemic medications. In patients taking antidiabetic agents, beta-blockers can decrease blood sugar, mask hypoglycemia, and delay recovery.[8-11,16-18]

Please see full prescribing information located in this kit.

1. Data on file, Allergan, Inc.

2. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Surv Ophthalmol.* 1996;41(suppl 1):S27-S37.

3. Schuman JS, Horwitz B, Choplin NT, et al, and the Chronic Brimonidine Study Group. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. *Arch Ophthalmol.* 1997;115(7):847-852.

4. Katz LJ, and the Brimonidine Study Group. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. *Am J Ophthalmol.* 1999;127(1):20-26.

5. LeBlanc RP, for the Brimonidine Study Group 2. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. *Ophthalmology.* 1998;105(10):1960-1967.

6. Melamed S, David R, for the Brimonidine Study Group II. Ongoing clinical assessment of the safety profile and efficacy of brimonidine compared with timolol: year-three results. *Clin Ther.* 2000;22(1):103-111.

7. ALPHAGAN® Prescribing Information.

8. Quinn CJ. A continuing role for topical beta-blockers. *Rev Optom.* 1999;136(6):127.

9. Kolker AE, May MM, Day SE. Frequency of contraindications to topical beta-blockers in a glaucoma population. Presented at: The Association for Research in Vision and Ophthalmology; May 9-14, 1999; Ft Lauderdale, Fla.

10. Fraunfelder FT, Meyer SM. Systemic side effects from ophthalmic timolol and their prevention. *J Ocul Pharmacol.* 1987;3(2):177-184.

11. Jou D, Lee DA. Glaucoma medications: first, do no harm. *Rev Ophthalmol.* 1998;5(6):84-89.

12. Stewart WC. When to switch patients to one of the newer glaucoma medications. *Rev Ophthalmol.* 1998;5(7):76-82.

13. Sadiq SA, Fielding K, Vernon SA. The effect of timolol drops on respiratory function. *Eye.* 1998;12(38):386-389.

14. Rait JL. Systemic effects of topical ophthalmic β-adrenoceptor antagonists. *Aust N Z J Ophthalmol.* 1999;27(1):57-64.

15. Doyle WJ, Weber PA, Meeks RH. Effect of topical timolol maleate on exercise performance. *Arch Ophthalmol.* 1984;102:1517-1518.

16. Gottfredsdottir MS, Allingham RR, Shields MB. Physicians' guide to interactions between glaucoma and systemic medications. *J Glaucoma.* 1997;6(6):377-383.

17. Eye drops can cause systemic effects. *Drugs Ther Perspect.* 1998;12(3):13-16.

18. Fraunfelder FT, Meyer SM. Systemic reactions to ophthalmic drug preparations. *Med Toxicol.* 1987;2:287-293.

19. Schuman JS. Antiglaucoma medications: a review of safety and tolerability issues related to their use. *Clin Ther.* 2000;22(2):167-208.

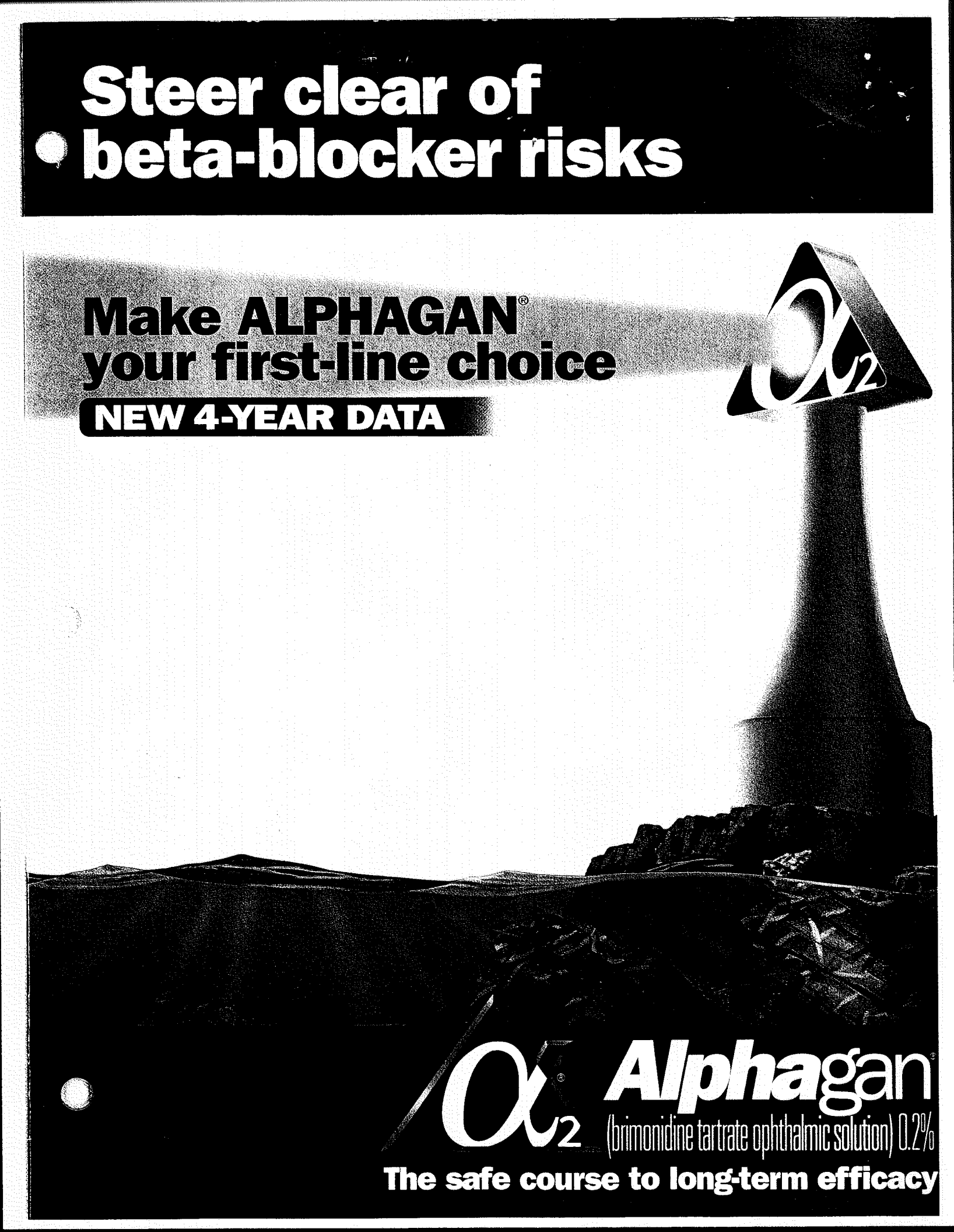
ALLERGAN

www.allergan.com

Steer clear of beta-blocker risks

Make ALPHAGAN® your first-line choice

NEW 4-YEAR DATA

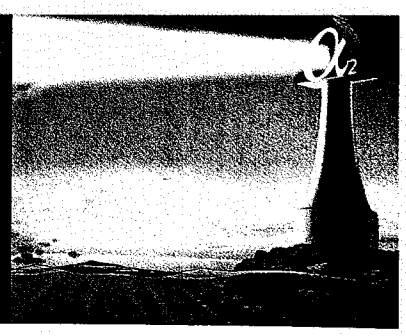


α_2 **Alphagan®**

(brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Proven first-line efficacy



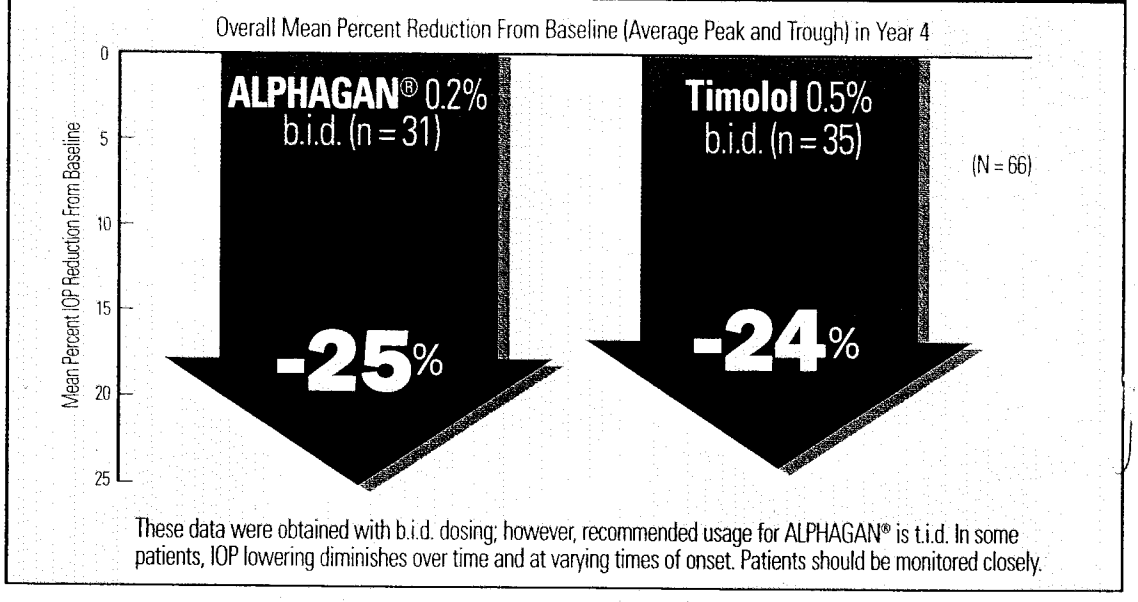
First-line mean peak IOP reduction (26.3%) comparable to timolol (24.4%) at the end of year 1 (N=837)[1-6]

First-line IOP reduction at trough comparable to timolol over 3 years (N=93)[1,2]

These data were obtained with b.i.d. dosing; however, recommended usage for ALPHAGAN® is t.i.d.

