NDA

20597

NDA 20-597

JUN - 5 1996

Pharmacia Inc.
Attention: Daniel G. Mannix, Ph.D.
Manager, Regulatory Affairs
Post Office Box 16529
Columbus, OH 43216-6529

Dear Dr. Mannix:

Please refer to your June 14, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xalatan (latanoprost solution) Sterile Ophthalmic Solution, 0.005% (50 μg/mL).

We acknowledge receipt of your correspondence dated July 6 and 21, August 2, 18, and 25, September 15, October 27, November 2, 6, 7, 10 (two), 13, and 15, and December 12, 13, and 22, 1995, and January 23 and 31, February 1, 14, 19, 21, and 22, March 7, 11, 15, 19, and 26, April 1, 3, 15, 17, 18, 23, 24, 25, and 26 (two), May 23 and 28, and June 4, 1996.

This new drug application provides for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and 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 lowering medication.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated June 4, 1996. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the June 4, 1996, draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-597. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Joanne Holmes, M.B.A.
Project Manager
(301) 827-2090

Sincerely yours,

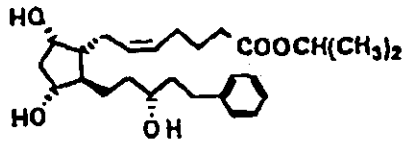
Michael Weintraub 6/5/96

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Xalatan™
(latanoprost solution) Sterile Ophthalmic Solution
0.005% (50 μg/mL)

DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:



M.W. 432.58

Latanoprost is a colorless to slightly yellow oil which is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.

Xalatan™ (latanoprost solution) Sterile Ophthalmic Solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7. Each mL of Xalatan, contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. One drop contains approximately 1.5 μg of latanoprost.

CLINICAL PHARMACOLOGY

Mechanism of Action

Latanoprost is a prostanoid selective FP receptor agonist which is believed to reduce the intraocular pressure by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main

mechanism of action is increased uveoscleral outflow.

Pharmacokinetics/Pharmacodynamics

Absorption: Latanoprost is absorbed through the cornea where the isopropyl ester pro-drug is hydrolyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Distribution: The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost could be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration.

Metabolism: Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid.

The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion: The elimination of the acid of latanoprost from human plasma was rapid ($t_{½}$=17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

Animal Studies

In monkeys, latanoprost has been shown to induce increased pigmentation of the iris.

The results from the preclinical program demonstrated that the increased pigmentation is unlikely to be associated with proliferation of melanocytes. It appears that the mechanism of increased pigmentation is stimulation of melanin production in melanocytes of the iris stroma.

In ocular toxicity studies, administration of latanoprost at a dose of 6μg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased palpebral fissure. This effect has been reversible and occurred at doses above the standard clinical dose level.

INDICATIONS AND USAGE

Xalatan is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and 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 lowering medication.

CLINICAL STUDIES

Patients with mean baseline intraocular pressure of 24-25 who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6-8 mmHg reductions in intraocular pressure. This IOP reduction with Xalatan 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

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 is currently unknown.

The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change. Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation in the treated eye and thus, heterochromia between the eyes. The increased pigmentation 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.

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 *Information for Patients*)

Patients may slowly develop increased brown pigmentation of the iris. This change 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, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris have been affected by treatment.

There is no experience with Xalatan in the treatment of angle closure, inflammatory or neovascular glaucoma and only limited experience in pseudophakic patients.

Xalatan has not been studied in patients with renal or hepatic impairment and should

therefore be used with caution in such patients.

Xalatan should not be administered while wearing contact lenses.

Information for Patients: Patients should be informed about the possibility of iris color change due to an increase of the 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.

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

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

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

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

administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Drug Interactions: *In vitro* studies have shown that precipitation occurs when eye drops containing thimersal are mixed with Xalatan. If such drugs are used they should be administered with an interval of at least five (5) minutes between applications.

revise 5/20/1999 per FDA

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 when administered by oral gavage at doses of 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 an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits 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, caution should be exercised when Xalatan is administered to a nursing woman.

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

ADVERSE REACTIONS

The ocular adverse events and ocular signs and symptoms reported in 5 to 15% of the patients on Xalatan in the 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; however, less than 1% of the Xalatan treated patients required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1 to 4% of the patients: dry eye, excessive tearing, eye pain, lid crusting, lid edema, lid erythema, lid discomfort/pain, and photophobia.

The following events were reported in less than 1% of the patients: conjunctivitis, diplopia and discharge from the eye.

During clinical studies, there were extremely rare reports of the following: retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

The most common systemic adverse events seen with Xalatan were upper respiratory tract infection/cold/flu which occurred at a rate of approximately 4%. Pain in muscle/joint/back, chest pain/angina pectoris and rash/allergic skin reaction each occurred at a rate of 1 to 2%.

OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Intravenous administration of large doses of latanoprost in monkeys has 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.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop (1.5 μg) in the affected eye(s) once daily in the evening.

The dosage of Xalatan should not exceed once daily since it has been shown that

more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours.

Xalatan may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

Xalatan™ (latanoprost solution) Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless solution 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 μg/mL), in cartons of 1 & 6.

Storage: Protect from light. Store unopened bottle under refrigeration at 2° to 8° C (36° to 46° F).

Once opened the container may be stored at room temperature up to 25° C (77° F) for 6 weeks.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:

Automatic Liquid Packaging, Inc.

Woodstock, Illinois 60098

Distributed by:

Pharmacia Inc.

Kalamazoo, MI 49001, USA

124000696 June 3, 1996

Pharmacia

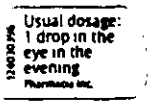
Labeling of Xalatan™ bottle

Enlarged

124050396
Xalatan
(latanoprost solution)
0.005% Sterile
Ophthalmic Solution
125µg/2.5 mL

124030396
Usual dosage:
1 drop in the
eye in the
evening
Pharmacia Inc.

Normal size



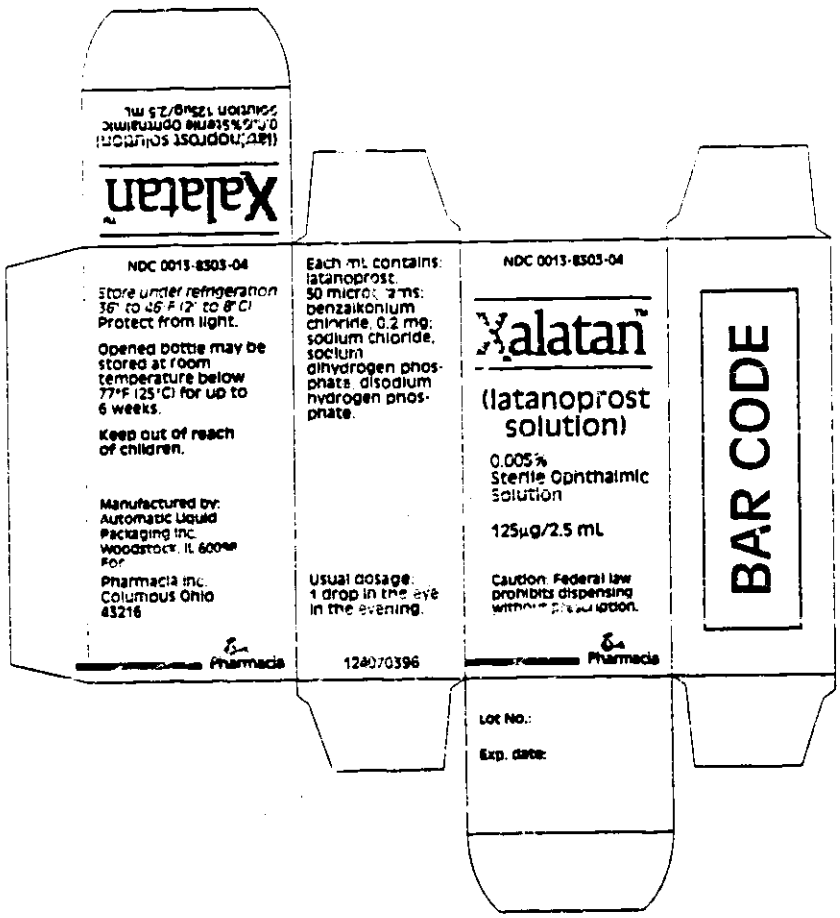
Lot No will be embossed on one side and Exp. date on the other side at the bottom of the bottle

