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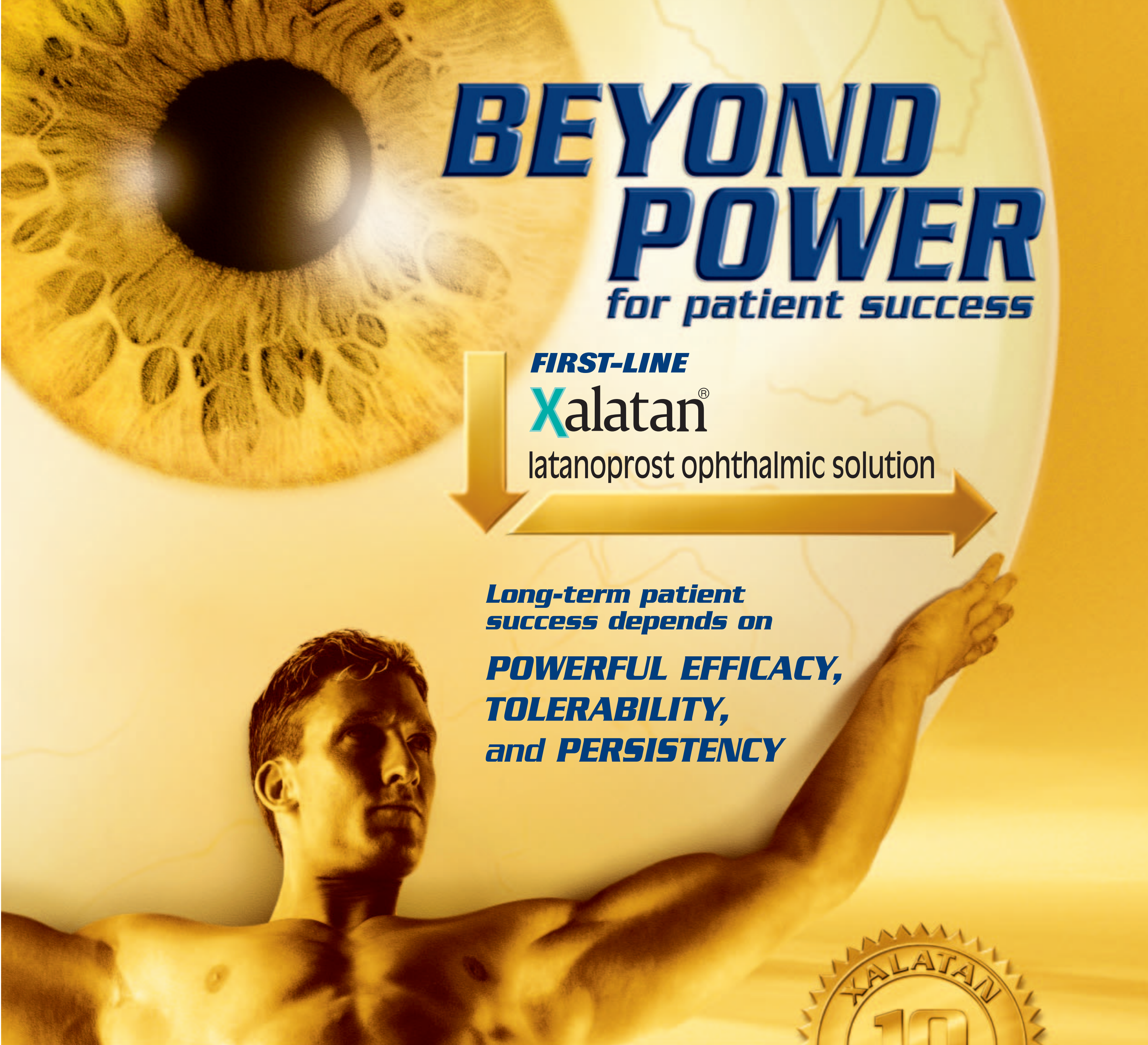

XALATAN revolutionized IOP management by offering patients the first prostaglandin therapy, along with the convenience of once-daily dosing

XALATAN is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH).

Important Safety Information: XALATAN can cause changes to pigmented tissues. Most frequently reported are increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as XALATAN is administered. Iris pigmentation is likely to be permanent while eyelid skin darkening and eyelash changes may be reversible. The effects beyond 5 years are unknown.