Year 1 | Year 2 | Year 3 | **NEW 4-Year Data**[1]

Sustained First-Line IOP Reduction Comparable to Timolol



These data were obtained with b.i.d. dosing; however, recommended usage for ALPHAGAN® is t.i.d. In some patients, IOP lowering diminishes over time and at varying times of onset. Patients should be monitored closely.

ALPHAGAN® is indicated for lowering IOP in patients with open-angle glaucoma or ocular hypertension.

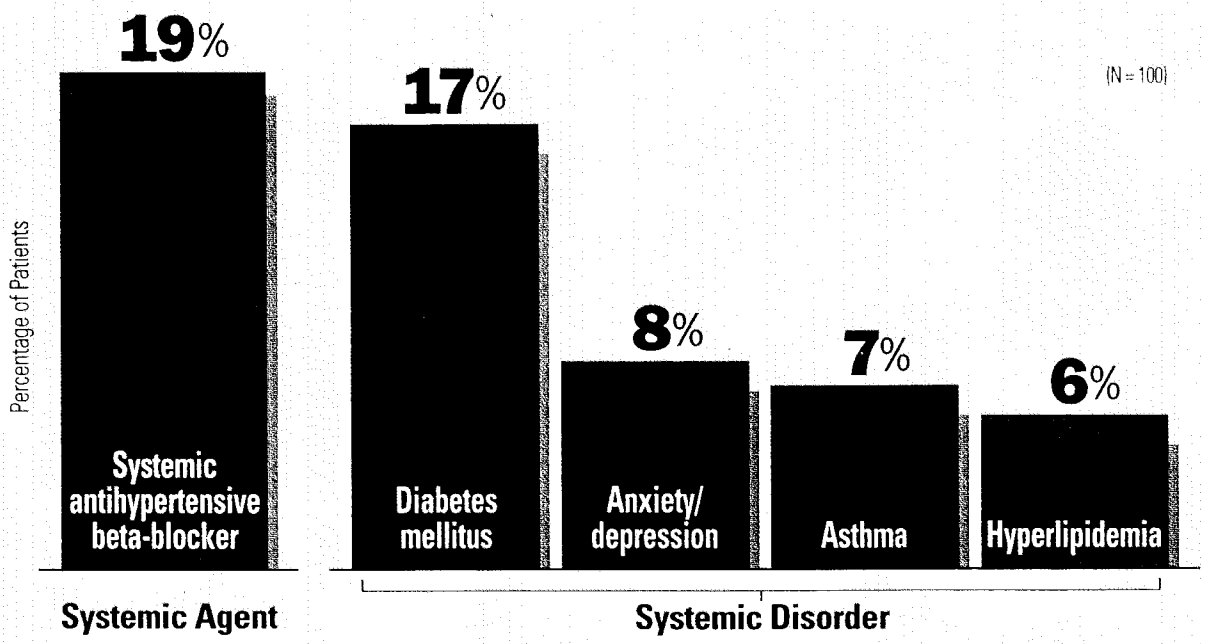
α_2 **Alphagan®**
(brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Steer clear of beta-blocker risks

Before you prescribe an IOP-lowering agent, consider the risks of a topical nonselective beta-blocker[7-11]

Prevalence of Coexisting Systemic Conditions and Systemic Beta-Blocker Use in Patients With Glaucoma[11]

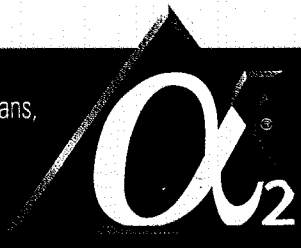


The records of 100 consecutive patients with chronic open-angle glaucoma (IOP greater than 21 mm Hg before therapy) were studied to determine the most common systemic medications prescribed in this population. Data were assessed to determine interactions of glaucoma and systemic medications, influence of glaucoma medications on general health, and influence of systemic medications on the ocular status.

Literature suggests that topical nonselective beta-blockers should typically be avoided or used with caution in these patients[7-11]

Caution should be exercised in treating patients with severe cardiovascular disease. Patients should be monitored carefully.

NOTE TO REPRESENTATIVE: When providing this material to physicians, present and leave full prescribing information.



Alphagan

(brimonidine tartrate ophthalmic solution) 0.

The safe course to long-term efficac

Steer clear of beta-blocker risks

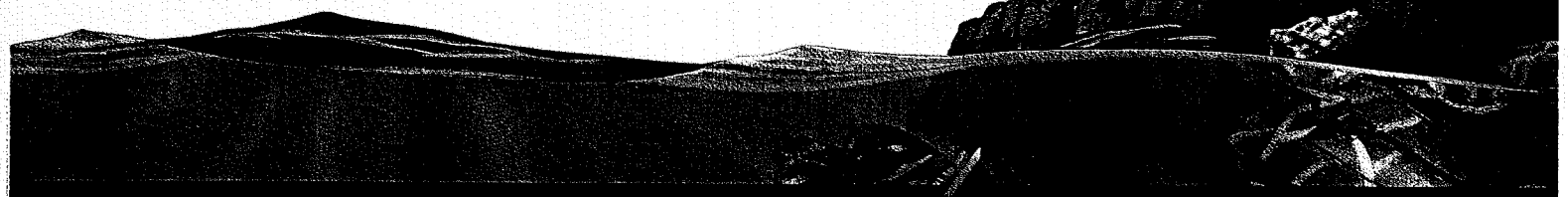
NEW 4-Year Data

Make ALPHAGAN® your first-line choice

First-line mean peak IOP reduction (26.3%) comparable to timolol (24.4%) at the end of year 1 (N=837)[1-6]

Sustained first-line IOP reduction comparable to timolol over 4 years (N=66)[1]

Favorable long-term ocular and systemic safety[1-6,12]



ALPHAGAN® is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy. Among the most frequently reported adverse events were oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign-body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