US/ Mars 8, 1996

Pharmacia

Labeling of Xalatan™ carton 2.5 mL

Normal size

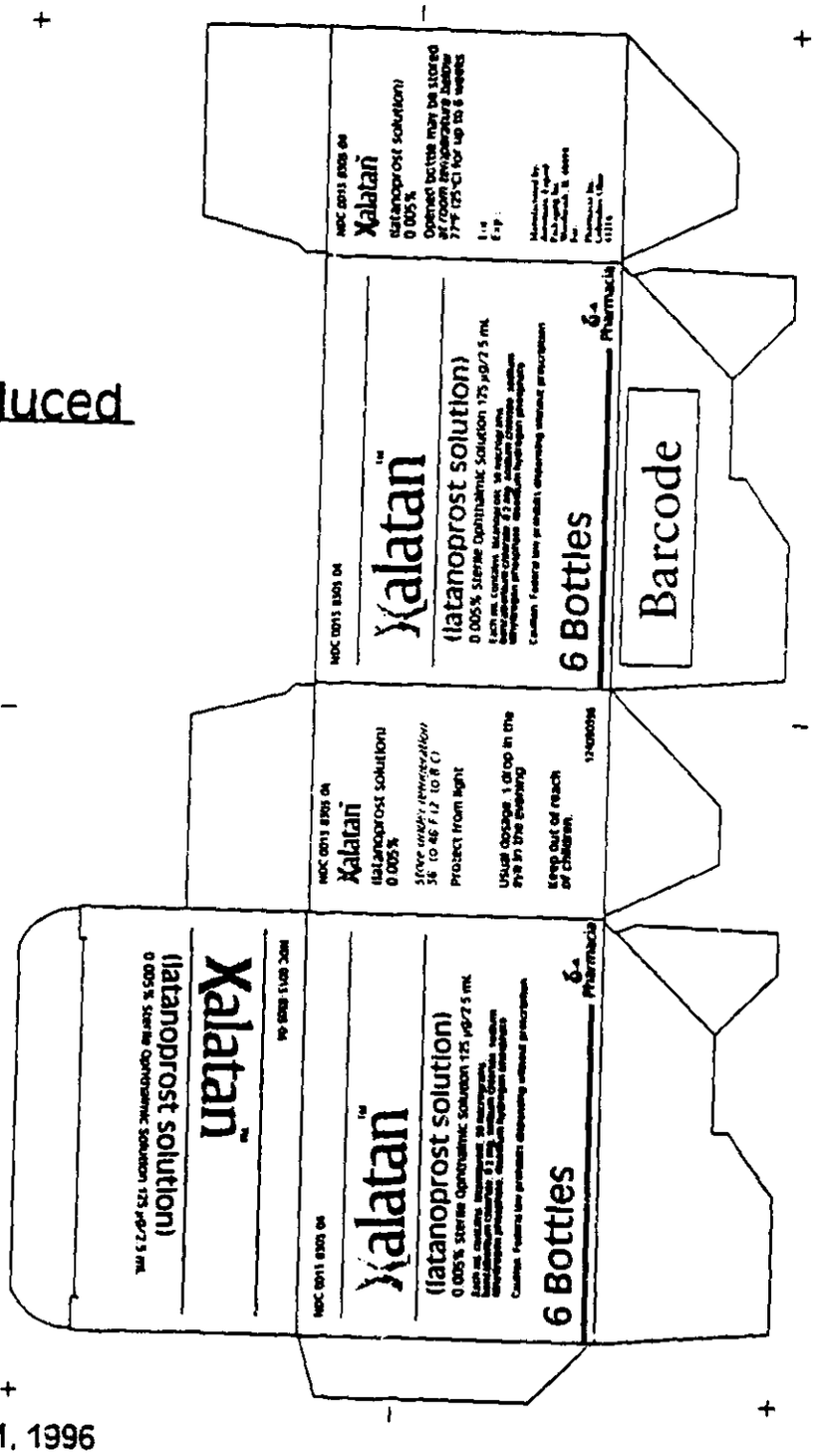


US/ Mars 8, 1996

Pharmacia

Labeling of Xalatan™ carton 6 x 2.5 mL

Reduced



Pharmacia

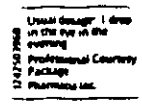
Labeling of Xalatan™ bottle
SAMPLE NOT FOR SALE

Enlarged

1242503396A
Xalatan
(latanoprost solution)
0.005% (125µg/2.5 mL)
Ophthalmic Solution
SAMPLE, NOT FOR SALE

1242503396B
Usual dosage: 1 drop in the eye in the evening
Professional Courtesy Package
Pharmacia Inc.

Normal size



Lot No will be embossed on one side and Exp. date on the other side at the bottom of the bottle

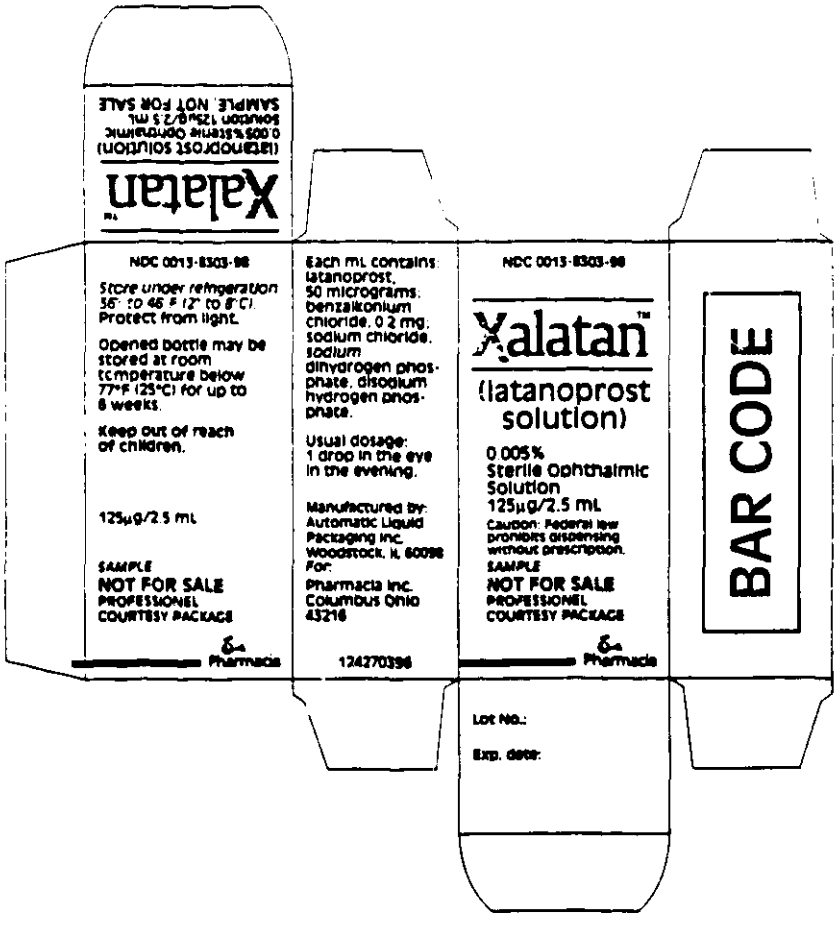
US/ Mars 11, 1996

Pharmacia

Labeling of Xalatan™ carton 2.5 mL

SAMPLE NOT FOR SALE

Normal size



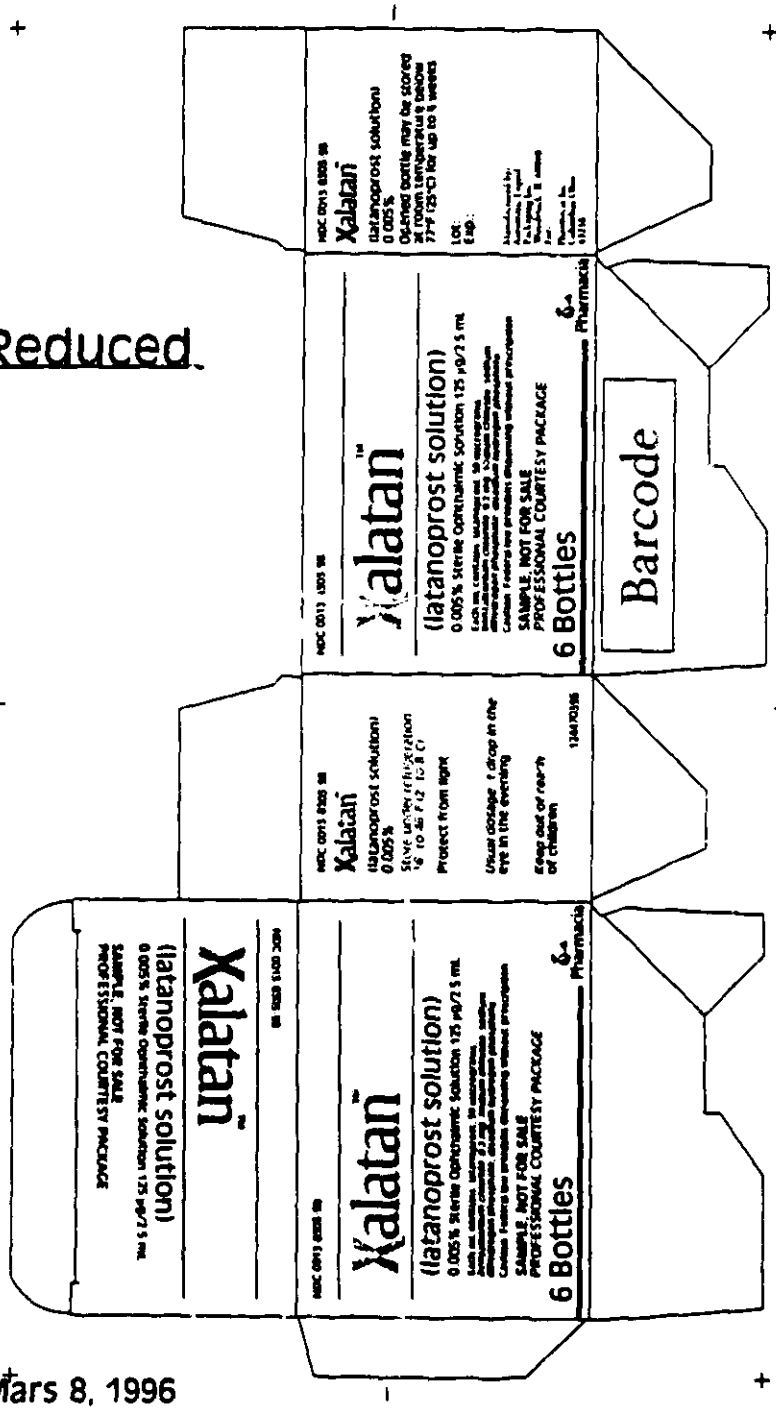
US/ Mars 8, 1996

Pharmacia

Labeling of Xalatan™ carton 6 x 2.5 mL

SAMPLE NOT FOR SALE

Reduced



Pharmacia

Draft Prescribing Information

XALATAN™
(latanoprost) Sterile Ophthalmic Solution
0.005% (50 μg/mL)