Most common ocular events/signs and symptoms (5% to 15%) reported with XALATAN in the three 6-month registration trials included blurred vision, burning and stinging, conjunctival hyperemia, foreign-body sensation, itching, increased iris pigmentation, and punctate epithelial keratopathy.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Please see brief summary of prescribing information on adjacent page.

Xalatan®

latanoprost ophthalmic solution

PHARMACIA

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 or ocular hypertension.

CONTRAINDICATIONS

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

WARNINGS

XALATAN has been reported to cause changes to pigmented tissues. Most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as XALATAN is administered. After discontinuation, iris pigmentation is likely to be permanent while periorbital tissue pigmentation and eyelash changes may be reversible in some patients. Inform patients of the possibility of increased pigmentation. Effects of increased pigmentation beyond 5 years are not known.

PRECAUTIONS

General: XALATAN may gradually increase iris pigmentation. Eye color change is due to increased melanin content in iris stromal melanocytes rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see **WARNINGS**). Typically, brown pigmentation around the pupil spreads concentrically towards the iris periphery and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. Treatment with XALATAN can be continued in patients who develop noticeably increased iris pigmentation, but these patients should be examined regularly.

During clinical trials, increased brown iris pigment has not progressed further upon treatment discontinuation, but the resultant color change may be permanent.

Eyelid skin darkening, which may be reversible, has been reported in association with use of XALATAN (see **WARNINGS**).

XALATAN may gradually change eyelashes and vellus hair in the treated eye; changes include increased length, thickness, pigmentation, number of lashes or hairs, and misdirected eyelash growth. Eyelash changes are usually reversible upon treatment discontinuation.

XALATAN should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with XALATAN. 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. XALATAN should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

There is limited experience with XALATAN in the treatment of angle closure, inflammatory or neovascular glaucoma. 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 **PRECAUTIONS,** *Information for Patients*).

Contact lenses should be removed prior to administration of XALATAN, and may be reinserted 15 minutes after administration (see **PRECAUTIONS,** *Information for Patients*).

Information for Patients (see **WARNINGS** and **PRECAUTIONS**): Advise patients about the potential for increased brown iris pigmentation, which may be permanent, and about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XALATAN.

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XALATAN which may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

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 damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Advise patients to immediately seek their physician's advice concerning continued use of the multiple-dose container if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery.

Advise patients to immediately seek their physician's advice if they develop any ocular reactions, particularly conjunctivitis and lid reactions.

Advise patients that XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses. Patients should remove contact lenses prior to administration of XALATAN and can reinsert lenses 15 minutes after administration.

If more than one topical ophthalmic drug is being used, administer drugs at 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 either mice or rats with oral gavage doses up to 170 µg/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 performed 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. XALATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this 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 three 6-month, multi-center, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy.

Local conjunctival hyperemia was observed; less than 1% of the patients treated with XALATAN discontinued therapy due to intolerance to conjunctival hyperemia.

Ocular events/signs and symptoms reported in 1 to 4% of the 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 the 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. Events, which have been chosen for inclusion due to either their seriousness, reporting frequency, possible causal connection to XALATAN, or a combination of these factors, include: asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; 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, in 11 patients with bronchial asthma treated with latanoprost, bronchoconstriction was not induced. Intravenous infusion of up to 3 µg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 µg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

If overdosage with XALATAN occurs, treatment should be symptomatic.

HOW SUPPLIED

XALATAN is supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

2.5 mL fill, 0.005% (50 µg/mL)

Package of 1 bottle NDC 0013-8303-04

Storage: Protect from light. Store unopened bottle under refrigeration at 2˚ to 8˚C (36˚ to 46˚F). During shipment to the patient, the bottle may be maintained at temperatures up to 40˚C (104˚F) for a period not exceeding 8 days. Once opened the 2.5 mL container may be stored at room temperature up to 25˚C (77˚F) for 6 weeks.