ALLERGAN 50 Years of Growth & Innovation

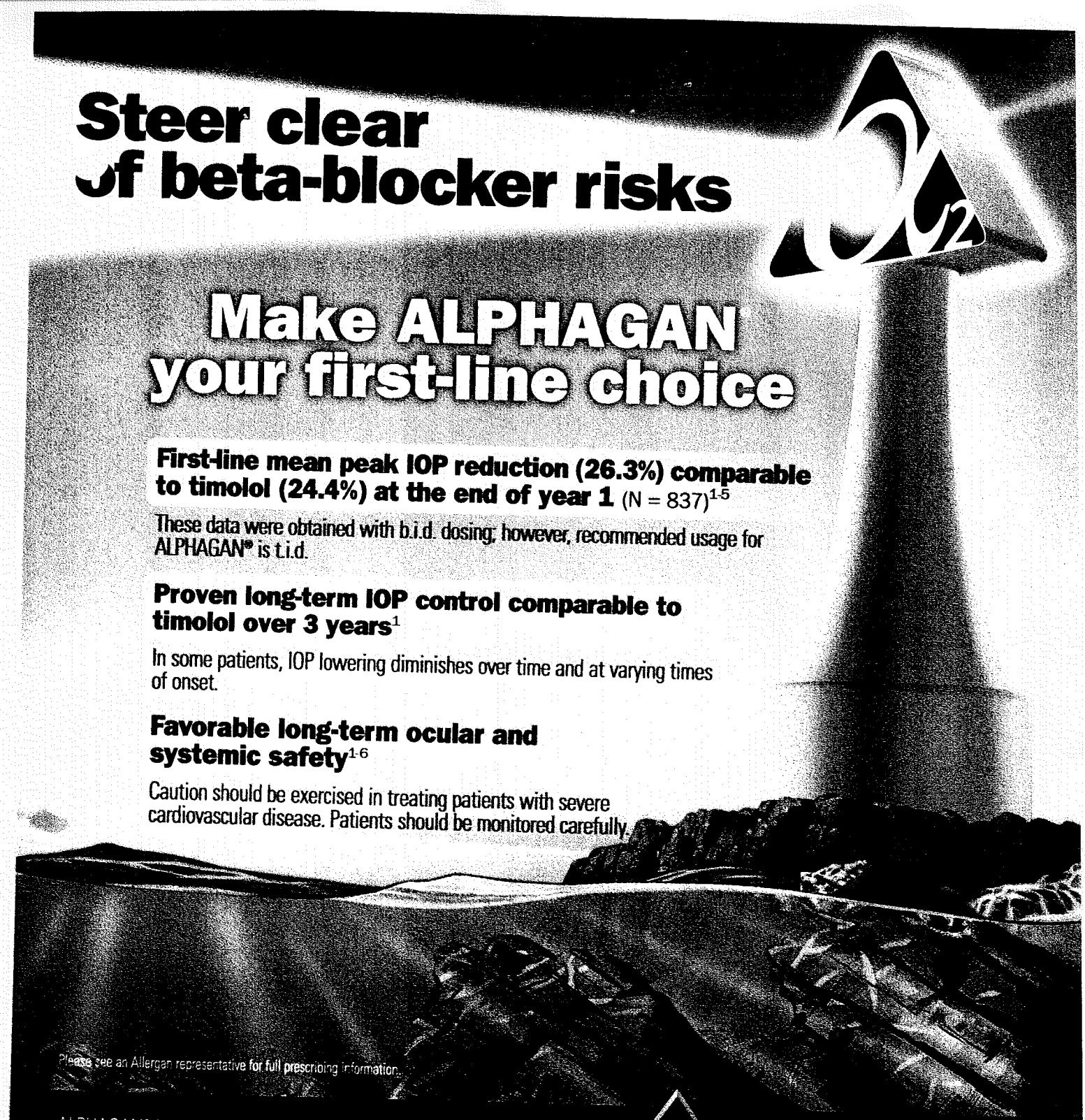
Alphagan
(brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

1. Data on file, Allergan, Inc. 2. Molarnes S, David R, for the Brimonidine Study Group II. Ongoing clinical assessment of the safety profile and efficacy of brimonidine compared with timolol: year-three results. *Clin Ther.* 2000;22(1):103-111. 3. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Surv Ophthalmol.* 1996;41 suppl 1:S27-S37. 4. Schuman JS, Horwitz B, Choplin NT, et al, and the Chronic Brimonidine Study Group. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. *Arch Ophthalmol.* 1997;115(7):847-852. 5. Katz LJ, and the Brimonidine Study Group. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. *Am J Ophthalmol.* 1999;127(1):20-26. 6. LeBlanc RP, for the Brimonidine Study Group 2. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. *Ophthalmology.* 1999;106(10):1960-1967. 7. Quinn CJ. A continuing role for topical beta-blockers. *Rev Optom.* 1999;136(6):127. 8. Eye drops can cause systemic effects. *Drugs Ther Perspect.* 1998;12(3):13-16. 9. Fraunfelder FT, Meyer SM. Systemic reactions to ophthalmic drug preparations. *Med Toxicol.* 1987;2:287-293. 10. Joo D, Lee DA. Glaucoma medications: first, do no harm. *Rev Ophthalmol.* 1998;5(6):84-89. 11. Gottfredsdottir MS, Allingham RR, Shields MB. Physician's guide to interactions between glaucoma and systemic medications. *J Glaucoma.* 1997;6:377-383. 12. ALPHAGAN® Prescribing Information.

RX3535

Steer clear of beta-blocker risks



Make ALPHAGAN your first-line choice

First-line mean peak IOP reduction (26.3%) comparable to timolol (24.4%) at the end of year 1 (N = 837)[1-5]

These data were obtained with b.i.d. dosing; however, recommended usage for ALPHAGAN® is t.i.d.

Proven long-term IOP control comparable to timolol over 3 years[1]

In some patients, IOP lowering diminishes over time and at varying times of onset.

Favorable long-term ocular and systemic safety[1-6]

Caution should be exercised in treating patients with severe cardiovascular disease. Patients should be monitored carefully.

Please see an Allergan representative for full prescribing information.

ALPHAGAN® is indicated for lowering IOP in patients with open-angle glaucoma or ocular hypertension.

ALPHAGAN® is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy. Among the most frequently reported adverse events were oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign-body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

ALLERGAN

Alphagan® (brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Steer clear of first-line risks

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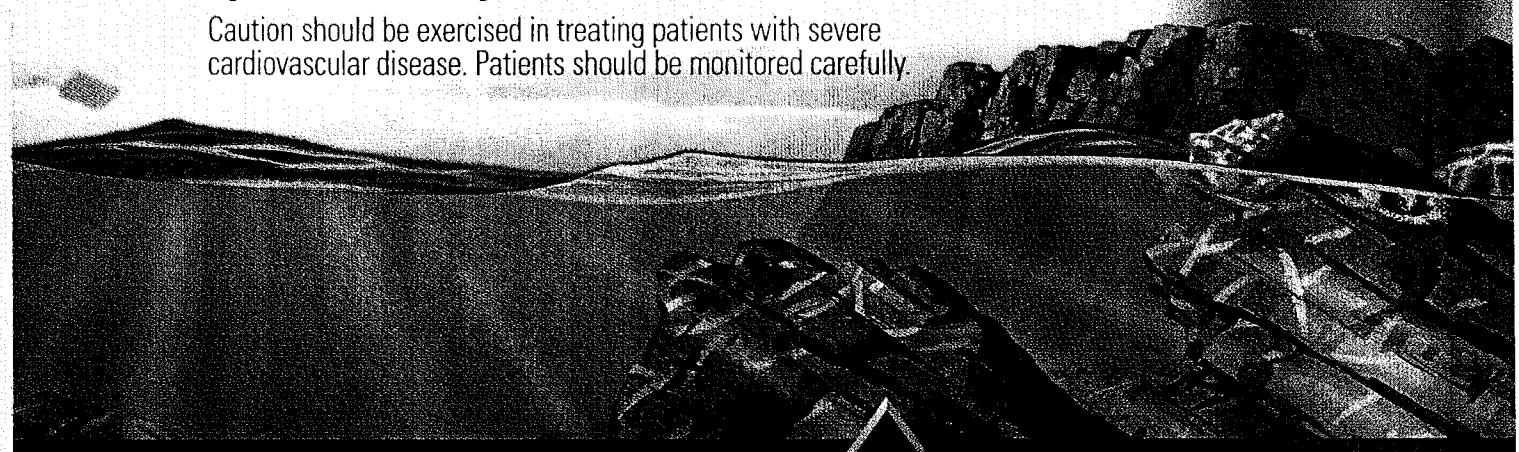

Please see brief prescribing information on adjacent page.

ALLERGAN

www.allergan.com

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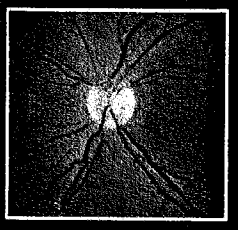
SInC 99-369

Cup-to-Disc Ratio Guid



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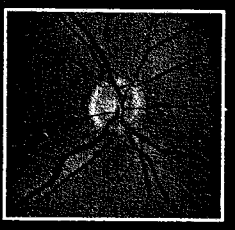

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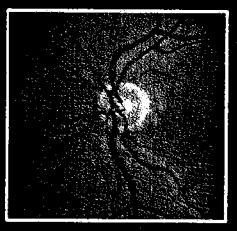

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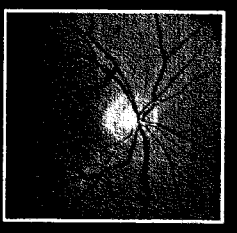

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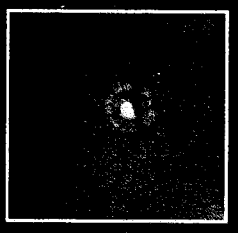

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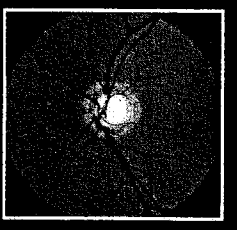