DESCRIPTION

XALATAN™ (latanoprost) Sterile Ophthalmic Solution, a novel prostaglandin $F_2\alpha$ analogue, is a selective FP receptor agonist. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its structural formula is:

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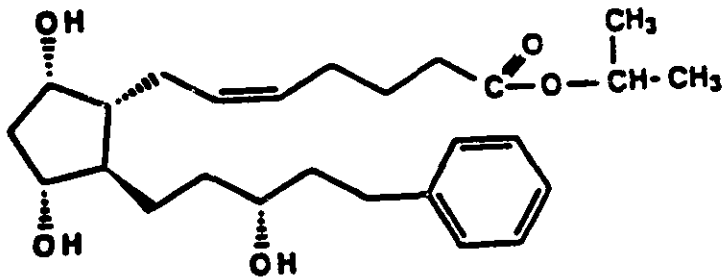
1.02/00005

Original

6/14/95

02-00001



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The active substance is an isopropyl ester pro-drug which is hydrolyzed in the cornea to the acid form to become biologically active.

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Latanoprost is a colorless to slightly yellow, oil which is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.	1.02/00016
XALATAN Ophthalmic Solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7. Each mL of XALATAN, contains 50 micrograms of latanoprost. The inactive ingredients are: sodium chloride, monosodium phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. Benzalkonium chloride, 0.02% is added as a preservative.	1.04/00867 1.05/01248
One drop contains approximately 1.5 μg of latanoprost.	

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CLINICAL PHARMACOLOGY

Mechanism of Action

Latanoprost, a novel prostaglandin F_2 α analogue, is a selective	1.13/00152
prostanoid FP receptor agonist which reduces the intraocular	1.39/11784
pressure by increasing the outflow of aqueous humor. Studies in	1.39/11794
animals and man indicate that the main mechanism of action is	1.39/11804
increased uveoscleral outflow.	1.45/00070

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Pharmacokinetics/Pharmacodynamics	
Latanoprost is well absorbed through the cornea and all of the drug which enters the aqueous humor is hydrolysed to the biologically active acid form during passage through the cornea.	1.34/09776 1.34/09749 1.34/09762 1.36/10791
Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.	
Following topical administration, latanoprost is primarily distributed in the anterior segment, conjunctiva and eyelids with only minute quantities reaching the posterior segment. Reduction of intraocular pressure following a single dose in man starts about 3 to 4 hours after topical administration and the maximum effect is reached after	1.86/17004

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8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

There is practically no metabolism of the acid of latanoprost in the eye. Primary metabolism of latanoprost occurs in the liver. In man, the half-life of the biologically active acid in plasma is approximately 17 minutes. In animal studies, the main metabolites, the 1,2 - dinor and 1,2,3,4 - tetranor exert no or only weak biologic activity and were excreted primarily in the urine. 1.41/00009 1.41/00011

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humor and no effect on the blood-aqueous barrier. Latanoprost, at clinical dose levels, has no or negligible effects on intraocular blood circulation. However, mild

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to moderate conjunctival hyperemia may occur as a result of topical administration. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophacic human eyes during short term treatment. 1.57/04788

Animal Studies

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Latanoprost was well-tolerated at intravenous doses of 1 μg/kg/day in the dog and 35 μg/kg/day in the rat for 13 weeks. These doses are approximately 16 and 560 times the recommended human dose given ocularly. In animal studies latanoprost has not been found to have sensitizing properties. 1.21/03952 1.20/03419 1.29/07471 1.29/07534

In the eye, no toxic effects have been detected with doses of up to 100 μg/eye/day in rabbits or monkeys. In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. Increased pigmentation of the iris has also been reported in humans with hazel eyes during chronic treatment with latanoprost. The results from a large pre-clinical program demonstrated that the effect is unlikely to be associated with proliferation of melanocytes, and neither naevi nor freckles in the eye have changed during chronic treatment with latanoprost. It appears that the mechanism of increased pigmentation is due to stimulation of melanin production in melanocytes of the iris. The change in iris color occurs slowly and may not be noticeable for several months and may be irreversible.

ANNOTATED REFERENCES

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1.14/00704
1.15/01157
1.16/01774
1.62/06935
1.70/10421
1.77/13450
1.86/16820

ANNOTATED REFERENCES

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In chronic ocular toxicity studies, administration of latanoprost at a dose of 6μg/eye/day (4 times the daily human dose) has also been shown to induce increased palpebral fissures. This effect is reversible and occurs at doses above the clinical dose level. This effect has not been observed in humans.	1.16/01774
Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction did not affect the retinal blood vessels as determined by fluorescein angiography.	1.13/00254

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INDICATIONS AND USAGE

XALATAN is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension.

CLINICAL STUDIES

Clinical trials show that latanoprost is effective both as monotherapy and in combination with other anti-glaucoma drug therapy. XALATAN is even effective in patients who respond inadequately to other single or multiple anti-glaucoma drug therapy. The trials also show that the intraocular pressure reducing effect of latanoprost is additive to that of beta-adrenergic antagonists (timolol).

1.57/05033
1.58/05318
1.58/05563
1.59/05826
1.60/06185

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adrenergic antagonists (dipivalyl epinephrine), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide).	
Results of placebo-controlled and active-treatment controlled studies demonstrated that latanoprost used at 50 to 60 μg/ml once daily has the intended effect of reducing intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Patients were treated for 6 or more months in the Phase III multi-center, randomized, double-blind, controlled trials; results of these trials showed the sustained benefit of long-term latanoprost therapy.	1.48/01461 1.50/02268 1.52/02873 1.55/04219 1.60/06195 1.62/06435 1.70/10421 1.77/13450 1.86/16960

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TABLE 1

IOP (mmHg) RESPONSE TO LATANOPROST IN PATIENTS TREATED FOR 6 MONTHS IN THE PHASE III CLINICAL TRIALS

	U. S. Study (9400369)	GB Study (9400243)	Scandinavian Study (9400194)	
Baseline IOP	24.4 ± 3.2 (n=125)	25.2 ± 3.4 (n=149)	25.1 ± 3.5 (n=183)	1.62/06935
IOP at 6 months	17.6 ± 3.1 (n=96)	16.7 ± 2.6 (n=133)	17.0 ± 2.8 (n=169)	1.70/10421 1.77/13450 1.86/16960
ΔIOP at 6 months	6.7 ± 3.4 (n=96)	8.5 ± 2.8 (n=133)	8.0 ± 3.1 (n=169)	

ANNOTATED REFERENCES

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CONTRAINDICATIONS

Known hypersensitivity to benzalkonium chloride or any other ingredients in this product.

WARNINGS

XALATAN may cause increased pigmentation of the iris in patients with blue-brown, gray-brown, green-brown or yellow-brown irides where brown areas are seen against the otherwise blue, gray, green and yellow irides (i.e. mixed color irides). When treating patients with mixed colored irides it is recommended that the patients are informed of the possibility of increased pigmentation. Until further long term experience is gained it is furthermore recommended that goniscopy be performed twice yearly if pigmentation occurs. Accumulation of pigment in the trabecular meshwork and chamber angle has not been observed in clinical trials, but withdrawal of treatment may be

1.86/16820
1.86/17060

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considered if marked accumulation of pigment is observed in these structures.

PRECAUTIONS

General

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 *Information for Patients*)

Patients with hazel colored eyes may slowly develop increased pigmentation of the iris. This change may not be noticeable for several months. Commonly, hazel colored eyes are brown around the pupil and green, gray, blue or yellow towards the periphery of the iris. Typically the

1.86/16820
1.86/17060

brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become darker. Increased iris pigmentation has not been noted in pure blue, gray, green or brown eyes. Until more information about increased pigmentation is available, patients predisposed to iris pigmentation (hazel eyes) should be examined more frequently and, depending on the clinical situation, treatment may be stopped if cosmetically disturbing increased pigmentation ensues. The increase in iris pigmentation does not progress further upon discontinuation of treatment but may be permanent.

There is no experience with XALATAN in the treatment of inflammatory or neovascular glaucoma and only limited experience in pseudophakic patients. Latanoprost has no effect on the pupil but has not been studied in acute attacks of closed angle glaucoma. Therefore, it is recommended

1.57/04788

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that XALATAN be used with caution in these conditions until more experience is obtained.

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

Benzalkonium chloride, the preservative in XALATAN, may be absorbed by contact lenses. Thus, XALATAN should not be administered while wearing contact lenses.

Information for Patients

Patients with mixed colored irides should be informed about the possibility of increased pigmentation and heterochromia between eyes. 1.86/16820 1.86/17060

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

Patients also should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eyes 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.