Rx only September 2003

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

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Older African Americans' Attitudes about Vision and Eye Care

Previous research has suggested that African Americans are less likely to receive routine eye care than are whites, which may be responsible for the higher vision impairment and eye disease rates in this population. Owsley et al. (p. 2797) assembled focus groups of older African Americans in Alabama to identify their perceptions about barriers to receiving eye care and their attitudes about vision and eye care. Separate groups were also assembled of the ophthalmologists and optometrists serving their communities. Transportation problems were by far the most commonly cited barrier by both older African Americans and their eye care providers. Whereas older African Americans had generally positive attitudes toward the importance of eye care, eye care providers tended to view older African Americans' knowledge basis and attitudes in a negative light, implying a serious communication gap between these two populations. ■

Anti-glaucoma Drugs and Ocular Perfusion Pressure

Quaranta et al. (p. 2917) performed a randomized clinical trial on the short-term effects of timolol, brimonidine, dorzolamide, and latanoprost on intraocular pressure (IOP), blood pressure (BP), and diastolic ocular perfusion pressure (DOPP). Each drug decreased significantly the IOP at all time-points. The mean 24-hour IOP after latanoprost administration was significantly lower than that after timolol, brimonidine, or dorzolamide administration. Brimonidine induced a significant decrease in the mean 24-hour DOPP value, while dorzolamide and latanoprost induced a significant increase. The study suggests that some pharmacologic therapies for POAG affect systemic BP, and, despite their favorable action in reducing the IOP, do not significantly increase DOPP. However, the importance of drug-induced changes in DOPP in determining optic nerve head damage requires further investigation. ■

Can Accommodation Be Restored in Presbyopic Eyes?

Accommodation can possibly be restored to presbyopic human eyes by refilling the capsular bag with a soft polymer. Previous studies of this surgical procedure in a primate eye model reported postoperative inflammation and early capsular opacification, making measurements of refractive changes difficult. Koopmans et al. (p. 2976) refilled the capsular bag in adolescent rhesus monkey eyes, while a specific intra- and postoperative treatment protocol was used to minimize postoperative inflammation and to delay capsular opacification. A certain level of accommodation could be restored after lens refilling. During the follow-up period of 37 weeks, refraction measurements were possible in all five monkeys that underwent the treatment aimed at the prevention of inflammation and capsular opacification. ■

MALDI Tissue Imaging of α-Crystallin

Han and Schey (p. 2990) used a new technique, MALDI tissue imaging, to observe protein profiles across equatorial sections of bovine lenses. αA- and αB-crystallins were imaged along with their truncated and phosphorylated forms. Extensive truncation was observed in the nuclear region for αA-crystallin, and rings of phosphorylated forms were observed in the inner cortical region for both crystallins. This new imaging method allows many protein forms to be observed in a spatially resolved manner in a single experiment. Thus, regional differences in lens proteins and their modified forms can be recorded. ■

Classifying the Proliferative Populations in Lens Epithelium

Zhou et al (p. 2997), using a long-term labeling and chase strategy, have shown that a hierarchal organization of proliferation exists in the adult mouse lens epithelium with the slowest or rarely cycling cells located in the central region and the more actively proliferating cells detected in the peripheral or germinative zone. The rarely cycling cells are proposed to be putative stem cells that divide very infrequently during homeostasis; however, upon perturbation, these cells enter the proliferative pool and provide progeny (transit amplifying cells) that will supply the central and germinative zones with cells capable of further division capacity. ■

Intrinsic and Extrinsic Factors Contribute to Photoreceptor Development

The mechanisms underlying the acquisition of a photoreceptor identity during development are still ill-defined. Garelli et al. (p. 3017) show here that photoreceptor precursors switch off the expression of Pax6, an early eye determinant, and start expressing Crx to initiate their differentiation. However, Crx expression alone is not sufficient to achieve fully differentiated photoreceptors, which require the action of docosahexaenoic acid (DHA) to move forward in their differentiation pathway. This suggests that both intrinsic and extrinsic signals are indispensable in photoreceptor development. These requirements should be considered when planning cell replacement therapies for retina degenerative diseases. ■

Apolipoproteins in RPE: A Role in Drusen Formation?

A hypothesis for a plausible pathway in the biogenesis of drusen, the lipid-rich extracellular lesions of aging and age-related maculopathy, is that the retinal pigment epithelium (RPE) assembles and basolaterally secretes a large lipoprotein particle containing apolipoproteins B and E (apoB, apoE). Li et al. (p. 3119) evaluated this hypothesis by examining retinal expression of apolipoproteins that appear on similar large particles secreted by hepatocytes and enterocytes. These investigators found evidence of apoA-II, C-I, and C-II immunoreactivity in drusen, either distributed diffusely throughout the druse or confined to an external shell, and evidence for the corresponding mRNA transcripts in native human RPE. An RPE-secreted lipoprotein may carry apoC-I and apoC-II, major modulators of lipoprotein lipase activity. ■