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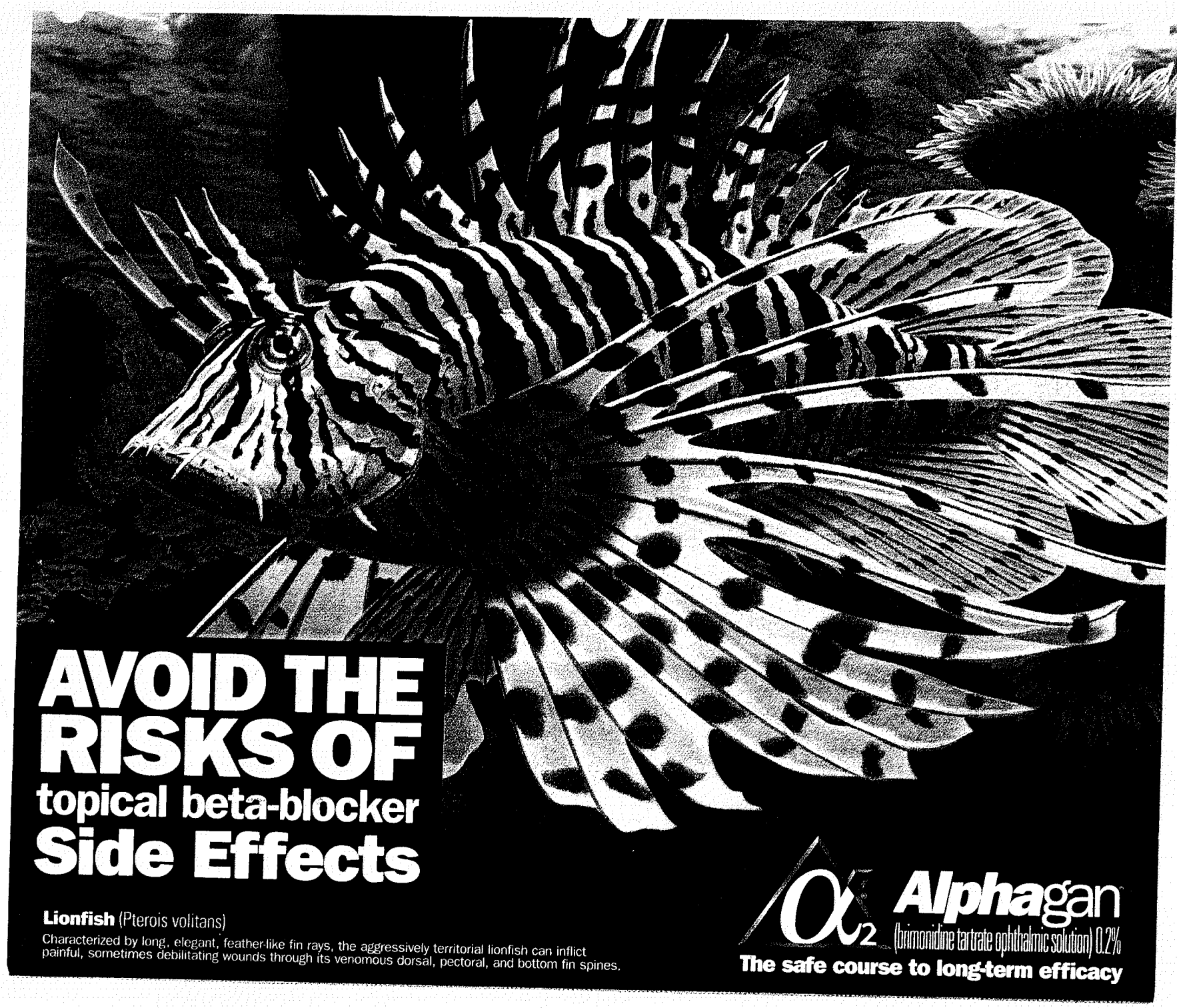
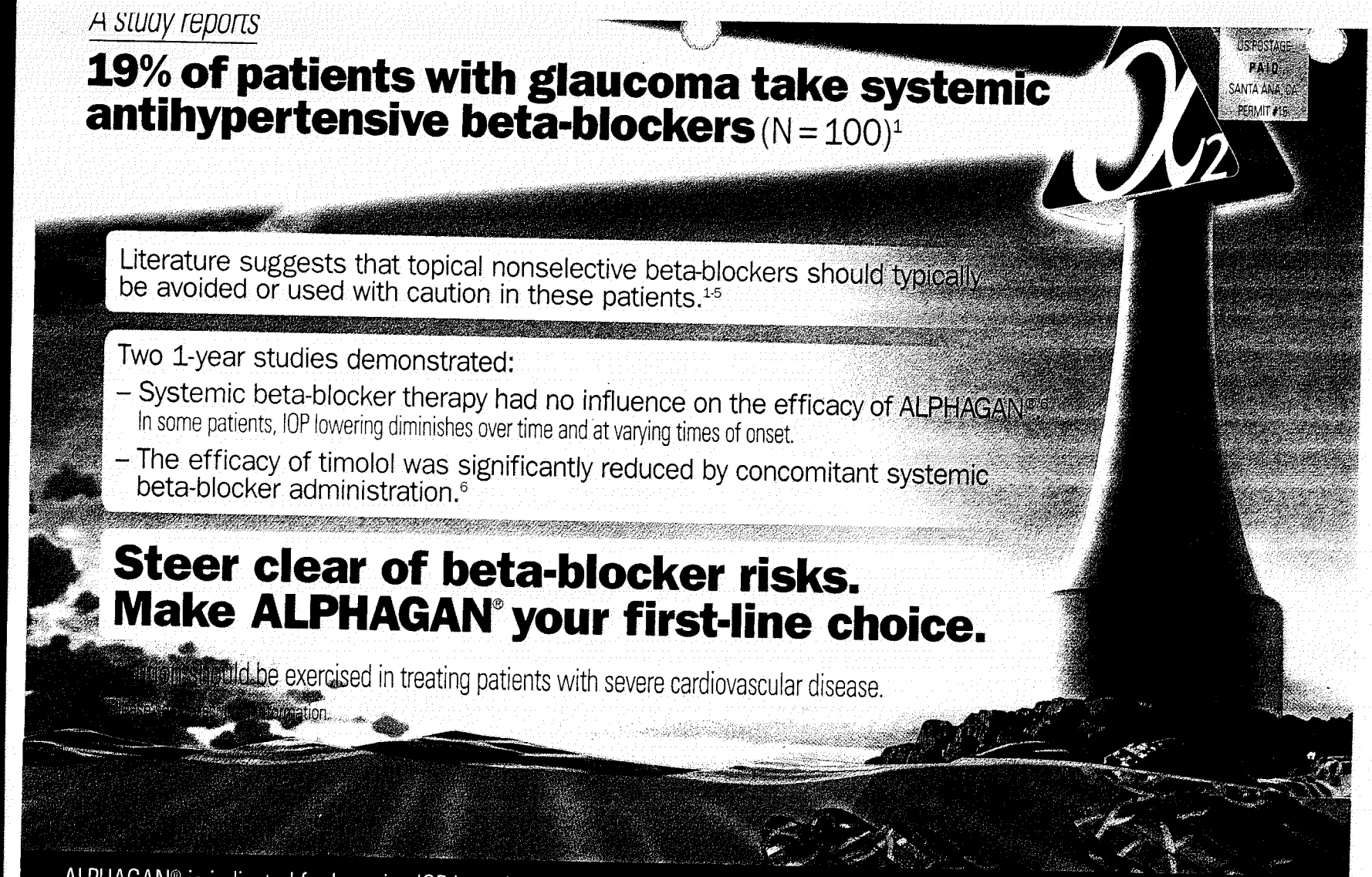
Provided as a professional education service by Allergan, Inc.
Please see accompanying full prescribing information.


AVOID THE
RISKS OF
topical beta-blocker
Side Effects
Lionfish (Pterois volitans)
Characterized by long, elegant, feather-like fin rays, the aggressively territorial lionfish can inflict painful, sometimes debilitating wounds through its venomous dorsal, pectoral, and bottom fin spines.
α2 Alphagan
(brimonidine tartrate ophthalmic solution) 0.2%
The safe course to long-term efficacy

A study reports

19% of patients with glaucoma take systemic antihypertensive beta-blockers (N = 100)[1]



Literature suggests that topical nonselective beta-blockers should typically be avoided or used with caution in these patients.[1-5]

Two 1-year studies demonstrated:

- Systemic beta-blocker therapy had no influence on the efficacy of ALPHAGAN®.[6] In some patients, IOP lowering diminishes over time and at varying times of onset.
- The efficacy of timolol was significantly reduced by concomitant systemic beta-blocker administration.[6]

Steer clear of beta-blocker risks. Make ALPHAGAN® your first-line choice.

caution should be exercised in treating patients with severe cardiovascular disease.