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

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

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Drug Interactions

The intraocular pressure reducing effect of XALATAN has been shown to be additive to that of beta-adrenergic antagonists (timolol), adrenergic antagonists (dipivalyl

1.57/05033
1.59/05318
1.58/05563
1.59/05826

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epinephrine), cholinergic agonists (pilocarpine) and carbonic acid anhydrase inhibitors (acetazolamide).	1.60/06185
In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with XALATAN. If such drugs are used they should be administered with an interval of at lease five (5) minutes between applications.	
Carcinogenesis, Mutagenesis, Impairment of Fertility	
Latanoprost was not carcinogenic in either mice or rats when administered at doses of up to 200 μg/Kg/day (6700 times the recommended human dose) for up to 20 and 24 months, respectively.	1.22/04343 1.26/05894
Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human	1.34/09546 1.34/09596 1.34/09626

ANNOTATED REFERENCES

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lymphocytes, however, similar effects were observed with prostaglandin $F_2\alpha$, a naturally occurring prostaglandin, suggesting that this is a class effect. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative.	1.40/12089 1.34/09673 1.34/09705
Latanoprost has not been found to have any effect on male or female fertility in animal studies. A systemic dose of 100 times the clinical dose has been shown to induce abortion in rabbits but not in rats. No teratogenic potential has been detected.	1.31/08451 1.32/08738

ANNOTATED REFERENCES

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Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 825 times the clinical dose (based on 0.06 $\mu g/Kg$ - 50 Kg human) and have revealed no evidence of impaired fertility or harm to the fetus due to latanoprost. A systemic dose of 100 times the clinical dose has been shown to induce abortion in rabbits but not in rats. There are, however, no adequate and well- controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

1.31/08451
1.32/08738

ANNOTATED REFERENCES

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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, caution should be exercised when XALATAN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

In clinical studies, latanoprost has been administered to a total of 890 patients and 99 healthy volunteers; almost 70% of the subjects were above age 60, and more than 1/3 were above age 70. The mean age, ±SD was 63 ± 14 years. Consequently, the majority of the clinical efficacy and

1.86/16960
1.86/17060

ANNOTATED REFERENCES

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safety data are from patients above age 60, and the efficacy and safety profile described in this labeling reflects this experience.

ADVERSE REACTIONS

In clinical studies, latanoprost has been administered to a total of 890 patients and 99 healthy volunteers. The adverse experiences that have occurred during treatment with latanoprost are divided into local adverse events and systemic adverse events. The rates of local ocular adverse events reported in more than 1% of the 460 patients in the Phase III multi-center trials treated for 6 months are provided below:

1.86/17060
1.62/06935
1.70/10421
1.77/13450

ANNOTATED REFERENCES

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Reported Local/Ocular Adverse Events	Rate (n = 460)	
Increased pigmentation of iris	31	(6.7%)
Conjunctival hyperemia	18	(3.9%)
Punctate epithelial erosions	13	(2.8%)
Foreign body sensation	12	(2.6%)
Blurred vision	9	(2.0%)
Itching	8	(1.7%)
Burning	5	(1.1%)
Excessive tearing	5	(1.1%)

1.86/17060

Local Ocular Adverse Events:

In addition to the above listed local ocular adverse events, minor local ocular symptoms and signs of no clinical consequence were observed in less than 0.5% of the patients. These symptoms and signs included conjunctivitis, diplopia, discharge from eye, eye discomfort, eye pain, lid edema, ophthalmic migraine and visual disturbance. These minor signs and symptoms involving either eyelid, conjunctiva, cornea, or visual acuity were of relatively little clinical consequence.

1.86/17092

Local conjunctival hyperemia was frequently observed, this was well tolerated and less than 1% of the patients required discontinuation of therapy because of intolerance to conjunctival hyperemia.

The effect of latanoprost on the integrity of the blood-aqueous barrier was evaluated with laser flare meter as well

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as other techniques. Latanoprost was shown to have no clinically significant effect on the blood-aqueous barrier in healthy volunteers or in patients. Latanoprost had no clinically significant effect on "flare/cells" in the aqueous humor. This indicates that latanoprost does not induce clinically significant leakage of proteins into the aqueous humor.	
Only two patients were withdrawn due to punctate epithelial erosions out of 460 (0.4%) during latanoprost treatment for 6 months.	1.86/17131
Increased Iris Pigmentation:	
Latanoprost caused increased pigmentation of the iris in certain individuals. The results from a large pre-clinical program demonstrated that the effect is unlikely to be associated with proliferation of melanocytes, and neither naevi nor freckles in the eye have changed during chronic	1.86/16820 1.86/17060

treatment with latanoprost. Individuals with mixed colored irides seem to be predisposed to this change. Typically individuals with green-brown, blue/gray-brown or yellow-brown irides are affected, but not individuals with homogenously blue/gray, green or brown irides. The actual clinical consequence of this side effect is unknown; however, so far there are no indications to suggest that increased pigmentation of the iris would have clinically detrimental consequences.

Systemic Adverse Events:

The most common systemic adverse events were upper respiratory tract infection/cold/flu which occured at a rate of 4.3%, pain in muscle/joint/back (1.5%) and chest pain/angina pectoris as well as rash/allergic skin reaction, each occuring at a rate of 1.1%. The rest of the systemic adverse events occur at a rate below 1%.

1.86/17144

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Latanoprost is administered topically at such a low concentration (50 μg/ml) that theoretical systemic side effects should not occur, except for possible immunogenic reactions. The results of a study in patients with asthma show that latanoprost, even when used at a concentration seven times higher than the intended clinical concentration, had no effect on pulmonary or cardiovascular functions. The majority of the systemic adverse events observed during the Phase III trials involving six months of treatment were similar to those one would observe in the general population of people above age 60. 1.56/04555

OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, there are no known ocular effects when latanoprost is administered at high doses. One bottle of XALATAN contains 125 micrograms of latanoprost. More than 90% of topically administered latanoprost is 1.47/00814 1.86/17259

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metabolized during the first pass through the liver. Intravenous infusion of up to 3 μg/kg in healthy volunteers induced no symptoms but a dose of 5.5 to 10 μg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

The half-life of the biologically active acid of latanoprost in plasma is about 10 minutes.

In monkeys, latanoprost has been infused intravenously in doses of up to 500 μg/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically to the eye at a dose of seven times the recommended clinical dose.

1.13/00189
1.86/17259

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If overdosage with XALATAN occurs, treatment should be symptomatic.	1.56/04555

DOSAGE AND ADMINISTRATION

The usual recommended dosage for adults (including those over 60 years of age) is one drop in the affected eye(s) once daily. Optimal effect is obtained if XALATAN is administered in the evening.

The dosage of XALATAN should not exceed once daily since it has been shown that more frequent administration decreases the intraocular pressure lowering effect.	1.61/06500

If one dose is missed, continue with the next dose the following evening.

While XALATAN is effective as monotherapy, it can also be used in combination with beta-adrenergic antagonists	1.57/05033 1.58/05318

	ANNOTATED REFERENCES Technical Section Vol./Pg. No.
(timolol), adrenergic antagonists (dipivalyl epinephrine), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide) to achieve an additive effect. If combined therapy is used, allow an interval of at least five (5) minutes between administration of the different eye drops.	1.58/05563 1.59/05826 1.60/06185
Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.	1.86/17004

HOW SUPPLIED

XALATAN™ (latanoprost) Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless solution supplied in plastic ophthalmic dispenser bottles with a dropper tip and tamper evident overcap.

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NDC 0013-8303-04, 0.005% (50 μg/mL), 2.5 mL fill.

Storage: Store unopened bottle under refrigeration at 2° to 8° C (36° to 46° F).
Protect from light.
Do Not Freeze.
Once opened the container may be stored at room temperature up to 25° C (77° F) for one month. 1.06/01380

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
Automatic Liquid Packaging, Inc.
Woodstock, Illinois 60098
Distributed by:
Pharmacia Inc.
Columbus, Ohio 43216
124000695 June 7, 1995 124000695

PATENT INFORMATION STATEMENT
UNDER 21 USC §355(b)(1)

The following patents either claim the drug for which applicant has submitted this application or claim a method of using the drug. Applicant is the exclusive licensee or assignee of these patents.

Patent No.	Expiration Date	Claims Cover
4,599,353	July 8, 2003	Method and compositions for treating hypertension or glaucoma
5,296,504	March 22, 2011	Method and compositions for the topical treatment of ocular hypertension

February 1, 1995

SUPPLEMENTARY PATENT INFORMATION STATEMENT
SUBMITTED UNDER 21 U.S.C. §335 (c) (2)

Pharmacia, Inc. hereby files this Supplementary Patent Information Statement in NDA No. 20-597 filed June 14, 1995 relating to the drug latanoprost. This Supplementary Patent Information Statement lists a recently allowed United States patent covering the drug latanoprost.

PATENT NO.	EXPIRATION DATE	TYPE OF CLAIMS
5,422,368	March 24, 2011	Composition & Use for treatment of glaucoma or ocular hypertension

Respectfully submitted,
Pharmacia, Inc.

BY: Daniel G. Mannix
Daniel G. Mannix, PhD
Manager, Regulatory Affairs

DATE: July 6, 1995

EXCLUSIVITY SUMMARY for NDA # 20-597 **SUPPL #** NA

Trade Name Xalatan **Generic Name** latanaprost

Applicant Name Pharmacia **HFD-** 550

Approval Date _____

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II **FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

[illegible] 4/23/96

Signature Date

Title: Medical Officer

[illegible] 5/2/96

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-597 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 550 Trade (generic) name/dosage form: Xalatan (latanoprost, Solution) Action: AP (AE) NA

Applicant Pharmacia, Inc Therapeutic Class 1S

Indication(s) previously approved N/A

Pediatric labeling of approved indication(s) is adequate ____ inadequate ____

Indication in this application Reduction of intraocular pressure in patients with open angle glaucoma and ocular hypertension who are intolerant or insufficiently responsive to another IOP lowering medication.

