DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ms. Kathleen Day
Senior Director
Global Regulatory Affairs, Labeling and Promotion
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

RE: **NDA 20-597**
Xalatan (latanoprost ophthalmic solution)
MACMIS # 10562

Dear Ms. Day:

This letter objects to Pharmacia & Upjohn Company's (P&U), dissemination of violative promotional materials for Xalatan. We specifically refer to an advertisement published in the November 2001 issue of *Federal Practitioner* identified as UJ0012412 and entitled, "How Long Can You Last?" The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the advertisement and concluded that it is false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow:

Minimization of Risk

Your advertisement lacks fair balance and is misleading because it minimizes important risk information contained in a bolded warning in the approved product labeling (PI) for Xalatan. This bolded warning concerns possible permanent changes to pigmented eye tissues such as increased pigmentation of the iris and periorbital tissue (eyelid), and increased pigmentation and growth of eyelashes. Your advertisement fails to present this important risk information with a prominence and readability reasonably comparable to the effectiveness claims. Specifically, you prominently presented effectiveness claims on the front page of the one page advertisement, whereas you presented the bolded warning information on the back of the advertisement adjacent to the brief summary. This presentation minimizes the importance of this important risk information.

Indication

Your advertisement is misleading because it suggests that Xalatan is useful in all patients with elevated intraocular pressure (IOP). For example, your advertisement prominently presents claims such as "IOP reduction...proven to last," "Powerful IOP control," and "Tolerable IOP Control." However, because of the above safety concerns, the approved product labeling (PI) states that "Xalatan Sterile Ophthalmic Solution is indicated for the reduction of elevated

intraocular pressure in patients with open angle glaucoma or ocular hypertension **who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure reducing medication** (emphasis added). This important information about Xalatan's limited indication as a second-line therapy, however, is presented in small type at the bottom of the first page of the advertisement. This disclosure fails to correct the suggestion that Xalatan may be used as a first-line therapy.

Requested Actions

In order to address these objections, we request that you immediately cease the dissemination of this violative advertisement and all similar promotional materials that have the same or similar misleading presentations.

You should respond in writing to us regarding this issue by January 30, 2002. Your response should include P&U's intent to comply with the above request, the date that it ceased disseminating this advertisement 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. DDMAC reminds P&U that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 10562 and NDA 20-597.

Sincerely,

{See appended electronic signature page}

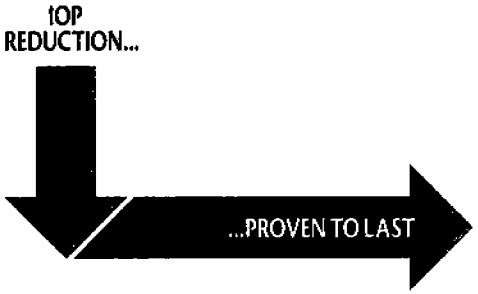
Warren Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Warren Rumble
1/16/02 09:57:40 AM

HOW LONG CAN YOU LAST?



Xalatan®
latanoprost ophthalmic solution

Powerful IOP Control[1-3]

- XALATAN maintained IOP reduction for up to 2 years, with no indication of rising, in open-label trial extensions*[4]

Tolerable IOP Control

- Most commonly reported ocular events/signs and symptoms (5% to 15%) included blurred vision, burning and stinging, conjunctival hyperemia, foreign-body sensation, itching, increased iris pigmentation, and punctate epithelial keratopathy

*During the 2-year study period, only 7% of patients required additional medication or a switch from XALATAN because of insufficient IOP control.

XALATAN® is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another IOP-lowering medication.

Please refer to additional safety information and a brief summary of prescribing information on next page.

PHARMACIA Ophthalmology

UX0012412 July 2001

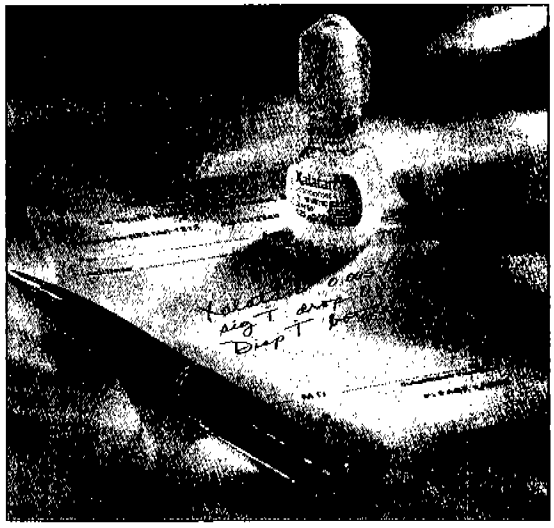
Xalatan®

latanoprost ophthalmic solution

Pigmented Tissue Changes

XALATAN has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent. Please refer to full prescribing information.

Patients who are expected to receive treatment in only 1 eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and, thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between eyes in length, thickness, and/or number of eyelashes.



References:

1. Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning: a comparison with timolol. *Ophthalmology*. 1995;102:1743-1752.
2. Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month, masked, multicenter trial in the United States. *Ophthalmology*. 1996;103:138-147.
3. Watson P, Stjernschantz J, the Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. *Ophthalmology*. 1996;103:126-137.
4. Data on file, Pharmacia & Upjohn Company, a subsidiary of Pharmacia Corporation, Kalamazoo, Mich. Hedman K, Alm A. Long-term effect of latanoprost on intraocular pressure. Presented at: the International Congress of Ophthalmology (ICO); June 1998; Amsterdam, the Netherlands.

PHARMACIA *Ophthalmology* UJ0012412 July 2001

XALATAN®
latanoprost ophthalmic solution
0.005% (50 mcg/mL)

Brief summary of prescribing information.