...information.

ALPHAGAN® is indicated for lowering IOP in patients with open-angle glaucoma or ocular hypertension.

ALPHAGAN® is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy. Among the most frequently reported adverse events were oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign-body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

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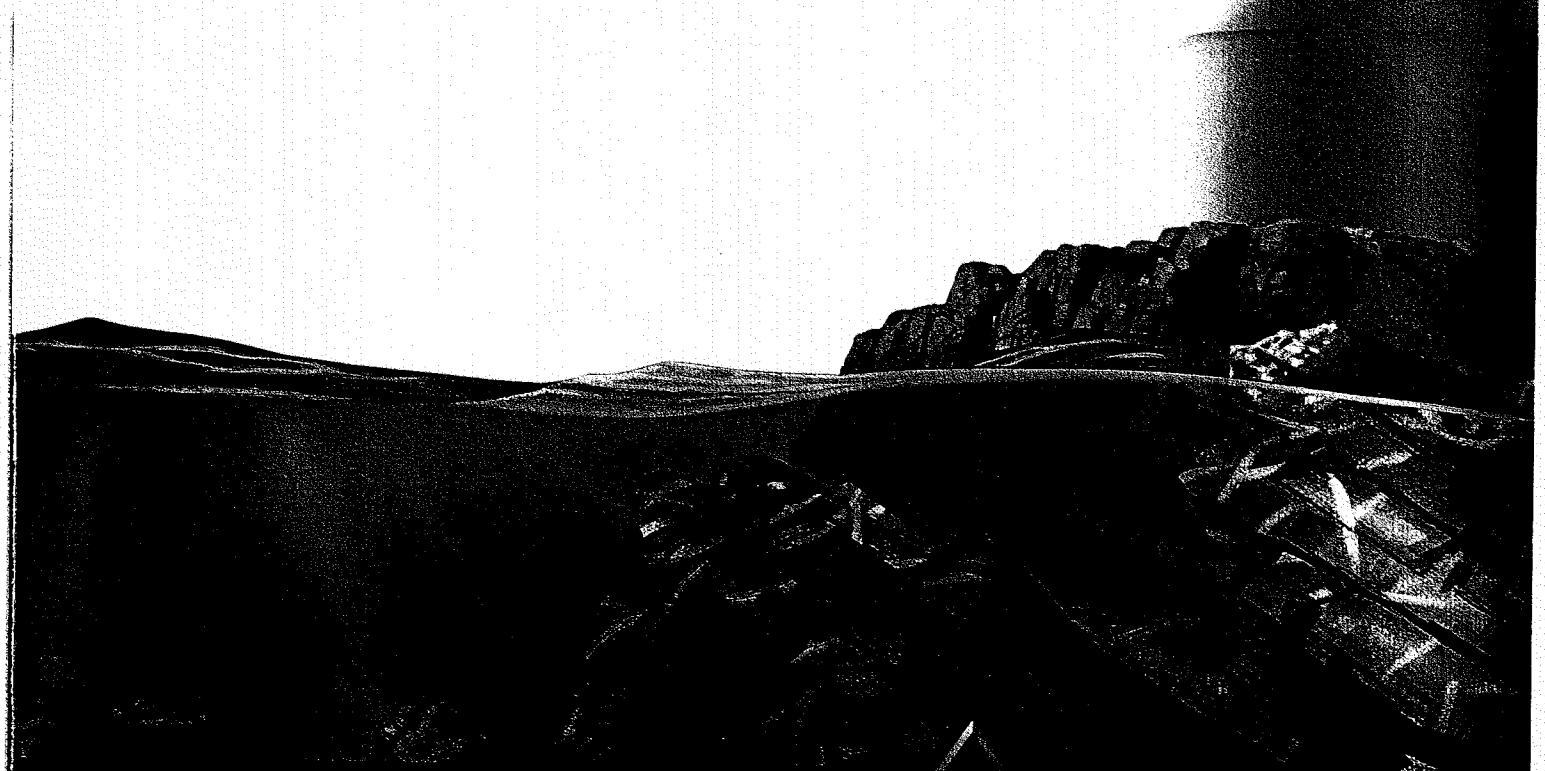
Alphagan® (brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Steer clear of first-line risks

Make ALPHAGAN® your first-line choice



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Alphagan® (brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Proven first-line efficacy

First-line mean peak IOP reduction (26.3%) comparable to timolol (24.4%) at the end of year 1 (N = 837)[1-5]

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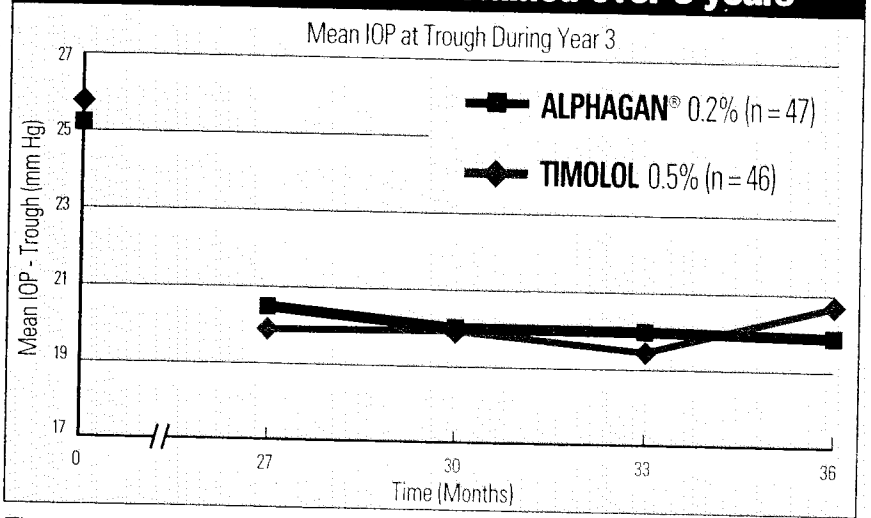
First-Line IOP reduction sustained over 3 years[1]



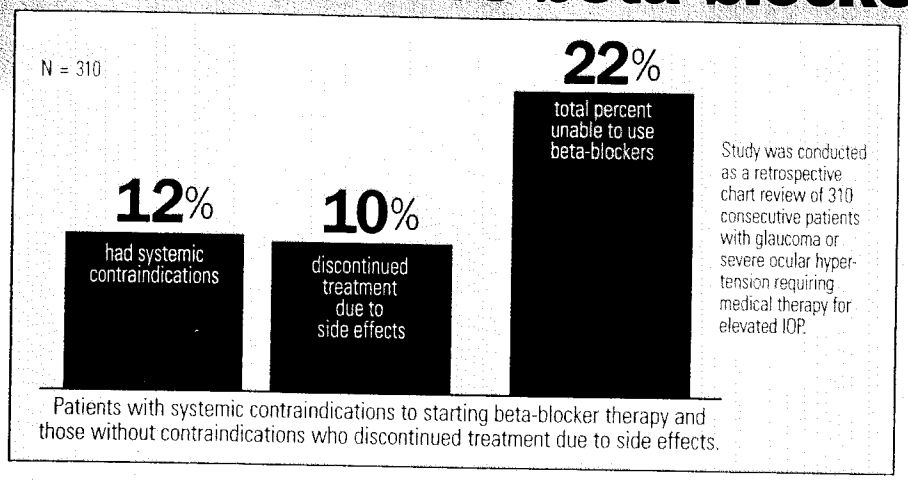
These data were obtained with b.i.d. dosing; however, recommended usage for ALPHAGAN® is t.i.d.

Minimize first-line concerns.
Make ALPHAGAN® your first-line choice.

Alphagan
(brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Many patients are unable to use nonselective beta-blockers[6]



Patients with systemic contraindications to starting beta-blocker therapy and those without contraindications who discontinued treatment due to side effects.

Side effects often go unreported

- Elderly patients regard many symptoms as consequences of aging[7]
- Patients do not necessarily associate systemic side effects with topically applied agents[8,9]
- As a result, patients do not report these often unrecognizable side effects[7,9,10]

Patients on other drug regimens may be adversely affected by topical ophthalmic agents[11]

Minimize first-line concerns.
Make ALPHAGAN® your first-line choice.