(For supplements, answer the following questions in relation to the proposed indication.)

____ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

____ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

____ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

____ b. The applicant has committed to doing such studies as will be required.
- ____ (1) Studies are ongoing.
- ____ (2) Protocols were submitted and approved.
- ____ (3) Protocols were submitted and are under review.
- ____ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

____ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

____ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[illegible], M.D. 4/22/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-597
HFD 550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

CERTIFICATION PURSUANT TO THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to 21 U.S.C. §335a (k)(1) Pharmacia Inc. ("Pharmacia") hereby certifies that to the best of its knowledge and belief it has not used in any capacity the services of any person debarred under subsections 21 U.S.C. § 335a(a) or (b) in connection with this Application and that it will not use in any capacity the services of any person debarred under 21 U.S.C. §335a(a) or (b) in connection with this Application.

Pharmacia has made a reasonable effort to list the convictions of all persons whose convictions are required to be listed under 21 U.S.C. §335a(k)(2) in connection with this Application. This effort included reviewing the Debarment List as published in the Federal Register and confirming that no employees of Pharmacia connected with this Application appear on that list. In addition, Pharmacia requires that all newly hired employees execute a certification concerning any convictions required to be listed. Finally, this effort included a requirement that all persons not employed by Pharmacia who provided significant services in connection with this Application certify to Pharmacia concerning any convictions of their organization or of any person employed by them. Relying in part on these certifications to Pharmacia, the following list of all convictions described in 21 U.S.C. §335a(a) or (b), which occurred in the previous five (5) years of Pharmacia and affiliated persons responsible for the development or submission of this Application is provided.

The listed convictions are: None.

Respectfully submitted,

By: Kenneth King
Kenneth F. King

Title: Senior Vice President, Regulatory and Scientific Affairs

Date: May 25, 1995

Medical Officer's Review NDA 20-597
Original

NDA 20-597 Original		Submission date: Received date: Review date:	6/14/95 6/16/95 2/12/96

Drug:	Xalatan (latanoprost solution)
Pharmacologic Category:	Prostaglandin analog
Sponsor:	Pharmacia Inc. Post office Box 16529 Columbus Ohio 43216-6529
Proposed Indication:	For the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.
Dosage Form and Route of Administration:	Topical ophthalmic solution.
Submitted:	This application consist of 135 volumes divided into 15 sections. The clinical section consist of 42 volumes (1.44-1.86). The sponsor has identified 3 Phase III studies as pivotal trials : #9200PG004, #9200PG005, #9200PG006 .
Manufacturing Controls:	See Chemist's Review.
Pharmacology:	See Pharmacology and Toxicology Review.
Related Submissions:	IND IND

List of Controlled Clinical Studies Performed with Latanoprost (PhXA41)

Paragraph	Study No.	Report No.	Title of Study/Report	Principal Investigator/Country	No. of Study Centers	Dose (µg/ml)	Patients§ Evaluated (lat.)	Placebo/ Active Treatment-Control	Patients§ Evaluated (control)	Duration of Treatment
3.1.1	90PG09	L411 G015	Comparison of intraocular pressure lowering effect and side effects of PhXA41 and PhXA34 in healthy volunteers	Alm/Sweden	1	35 x 1 115 x 1 350 x 1	36HV	Placebo	CCE	1 day
3.1.2	91PG02	L411 G017	Effect of PhXA41, a new $PGF_{2\alpha}$ analogue, on aqueous humor dynamics	Brubaker/USA	1	60 x 2	20HV 20	Placebo	CCE	5 days
3.1.3	91PG03	L411 G018	IOP lowering effect and side effects of PhXA41. A 4-week dose titration study.	Alm/Sweden, Finland	3	35, 60, 115 x 2	45	Placebo	15	4 weeks
3.1.4	91PG01	9300175	A double-masked, randomized, placebo-controlled evaluation of the IOP response to topical treatment with PhXA41. A 2-week dose regimen study in ocular hypertensives.	Nagasubramanian/ England	1	60 x 1 or 2	38	Placebo	10	2 weeks
3.1.5	90PG05	L411 G023	PhXA41 administered once daily for 5 days in primary open angle glaucoma patients.	Rácz/Hungary	1	60 x 1	9	Placebo	6	5 days
3.1.6	9200PG003	L411 G025	Administration of latanoprost (PhXA41) eye drops once daily for 14 days	Coakes/England	4	12.5, 25, 50 x 1	35	Placebo	10	2 weeks
3.1.7	91PG06	9300148	Effect of PhXA41, a new prostaglandin analogue on IOP in low tension glaucoma patients. A two-center study.	Drance/Canada, Sweden	2	60 x 2	10	Placebo	10	2 weeks
3.1.8	9200PG001	9400215	Effect of latanoprost in pseudophakic eyes.	Greve/Holland	1	60 x 2	16	Placebo	8	4 weeks
3.1.9	9300PG012	9400648	Effect of repeated administration of latanoprost on nocturnal IOP. A randomized double-masked study in hospitalized patients.	Rácz/Hungary	1	50 x 1	19	Placebo	CCE	10 days
3.1.10	9300PG023	9400307	Effect of latanoprost on IOP in patients treated with acetazolamide. A randomized, double-masked placebo-controlled study.	Greve/Holland	1	50 x 1	11	Placebo	11	2 weeks**

Para-graph	Study No.	Report No.	Title of Study/Report	Principal Investigator/Country	No. of Study Centers	Dose (µg/ml)	Patients§ Evaluated (lat.)	Placebo/ Active Treatment-Control	Patients§ Evaluated (control)	Duration of Treatment
3.1.11	9300PG014	9400305	Comparison of the effect of latanoprost 50 µg/ml once daily and 15 µg/ml twice daily on IOP in normal tension glaucoma. A randomized placebo-controlled, double-masked crossover study.	Greve/Holland	1	50x1 or 15x2	29	Placebo	29	3+3+3 weeks***
3.2.1	9200PG002	L411 G024	A double-masked comparison of two dose regimens of PhXA41 in patients treated with timolol.	Alm/Sweden	5	60x1 or x2	48 (23 and 25)#	Latanoprost	(23 and 25)#	3 months
3.2.2	9300PG013	9400370	Comparison of PhXA41 (latanoprost) 50 µg/ml once daily and 15 µg/ml twice daily for 3 weeks. A randomized, double-masked, crossover study in patients with elevated IOP.	Lusky/Israel	3	50x1 or 15x2	50	Latanoprost	(50)	3+3 weeks
3.2.3	9300PG015	9400306	Effect of latanoprost on IOP and aqueous humor protein concentration. A randomized double-masked comparison of two different dose regimens with timolol as control.	Diestelhorst/Germany	1	50x1 or 15x2	18	Timolol 0.5%x2 Latanoprost	10 18	3+3 weeks
3.2.4	91PG07	L411 G022	Additive effect of PhXA41 to timolol in patients with elevated IOP.	Greve/Holland	1	60 x 2	9	Timolol 0.5% x 2	10	w week*
3.2.5	91PG09	L411 G021	Additive effect of PhXA41 to dipivefrin in patients with primary open angle glaucoma.	Watson/England	1	60 x 2	10	Dipivefrin 0.1% x 2	10	1 week*
3.3.1	9200PG004	9400369	A 6-month, randomized, double-masked comparison of PhXA41 with timolol in patients with open angle glaucoma or ocular hypertension. A multicenter study in the United States.	Camras/USA	17	50 x 1	96	Timolol 0.5% x 2	110	6 months
3.3.2	9200PG005	9400243	A 6-month, randomized, double-masked comparison of PhXA41 with timolol in patients with open angle glaucoma or ocular hypertension. A multicenter study in the United States.	Watson/England	14	50 x 1	133	Timolol 0.5% x 2	129	6 months
3.3.3	9200PG006	9400194	A 6-month, randomized, double-masked comparison of latanoprost with timolol in patients with open angle glaucoma or ocular hypertension. A multicenter study in Scandinavia.	Alm/Sweden (Norway) (Denmark)	13	50 x 1 p.m. or a.m.	169	Timolol 0.5% x 2	79	6 months

Rationale for dose Selection:

The selection of 50 μg/ml of latanoprost once daily as a suitable dose for the phase III clinical trial was based on 4 dose-finding and 2 dose-regimen studies. In the first phase I dose titration study (L411 G015), a single dose of a 35 μg/ml concentration resulted in approximately half of the IOP-reduction of the largest dose (350 μg/ml) in healthy volunteers. In the next dose titration study performed with PhXA34, the epimeric mixture containing about 50 % latanoprost (PhXA41) and 50 % of the much less pharmacologically active 15-S epimer, a single dose of 3 μg (~1.5 μg 50 μg/ml latanoprost [PhXA41]) induced near maximum IOP-reduction (Villumsen and Alm, 1992). In the next dose-finding study 3 different doses and placebo were administered twice daily for 4 weeks (L411 G018). The concentration of 35 μg/ml latanoprost (PhXA41) was as effective as 60 μg/ml and 115 μg/ml. Thus the 35 μg/ml concentration administered twice daily was already on the top of the dose-response curve. In the next 2 dose-regimen studies it was shown that administration of latanoprost once daily at a concentration of 60 μg/ml was at least as effective as twice daily during a 2 week treatment period (KP 9300175) as well as a 3 month treatment period (L411 G024). In fact once daily administration was somewhat better than twice daily administration in both studies. In a final dose-finding study (L411 G025) in which 12.5 μg/ml, 25 μg/ml and 50 μg/ml latanoprost was administered once daily for 2 weeks it was demonstrated that the 50 μg/ml concentration was most effective. Subsequently 3 dose-finding/dose-regimen studies were carried out and in all of these the dose of 50 μg/ml once daily has been tested against 15 μg/ml twice daily (KP9400305, KP9400306, KP9400307). All these studies confirm that the 50 μg/ml dose once daily is optimal or close to optimal in that near maximum IOP-reducing effect is achieved with a minimum of conjunctival hyperaemia. Administration of a lower dose (15 μg/ml) twice daily resulted in less IOP-reduction and did not reduce the amount or frequency of conjunctival hyperaemia. Thus, a dose of 50 μg/ml (0.005 %) administered once daily was regarded as suitable for the phase III clinical trials with latanoprost.