INDICATIONS AND USAGE
Indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive (failed to achieve target IOP after multiple measurements over time) to another IOP-lowering medication.

CONTRAINDICATIONS
Known hypersensitivity to latanoprost, benzalkonium chloride, or any other product ingredient.

WARNINGS
XALATAN has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent. XALATAN may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The iris color change occurs slowly and may not be noticeable for several months to years. Inform patients of the possibility of iris color change. Eyelid skin darkening has also been reported in association with the use of XALATAN. XALATAN may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes. Inform patients who are expected to receive treatment in only one eye about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and, thus, heterochromia between the eyes. Also advise them of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent.

PRECAUTIONS
General: Latanoprost is hydrolyzed in the cornea. The effect of continued administration of XALATAN on the corneal endothelium has not been fully evaluated. Bacterial keratitis has been 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 **Information for Patients**). Patients may slowly develop increased brown pigmentation of the iris that may not be noticeable for several months to years (see **WARNINGS**). Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, examine patients regularly; depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. During clinical trials, the increase in brown iris pigment has not progressed further upon treatment discontinuation, but the resultant color change may be permanent. Neither nevi nor freckles of the iris have been affected by treatment. Use XALATAN with caution in patients with active intraocular inflammation (iritis/uveitis). Macular edema, including cystoid macular edema, has been reported during treatment with XALATAN. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Use XALATAN with caution in these patients. There is limited experience with XALATAN in treating angle closure or inflammatory or neovascular glaucoma. XALATAN has not been studied in patients with renal or hepatic impairment; use with caution in such patients. Patients should not administer XALATAN while wearing contact lenses.
Information for Patients (see **WARNINGS**): Inform patients about the possibility of iris color change, due to an increase of brown pigment, and resultant cosmetically different eye coloration that may occur when only one eye is treated. Iris pigmentation changes may be more noticeable in patients with green-brown, blue/gray-brown, or yellow-brown irides. Also inform patients of the possibility of eyelash changes in the treated eye, which may result in a disparity between eyes in lash length, thickness, pigmentation, and/or number. They should also be informed about the possibility of eyelid skin darkening. The increased pigmentation to the iris and eyelid, as well as the changes to the eyelashes, may be permanent. Instruct patients to avoid allowing the dispensing container tip to contact the eye or surrounding structures, which can contaminate the tip with common bacteria known to cause ocular infections. Serious eye damage and subsequent vision loss may result from using contaminated solutions. Advise patients to immediately seek their physician's advice regarding continued use of their multidose container if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery. Patients should immediately seek their physician's advice if they develop any ocular reactions, particularly conjunctivitis and lid reactions. Also advise patients that XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses. Patients should remove contact lenses prior to administering XALATAN and can reinsert lenses 15 minutes following administration. If more than one topical ophthalmic drug is being used, administer drugs as least 5 minutes apart.
Drug Interactions: *In vitro* studies show that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. Administer XALATAN and such drugs at least 5 minutes apart.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Latanoprost was not carcinogenic in mice or rats when administered by oral gavage at doses up to 170 mcg/kg/day (approximately 2,800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Reproduction studies have been done in rats and rabbits. In rabbits, 4 of 16 dams had no viable fetuses at a dose approximately 80 times the maximum human dose; the highest nonembryocidal dose was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Use XALATAN during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: It is not known whether the drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering XALATAN to a nursing woman.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
Adverse events referred to in other sections of this insert: Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and macular edema, including cystoid macular edema (see **WARNINGS** and **PRECAUTIONS**).
Controlled Clinical Trials: Ocular adverse events/signs and symptoms reported in 5% to 15% of the patients on XALATAN in the 6-month, multicenter, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased iris pigmentation, and punctate epithelial keratopathy. Local conjunctival hyperemia was observed; however, less than 1% of patients treated with XALATAN discontinued therapy because of intolerance to conjunctival hyperemia. Ocular signs and symptoms reported in 1% to 4% of patients were dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia. Events reported in less than 1% of patients were conjunctivitis, diplopia, and discharge from the eye. During clinical studies, there were extremely rare reports of retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy. The most common systemic adverse events with XALATAN were upper respiratory tract infection/cold/flu, which occurred in approximately 4% of patients. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1% to 2%.
Clinical Practice: The following events have been identified during postmarketing use of XALATAN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to XALATAN, or a combination of these factors, include: asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; and toxic epidermal necrolysis.

OVERDOSAGE
Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Large intravenous latanoprost doses in monkeys have been associated with transient bronchoconstriction; however, bronchoconstriction was not induced in 11 patients with bronchial asthma treated with latanoprost. Intravenous infusion of up to 3 mcg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment, and no adverse reactions were observed. Intravenous doses of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating. If overdosage with XALATAN occurs, administer symptomatic treatment.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop (1.5 mcg) in the affected eye(s) once daily in the evening. Do not exceed the once-daily dosing; more frequent administration may decrease the IOP-lowering effect. IOP reduction starts approximately 3 to 4 hours after administration, and the maximum effect is reached after 8 to 12 hours. XALATAN may be used with other topical ophthalmic drug products to lower IOP. Administer drugs at least 5 minutes apart if more than one topical ophthalmic drug is used.

HOW SUPPLIED
XALATAN is supplied in plastic ophthalmic dispenser bottles with a dropper tip and tamper-evident overcap.
NDC 0013-8303-04: 2.5-mL fill, 0.005% (50 mcg/mL).

Storage: Protect from light. Store the unopened bottle under refrigeration at 2°C to 8°C (36°F to 46°F). Once opened, the container may be stored at room temperature up to 25°C (77°F) for 6 weeks.

Rx only

U.S. Patent Nos. 4,599,353; 5,296,504 and 5,422,368.

Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By:
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098, USA

B-6-S