Alphagan®
(brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

Make ALPHAGAN® your first-line choice for new starts and switches

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Favorable long-term ocular and systemic safety[1-5,12]

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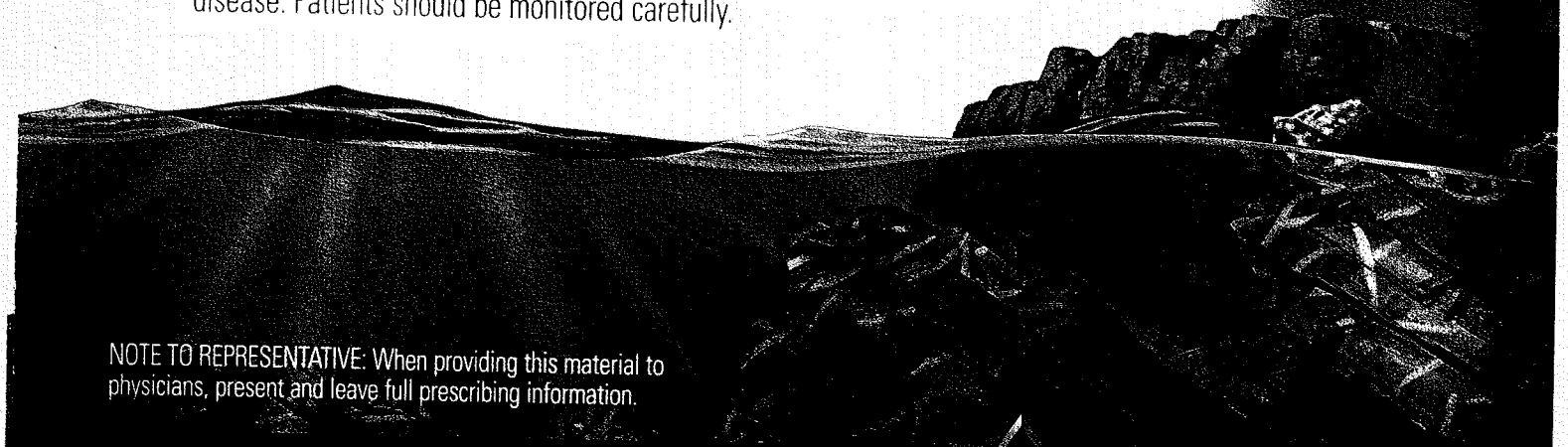

NOTE TO REPRESENTATIVE: When providing this material to physicians, present and leave full prescribing information.

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α_2 **Alphagan** (brimonidine tartrate ophthalmic solution) 0.2%

The safe course to long-term efficacy

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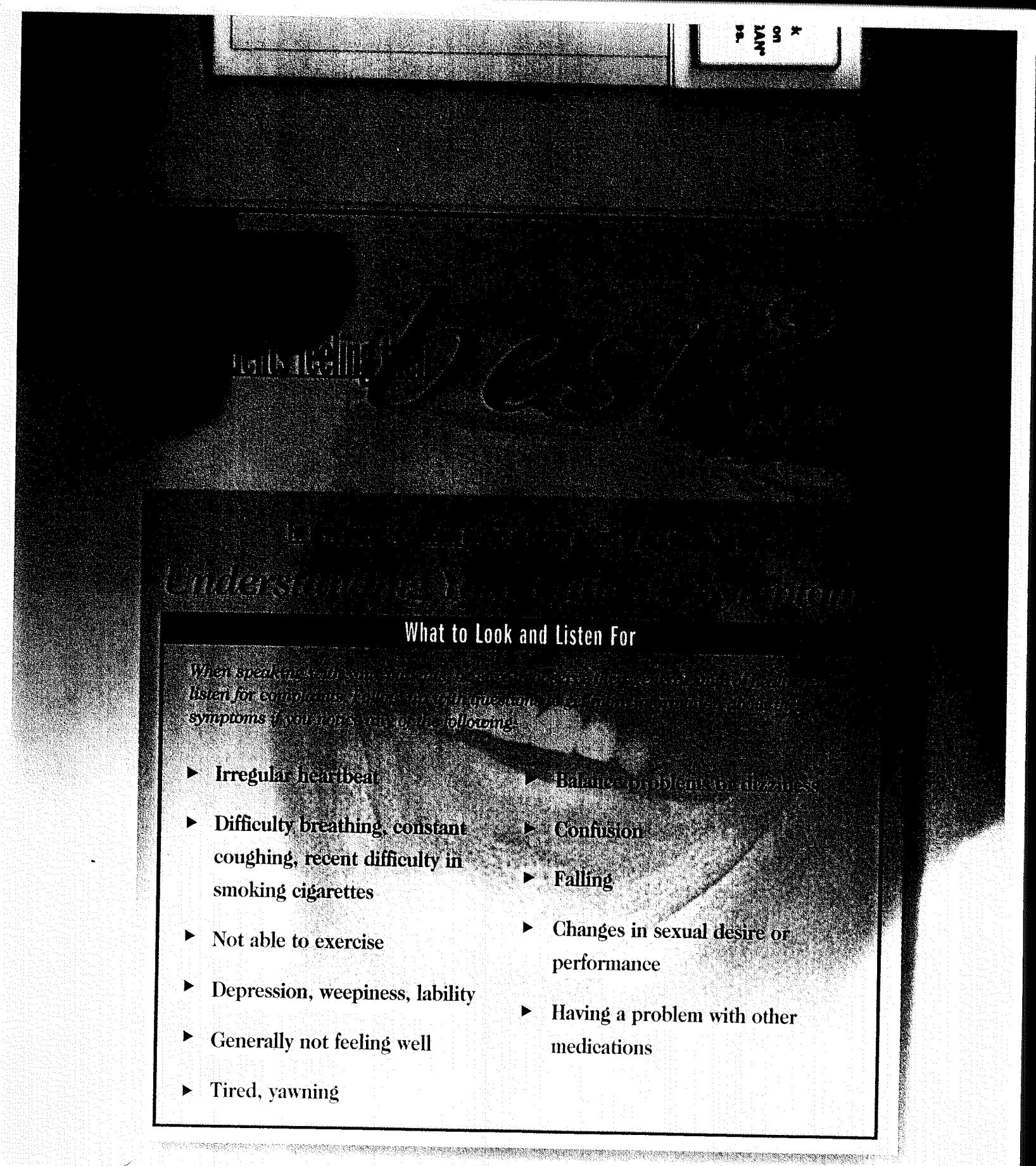
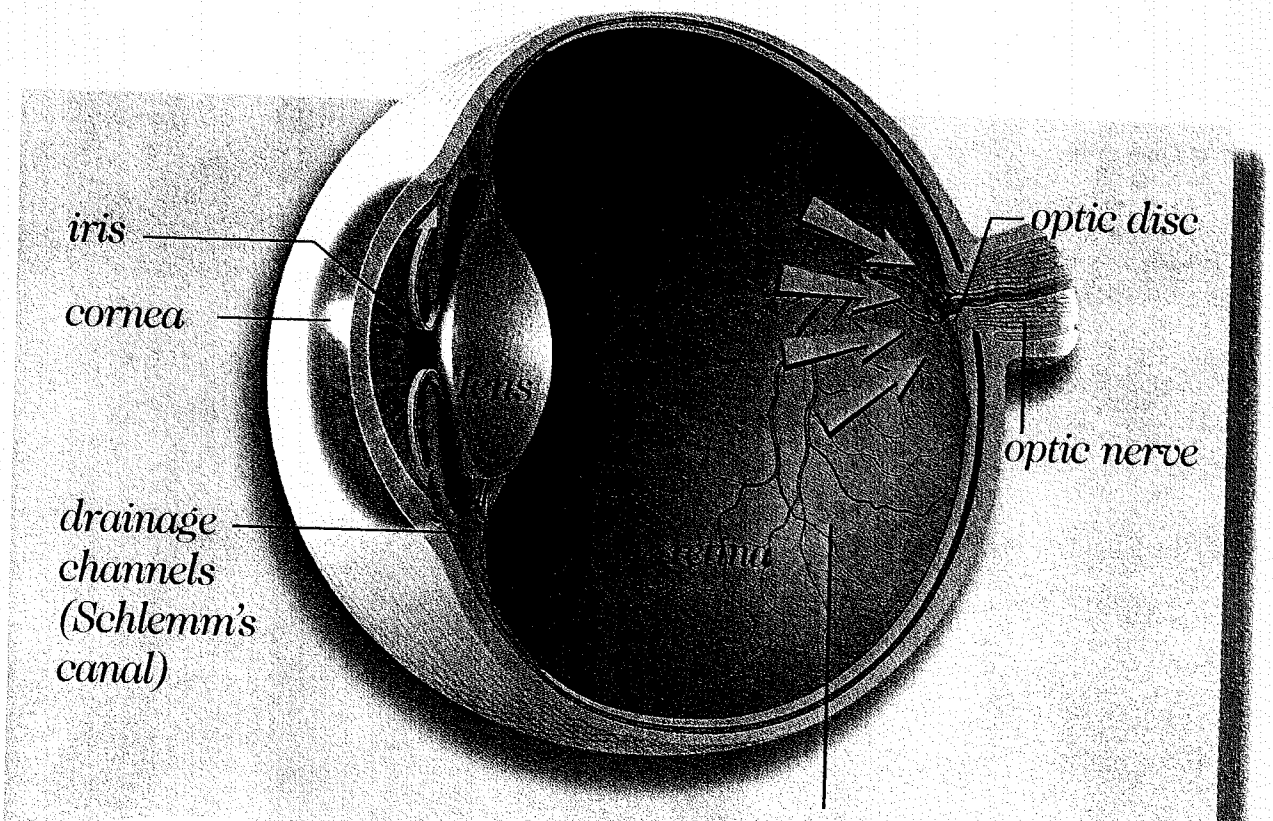
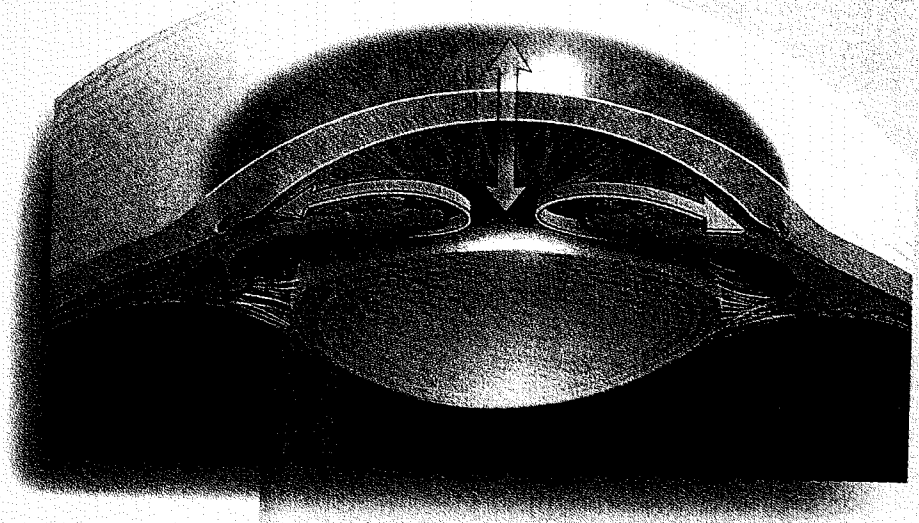
RX0476