Study #1

Protocol #943200PG004,

Title: A 6-month, randomized, double-masked comparison of latanoprost (PhXA41) with timolol in patients with open angle glaucoma or ocular hypertension. A multicenter study in the United States.

Objectives: The primary objective was to demonstrate that the IOP-reducing effect of latanoprost was comparable to that of timolol at the end of 6 months of treatment. The extreme limit for this comparison was defined as a difference in IOP-reduction between the two treatments not exceeding 1.5 mmHg in favor of timolol.

The secondary objectives were to describe the IOP-reduction throughout the study period, and to follow the safety variables in the two treatment groups.

INVESTIGATORS

Principal Investigator of the study:

Carl B. Camras, M.D.
Professor of Ophthalmology
University of Nebraska
Omaha, Nebraska

Study Center 1:
Principal Investigator:
Carl B. Camras, M.D.
University of Nebraska — Treatment started: Feb. 1, 1993
Omaha, Nebraska — Treatment completed: Nov. 22, 1993

Study Center 2:
Principal Investigator:
Don S Minckler, M.D.
Univ. of S. California — Treatment started: Mar. 25, 1993
Los Angeles, California — Treatment completed: Jan. 25, 1994

Study Center 3:
Principal Investigator:
Robert Weinreb, M.D.
Univ. of California, San Diego — Treatment started: Mar. 26, 1993
La Jolla, California — Treatment completed: Jan. 19, 1994

Study Center 4:
Principal Investigator:
Mark Sherwood, M.D.
University of Florida — Treatment started: Feb. 18, 1993
Gainesville, Florida — Treatment completed: Oct. 7, 1993

Study Center 5:
Principal Investigator:
Jacob Wilensky, M.D.
University of Illinois — Treatment started: Mar. 4, 1993
Chicago, Illinois — Treatment completed: Jan. 26, 1994

Study Center 6:
Principal Investigator:
Theodore Krupin, M.D.
Northwestern University Medical School — Treatment started: Feb. 25, 1993
Chicago, Illinois — Treatment completed: Feb. 8, 1994

Study Center 7:
Principal Investigator:
Thom Zimmerman, M.D.
Univ. of Louisville — Treatment started: Mar. 5, 1993
Louisville, Kentucky — Treatment completed: Jan. 28, 1994

Study Center 8:
Principal Investigator:
Alan L. Robin, M.D.
Lake Falls Professional Bldg. — Treatment started: May 12, 1993
Baltimore, Maryland — Treatment completed: Jan. 7, 1994

Study Center 9:
Principal Investigator:
Eve J. Higginbotham, M.D.
University of Michigan
Ann Arbor, Michigan

Treatment started: Apr. 15, 1993
Treatment completed: Dec. 28, 1993

Study Center 10:
Principal Investigator:
Martin B. Wax, M.D.
Wash. Univ. School of Med.
St. Louis, Missouri

Treatment started: May 7, 1993
Treatment completed: Feb. 3, 1994

Study Center 11:
Principal Investigator:
Jacqueline Lustgarten, M.D.
River Edge, New Jersey

Treatment started: Feb. 11, 1993
Treatment completed: Nov. 30,

Study Center 12:
Principal Investigator:
Robert Schumer, M.D.
Mount Sinai Med. Center
New York, New York

Treatment started: Jan. 20, 1993
Treatment completed: Nov. 10, 1993

Study Center 13:
Principal Investigators:
E. Michael Van Buskirk, M.D.
George A. Cioffi, M.D.
Devers Eye Institute
Portland, Oregon

Treatment started: Apr. 2, 1993
Treatment completed: Jan. 10, 1994

Study Center 14:
Principal Investigators:
L. Jay Katz, M.D.
Marlene R. Moster, M.D.
Wills Eye Hospital
Philadelphia, Pennsylvania

Treatment started: May 17, 1993
Treatment completed: Feb. 16, 1994

Study Center 15:
Principal Investigator:
William C. Stewart, M.D.
Medical Univ. of S. Carolina
Charleston, South Carolina

Treatment started: Mar. 8, 1993
Treatment completed: Nov. 22, 1993

Study Center 16:
Principal Investigator:
Paul L. Kaufman, M.D.
University of Wisconsin
Madison, Wisconsin

Treatment started: Apr. 13, 1993
Treatment completed: Feb. 3, 1994

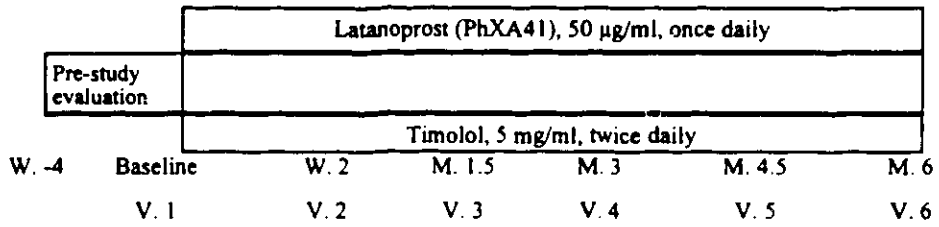
Study Center 17:
Principal Investigator:
Robert Ritch, M.D.
N.Y. Eye and Ear Infirmary
New York, New York

Treatment started: Feb. 12, 1993
Treatment completed: Jan. 14, 1994

Study design

The study was designed as a randomized, parallel group, double-masked comparison of latanoprost and timolol over a 6-month period.

During the month preceding the start of the study (baseline day), patients were assessed for eligibility. During the treatment period of 6 months, there were six scheduled visits. Visit 1 at baseline (full day visit), visit 2 after 2 weeks (morning visit), visit 3 after 1.5 months (morning visit), visit 4 after 3 months (morning visit), visit 5 after 4.5 months (morning visit), and visit 6 after 6 months (full day visit) of treatment. A deviation of 4 days for visit 2 and one week for the subsequent visits was accepted. Additional visits numbered #91, #92 etc. (if the patient was on study drug), and #51, #52 etc. (after discontinuation) could be performed at the discretion of each investigator.



W = Week, M = Month, V = Visit

Examinations	Pre-study	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		
	-4 w.	Day 0			Week 2 ±4 days	Month 1.5 ±1 week	Month 3 ±1 week	Month 4.5 ±1 week	Month 6 ±1 week		
		8	12	16	8	8	8	8	8	12	16
Medical and ocular history	X										
Gonioscopy	X										
Visual fields	X X									X	
Ophthalmoscopy	X										X
Symptomatology	X			X	X	X	X	X	X		X
Visual acuity	X	X			X	X	X	X	X		
Refraction		X			(X)	(X)	(X)	(X)	X		
Slitlamp examination	X	X	X	X	X	X	X	X	X	X	X
Conjunctival hyperaemia	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X	X	X
Photography (iris)	X						X	X	X		
Photography (external)	X								X		
Blood Pressure	X	X			X		X		X		
Heart Rate	X	X			X		X		X		
Blood sample	X								X		
Urine sample	X								X		

Study population: Two hundred and fifty to three hundred patients were planned to be included; with at least 125 per treatment group

Criteria for Inclusion:

Patients of either sex, 40 years or older, with unilateral or bilateral primary open angle glaucoma, exfoliation (capsular) glaucoma, pigmentary glaucoma or ocular hypertension, with IOP of 22 mmHg or higher measured during the pre-study period, were eligible for the study.

Patients previously not treated or on single drug treatment for elevated IOP were eligible after a medication free period (wash-out) of:

- 3 weeks for ß-adrenergic antagonists,
- 2 weeks for adrenergic agonists,
- 5 days for cholinergic agonists,
- 5 days for oral carbonic anhydrase inhibitors.

Patients requiring treatment bilaterally had to fulfil eligibility criteria for both eyes. All patients had to sign an informed consent before enrolment.

Exclusion criteria

Women of childbearing potential and nursing mothers were excluded from the study, as were patients who were unable to adhere to the treatment/visit plan or who had participated in any other clinical study within one month of inclusion.

The following were specific reasons for exclusion:

Ocular conditions
- history of acute angle closure;
- severe trauma at any time;
- intraocular surgery or argon laser trabeculoplasty within 6 months;
- current use of contact lenses;
- history of severe dry eye syndrome;
- ocular inflammation/infection within three months of inclusion;
- any condition preventing reliable applanation tonometry;
- unacceptable finding at the pre-study ocular examination as specified in the Case Report Forms;
- monotherapy regarded by investigator to be insufficient with respect to optic nerve head and/or visual field status.

Concomitant diseases
- cardiac failure, sinus bradycardia, second and third degree of atrio-ventricular block.
- bronchial asthma, history of bronchial asthma or chronic obstructive pulmonary disease.