Avoid beta-blocker risks. Choose ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% for new and existing patients. Please see the "Are you feeling your best?" clinical staff training brochure for more information about recognizing the signs and interpreting the symptoms that indicate when beta-blockers should be avoided. Caution should be exercised in treating patients with severe cardiovascular disease.

Are your patients feeling their best?





Fluid builds up inside the eye, causing increased pressure that may damage the optic nerve.

IOP-lowering medications work to either:

- Limit the amount of fluid produced inside the eye

And/Or

- Increase the flow of fluid out of the eye

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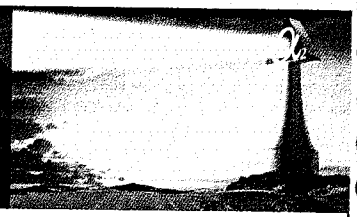
Alphagan® (brimonidine tartrate ophthalmic solution) 0.2%

course to long-term efficacy

ke ALPHAGAN®
ır first-line choice



2000

January

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August

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September

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October

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November

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December

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31						

AN® is contraindicated in patients
monoamine oxidase (MAO)
therapy.

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(brimonidine tartrate ophthalmic solution) 0.2%
The safe course to long-term efficacy

Steer clear of beta-blocker risks

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Favorable long-term ocular and systemic safety[1-7]

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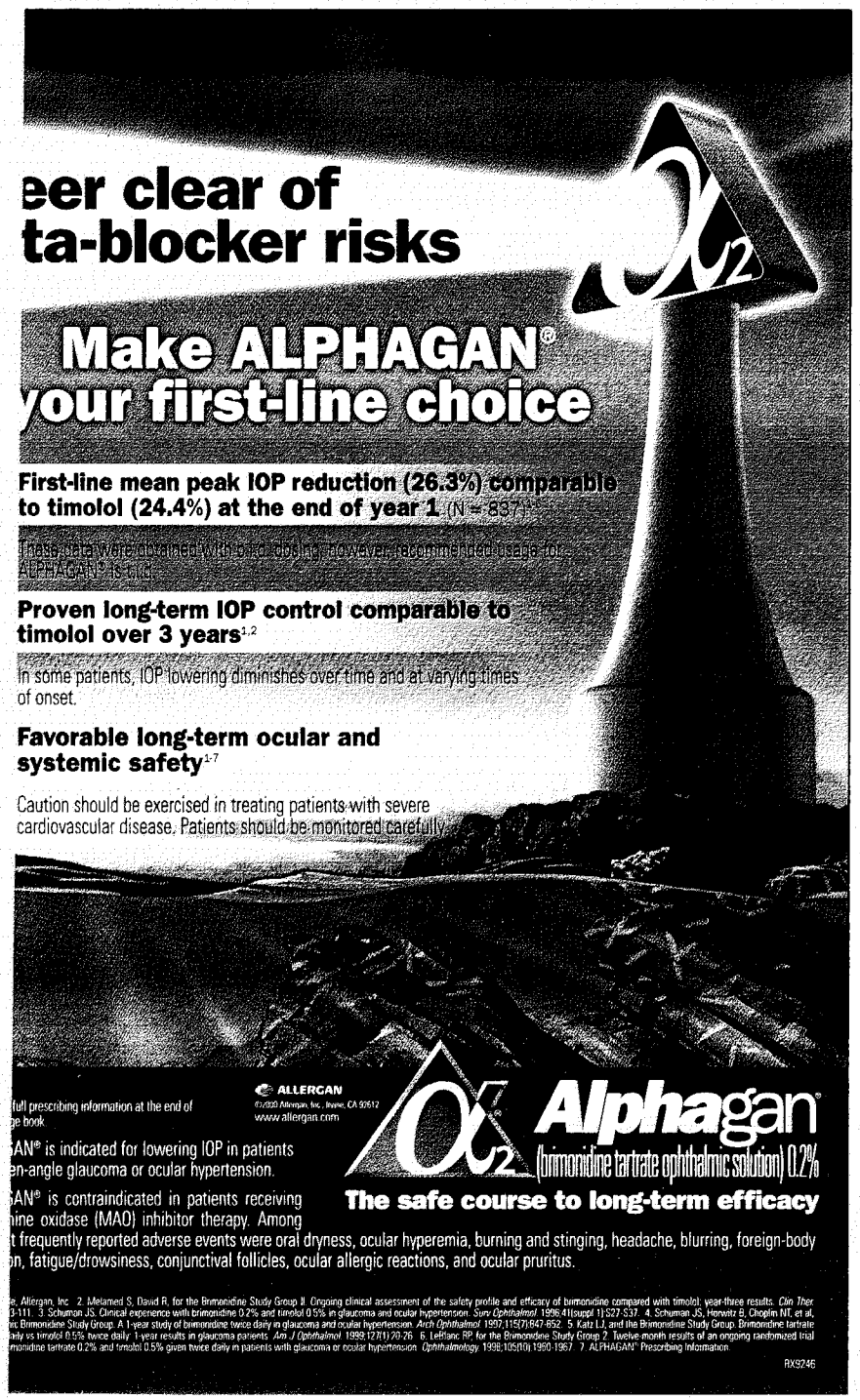
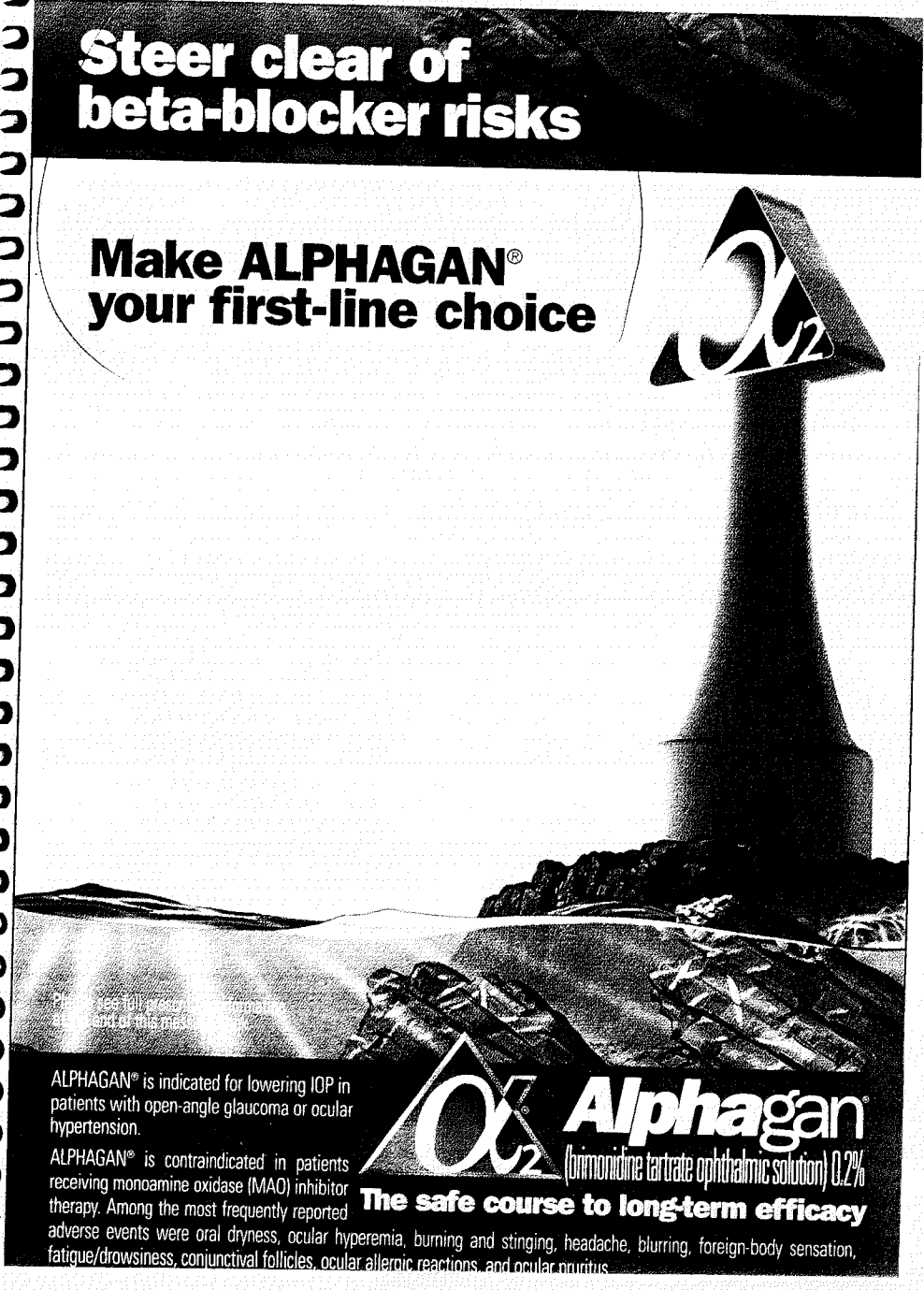
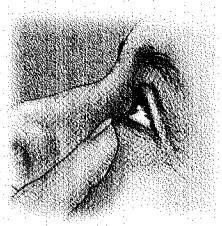