Study Drug: Latanoprost (PhXA41) eye drop solution 50 µg/ml (Batch No. B179208) and placebo (vehicle) eye drop solution (Batch No. B019208), were used.

To obtain complete masking of the study, placebo eye drops had to be used for the latanoprost treatment group, since latanoprost was administered once daily and timolol twice daily.

Composition

Active substance:

Latanoprost	50 µg

Reference Drug:

Timolol 5 mg/mL (Timoptic® ophthalmic solution 0.5 %, Merck, Sharp & Dohme, USA) refilled by Pharmacia AB in bottles identical with bottles for latanoprost and placebo (Batch No. B179209). The stability of the timolol solution in the new dispenser was investigated and found adequate.

Composition

Active substance:

Timolol maleate	6.8 mg (equivalent to 5 mg base)

Treatment schedule

Patients were instructed to instil one drop (approx. 30 µl) in the affected eye(s) every morning at approximately 8.00 h. from the morning bottle, and one drop every evening at approximately 20.00 h. from the evening bottle.

On the examination days, however, the patients were instructed not to take the morning drop before the visit to the clinic. On these days, the morning drop was administered after the 8.00 h. examination.

The first eye drop was applied in the evening of the baseline day and the last eye drop was instilled after the morning examination of the last visit.

Continuation of treatment

All patients completing the 6-month double-masked study were given the opportunity to participate in a 6-month, open label study with latanoprost as a continuation to the double-masked study. The open label study is described in a separate protocol (9200PG010). Patients not transferred to this protocol were to be treated at the discretion of the investigator.

Concomitant therapy

No other topical ophthalmic medication known to affect IOP were to be used during the study. Patients in whom systemic medication, known to affect IOP, was initiated or changed during the study were to be withdrawn.

Patient characteristics

Demographic data including sex, date of birth, race, eye color, diagnosis and duration of the glaucoma/ocular hypertension were recorded together with information about ocular/non-ocular other diseases and medications and previous ocular medications.

Efficacy assessments

Clinical efficacy assessments

Intraocular pressure (IOP)

Preferably, in each patient, IOP was to be measured with the same tonometer throughout the study period and by the same Investigator. The intraocular pressure was measured with a Goldmann applanation tonometer. Three consecutive measurements were made in each eye at each assessment. The mean of the three measurements was used in the statistical analysis if the patient had one study eye, and the mean of the six measurements were used if both eyes were study eyes.

Laboratory efficacy assessments

There were no laboratory efficacy variables.

Safety assessments

Preferably the same Investigator should perform the same assessments at each visit for a given patient during the study. All ocular assessments were to be performed in both eyes.

Symptomatology

Ocular and general discomfort experienced since last visit were specifically asked for in the morning on days of examination.

Conjunctival hyperaemia

Conjunctival hyperaemia was examined in the morning at each visit and graded using an arbitrary scale from 0 (none) to 3.0 (severe) in steps of 0.5 units. On Day 0 and Month 6 hyperaemia was also evaluated at noon and in the afternoon. The grading was performed by comparing the hyperaemia with standard photographs showing conjunctival hyperaemia of grade 0, 1, 2 and 3 (none, mild, moderate, severe).

Slit lamp examination

Slit lamp examination was performed with special emphasis on aqueous flare only in the morning to avoid misinterpretation caused by fluorescein induced flare. Flare, if present, was graded according to a scale of slight (1), moderate (2), severe (3). The aqueous humor was investigated for cells at each examination. If present cells were counted.

The cornea, conjunctiva and iris were also examined. Any abnormal finding was described and graded; 1, 2 or 3 (mild, moderate, severe).

Visual fields

Preferably automated perimetry (threshold program), e.g. Humphrey program 24:2, 30:2, Octopus program G1 or Competer, was to be used. For each patient the same perimetry program was to be used before the study (within one month prior to study start) and at the end of the study.

Visual acuity and refraction

Best corrected Snellen visual acuity and the refractive error were determined on baseline day and at the 6 month visit. Best corrected visual acuity was determined at every visit, and if it had changed from day 0 the refractive error had to be determined. A phoropter was used and the distance was 20 feet or adjusted to 20 feet.

Ophthalmoscopy

Ophthalmoscopy was performed after dilatation of the pupils to examine:

the lens	for opacities or other changes. Findings were graded as mild, moderate or severe. The location and character of the findings were also described.
the vitreous	if the vitreous was found to be abnormal, changes were described with respect to character and location.
the retina	any pathological findings in the retina were described in detail with respect to character and location.
the optic nerve head	was classified as normal or glaucomatous and the cup/disc ratio was recorded both horizontally and vertically.

Blood pressure/heart rate

Blood pressure and heart rate were measured in the right arm with the patient in sitting position after 10 minutes of rest. The heart rate had to be based on at least a 30 sec. recording. The measurements were performed in the morning of baseline, visit 2 (2 weeks), visit 4 (3 months) and visit 6 (6 months).

Photography of the iris

Color photographs (slides) of the irides were taken at pre-inclusion, at months 3.0, 4.5 and 6.0, for evaluation of the iris color. The photographs were evaluated by an independent consultant (ophthalmologist) to Pharmacia.

During the course of the study, and two other phase III clinical studies running parallelly in England and Scandinavia, some patients developed increased iris pigmentation. To investigate the phenomenon it was necessary to classify the iris color in more detail according to the following:

1	=	Blue/grey iris
2	=	Blue/grey iris with slightly brown, usually around the pupil
3	=	Blue/grey and brown iris (mixed color iris)
4	=	Green
5	=	Green iris with slightly brown, usually around the pupil
6	=	Green-brown iris (mixed color iris)
7	=	Brown iris (Caucasian)
8	=	Yellow-brown iris (Caucasian)
9	=	Brown iris (Black)
10	=	Brown iris (Asian)

Protocol Change

The Sponsor also decided in a meeting held September 6, 1993 that all patients with increased pigmentation of the iris should be withdrawn from the study and followed up at least twice yearly for a minimum of 2 years to investigate whether the increase in iris pigmentation is reversible or not.

External (en face) photography

En face photographs were taken at pre-inclusion and at Month 6 for evaluation of the palpebral fissure and eyelids. The photographs were evaluated by an independent consultant (ophthalmologist) to Pharmacia.

Laboratory safety assessments

The following tests were included in the laboratory safety assessments:

Hematology	Hematocrit, Hb, MCV, MCH, MCHC, RBC, WBC including differential count, platelets, PT, PTT.
Blood chemistry	
Serum-cholesterol (total, HDL, LDL)	
Serum triglycerides	
Serum proteins (total)	
Blood glucose	
Kidney function	Serum creatinine, urea.
Liver function	Serum bilirubin, alkaline phosphate, ASAT (SGOT), ALAT (SGPT).
Electrolyte and	Serum Na^+, K^+, Ca^{2+}, Cl, fluid balance
Urinalysis	Protein, glucose.

Adverse events

An adverse event was defined as any undesirable experience even if not considered related to the study drug.

All spontaneously occurring adverse events were to be reported.
All recorded events were to be specified with respect to severity, intensity, action taken and outcome.

Statistical methods

Protocol deviation and data evaluation

The primary objective, comparison of the latanoprost and timolol groups with respect to reduction in IOP at Month 6, was analyzed in two ways: an intention-to-treat analysis and a per-protocol analysis. The secondary efficacy objectives were only assessed using a per-protocol analysis. Safety analysis were based on all patients who received study drug.

Reviewer's Comments: *The comparison should be made at each time point measured.*

The intention-to-treat analysis of reduction in IOP was based on all randomized patients. For patients with missing data at Month 6, the baseline IOP measurement was carried forward to Month 6; thus, for those patients, the IOP-reduction was defined to be 0. This approach differs from that specified in the protocol where it was stated that the last value should be carried forward. Prior to breaking the randomization blind and conducting the analysis, however, it was decided to adopt the more conservative approach of carrying forward the baseline value.

6 Pages
Purged

Demographics: Patient characteristics.

Variable		Latanoprost	Timolol	All
Number of patients		128	140	268
Age (mean ±SD) (min-max)		61.4±12.0 (30-89)	63.1±10.7 (33-90)	62.3±11.3 (30-90)
Sex	Males	58	56	114
	Females	70	84	154
Ethnic origin	Caucasian	94	91	185
	Black	27	38	65
	Hispanic	6	10	16
	Asian	1	1	2
Ocular diagnosis	Primary open angle glaucoma	39	45	84
	Exfoliation glaucoma	3	2	5
	Pigmentary glaucoma	3	1	4
	Ocular hypertension	80	90	170
	Different diagnosis, in right and left eyes	3	2	5
Family history of glaucoma/ocular hypertension		43	52	95

STUDY POPULATION:

A total of 268 patients were included in the study; 128 were allocated to latanoprost and 140 to timolol. All 268 patients were included in the intention to treat analysis. Of the patients 206 (96 in the latanoprost group and 110 in the timolol group) completed the last visit (Month 6) according to the protocol and are included in the per-protocol analysis of the primary objective. The number of evaluable patients in the per-protocol analysis changed per visit according to the following:

Treatment	Visit					
	1 (Day 0)	2 (2 weeks)	3 (1.5 months)	4 (3 months)	5 (4.5 months)	6 (6 months)
Latanoprost	125	117	119	117	114	96
Timolol	138	136	136	130	129	110

The reason for the large exclusion of patients at the Month 6 visit was a misunderstanding by a few of the investigators that patients should not be administered medication in the morning of the last visit. According to the protocol the study drug had to be administered after the morning examination during the last visit. Omitting the last drop could have affected the response in the timolol group, since the morning drop in the timolol group was active timolol, while it was placebo in the latanoprost group.