Phone Messages

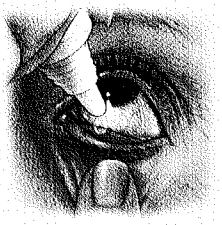


How do I use my eye drops?



1. Wash your hands.
2. Tilt your head back and look at the ceiling.

3. Using your index finger, gently pull down your lower eyelid and form a pocket.



4. Gently squeeze 1 drop into the pocket. Do not let the bottle tip touch your eye, your fingers, or any other surface.

5. Close your eye for about 2 to 5 minutes, and apply gentle finger pressure at the junction of the eye and nose (nasolacrimal duct). This helps keep your medication in contact with your eye and helps prevent absorption into the bloodstream.

If your eye doctor or healthcare provider has told you to use your drops in both eyes, repeat the steps above with the other eye. Remember to use your drops as many times a day as your eye doctor or healthcare provider recommends. If you have any trouble using your eye drops, ask your eye doctor's or healthcare provider's staff for assistance.

Please see full prescribing information.

ALLERGAN

www.allergan.com

Alphagan® (brimonidine tartrate ophthalmic solution) 0.2%

*For **glaucoma** patients using intraocular pressure–lowering eye drops*

Are you feeling your best?

If not, your intraocular pressure–lowering eye drops could be the problem. This pamphlet was prepared to help you and your eye doctor or healthcare provider recognize medication side effects and ensure you are taking the glaucoma medication that will keep you feeling your best.

Alphagan® (brimonidine tartrate ophthalmic solution)

For One of the Millions of People Who Have

Primary Open-Angle

or

Glaucoma Ocular Hypertension.

Most likely, your eye doctor or healthcare provider has prescribed eye drops to control your intraocular pressure (IOP) and help prevent vision loss. Remembering to take your medication is absolutely necessary to reduce the elevated pressure in your eye to a safe level. But it may also be the cause of some unwanted side effects—especially if you're using a topical beta-blocker. These agents are known to cause systemic side effects. And you may not even be aware of them, or you might regard your symptoms as consequences of aging. Or like many patients, you may not associate the systemic side effects with your IOP-lowering eye drops. That's why it is important to frequently update your eye doctor or healthcare provider about any changes in your overall state of health. This information will help your eye doctor or healthcare provider in selecting a drug that is safer and more appropriate for you.

What to look for

If you're like most glaucoma patients, you probably see your eye doctor or healthcare provider twice a year. A lot can happen between office visits. You may be experiencing breathing difficulties, an irregular heartbeat, or a reduction in exercise tolerance. Climbing stairs might not be as easy for you, leaving you winded and out

of breath. You may have fallen recently, felt dizzy or faint, and at times seem confused, even depressed, or unusually sad. You may also have noticed a recent change in sexual desire or performance. It's important for your eye doctor or healthcare provider to know if you have any of these symptoms, or others, that may be caused by the eye drops you're using.

Advise *your eye doctor or healthcare provide of any of the following changes to your healt*

- **Irregular heartbeat (too fast or too slow)**
- **Difficulty breathing or constant coughing**
- **Tightness in your chest**
- **Exercise intolerance**
- **Hard to catch your breath**
- **Feeling tired, depressed, or sad**
- **Feeling dizzy or light-headed**
- **Confusion**
- **Recently fallen down**
- **Reduction in sexual desire or performance**

Talk to your eye doctor or healthcare provider about existing conditions

It's also very important for your eye doctor or healthcare provider to know if you have diabetes, asthma, high blood pressure, high cholesterol, a family history of heart or lung problems, and if you are presently or have ever been a smoker. One or more existing conditions may require you to take other medications. Tell your eye doctor or healthcare provider which medications you are taking. And be sure to ask if you don't know the name because using a beta-blocker eye drop along with your current regimen may result in unwanted systemic side effects or a reduction in the efficacy of the medication you are taking for your other condition. These problems can be avoided by switching to another intraocular pressure (IOP)-lowering eye drop. There are safer alternatives available—but your eye doctor or healthcare provider can make the right choice only if they are fully aware of your health condition.

Advise your eye doctor or healthcare provider if any of the following conditions apply to you:

- Family history of heart problems
- Taking medication to lower high blood pressure or cholesterol levels
- Taking medication for asthma
- Are presently or have been a smoker
- Inject insulin or take oral medication to control diabetes
- Currently being treated for depression
- Allergic reaction to any medication
- Taking additional medications for elevated IOP or other conditions

Ask about ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Don't wait for your next office visit if you are experiencing any changes in your general health condition. Report them immediately to your eye doctor or healthcare provider. And ask about ALPHAGAN® ophthalmic solution—a safe, effective IOP-lowering agent that is well tolerated by most patients. Of course, side effects are possible with any medication, but they are usually not severe enough to cause you to stop using ALPHAGAN®.

The most frequently reported side effects were dry mouth; blurred vision; burning, stinging, or redness in the eye; and drowsiness. ALPHAGAN® is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy. Of course, caution should be exercised if you're a patient with severe cardiovascular disease.

ALPHAGAN® is available in an easy-to-use 5-mL bottle as well as conveniently sized 10- and 15-mL bottles. Talk to your eye doctor or healthcare provider about ALPHAGAN®—a safe IOP-lowering eye drop that can keep you feeling your best.

Glaucoma Information Resources

The Glaucoma Foundation
116 John Street, Suite 1605
New York, NY 10038
Phone: 1-800-Glaucoma
Internet address:
www.glaucoma-foundation.org/info

Glaucoma Research Foundation
200 Pine Street, Suite 200
San Francisco, CA 94104
Phone: 1-800-826-6693
Internet address:
www.glaucoma.org