Reviewer's Comments: *The ITT analysis will favored Latanaprost over Timoptic. The most fair comparison will be in the per protocol analysis.*

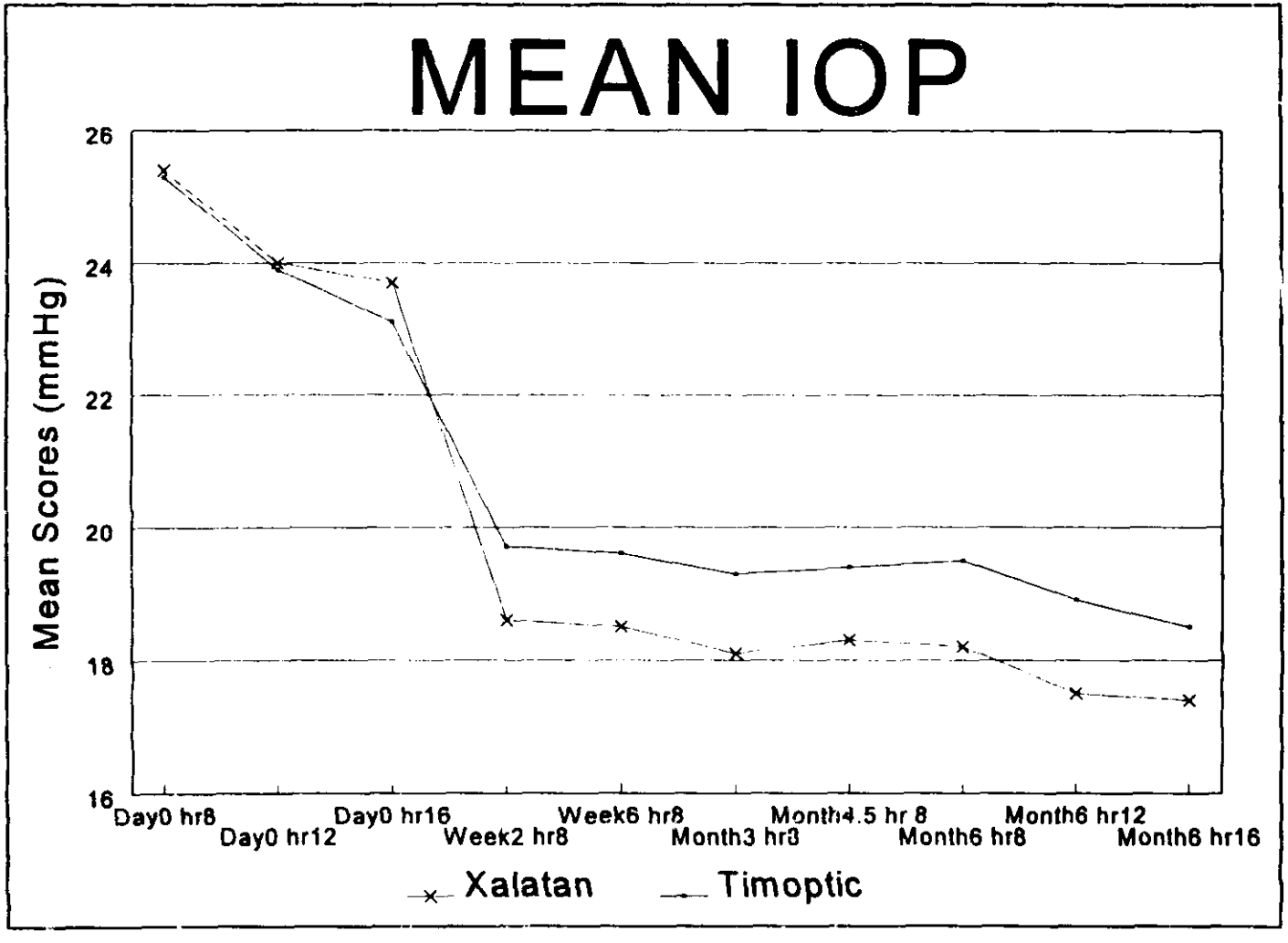
Number of patients recruited per center. Evaluable patients in per protocol analysis in parenthesis.

Study center and principal investigator	Latanoprost	Timolol	All
Omaha, Camras	12 (10)	13 (13)	25 (23)
Los Angeles, Minckler	6 (4)	4 (1)	10 (5)
La Jolla, Weinreb	10 (9)	10 (10)	20 (19)
Gainsville, Sherwood	7 (7)	8 (7)	15 (14)
Chicago I, Wilensky	7 (3)	8 (3)	15 (6)
Chicago II, Krupin	8 (1)	7 (3)	15 (4)
Louisville, Zimmerman	3 (2)	6 (6)	9 (8)
Baltimore, Robin	9 (9)	9 (8)	18 (17)
Ann Arbor, Higginbotham	7 (6)	9 (8)	16 (14)
St. Louis, Wax	12 (11)	13 (12)	25 (23)
River Edge (NJ), Lustgarten	7 (7)	8 (8)	15 (15)
New York I, Schumer	4 (3)	6 (6)	10 (9)
Portland, Van Buskirk	6 (4)	7 (4)	13 (8)
Philadelphia, Katz	6 (5)	6 (5)	12 (10)
Charleston, Stewart	7 (7)	8 (8)	15 (15)
Madison, Kaufman	5 (5)	5 (4)	10 (9)
New York II, Ritch	12 (3)	13 (4)	25 (7)

Efficacy
Intraocular pressure[a] (mmHg) at each scheduled examination.

Treatment Group	Statistics	Visit and time						
		1			2	3	4	5
		8:00	12:00	16:00	8:00	8:00	8:00	8:00
Latanoprost	MEAN	25.4	24.0	23.7	18.6	18.5	18.1	18.3
	STD	3.8	3.5	3.5	3.7	3.7	4.1	3.6
	N	125	125	125	117	119	117	114
	MIN	18.0	16.5	16.0	10.8	10.7	8.5	10.0
	MAX	40.0	35.0	33.5	34.0	30.7	36.0	31.7
Timolol	MEAN	25.3	23.9	23.1	19.7	19.6	19.3	19.4
	STD	4.0	4.1	3.9	3.6	3.7	3.5	3.3
	N	138	138	138	136	136	130	129
	MIN	17.0	13.5	14.5	11.7	10.8	10.8	11.5
	MAX	37.2	42.0	37.7	33.0	33.5	29.3	28.0

[a] If both eyes are study eyes the mean of both eyes is used in the analysis.


MEAN IOP
Mean Scores (mmHg)
26
24
22
20
18
16
Day0 hr8
Day0 hr12
Day0 hr16
Week2 hr8
Week6 hr8
Month3 hr3
Month4.5 hr 8
Month6 hr8
Month6 hr12
Month6 hr16
Xalatan
Timoptic

Subgroup Analysis:

IOP-response in males and females (per protocol)

Latanoprost reduced the mean diurnal IOP by 7.0 mmHg in males and by 6.4 mmHg in females (p>0.05; Ancova). The corresponding figures for timolol were 5.2 mmHg and 4.7 mmHg, respectively (p>0.05; Ancova)

Diurnal* intraocular pressure (mmHg) at baseline, visit 6 (6 months of treatment) and change from baseline to visit 6 in males and females.

Sex	Visit	Intraocular pressure mean±SD (No. of patients)	
		Latanoprost	Timolol
Males	Baseline	24.2±3.4 (57)	23.9±3.7 (54)
	Visit 6	17.0±3.3 (46)	18.5±3.1 (46)
	Change	-7.0±3.6 (46)	-5.2±2.5 (46)
Females	Baseline	24.5±3.0 (68)	24.2±3 6 (84)
	Visit 6	18.1±2.8 (50)	19.2±2.9 (64)
	Change	-6.4±3.2 (50)	-4.7±3.2 (64)

* Mean of measurements at 8:00, 12:00 and 16:00.
If both eyes are study eyes the mean of both eyes is used in the analysis.

IOP-response in different races (per protocol)

The diurnal IOP-response to latanoprost was 7.3 mmHg in Blacks, and 6.6 mmHg in Caucasians. There was no difference in response (p>0.05 Ancova).
Timolol reduced mean diurnal IOP equally well in Blacks and Caucasians; 5.0 mmHg (p>0.05; Ancova)

Diurnal[a] intraocular pressure (mmHg) at baseline, visit 6 (6 months of treatment), and change from baseline to visit 6 in different races.

Ethnic origin	Visit	Intraocular pressure mean±SD (No. of patients)	
		Latanoprost	Timolol
Caucasian	Baseline	24.2±2.9 (92)	24.1±3.5 (89)
	Visit 6	17.5±2.9 (74)	18.7±2.9 (73)
	Change	-6.6±3.5 (74)	-5.0±3.1 (73)
Black	Baseline	24.3±3.7 (27)	23.6±3.4 (38)
	Visit 6	17.2±3.4 (20)	18.8±3.1 (30)
	Change	-7.3±3.5 (20)	-5.0±2.6 (30)
Asian	Baseline	21.6 (1)	22.9 (1)
	Visit 6	--	--
	Change	--	--
Hispanic	Baseline	28.0±3.1 (5)	25.9±5.0 (10)
	Visit 6	23.5±1.3 (2)	21.2±3.7 (7)
	Change	-6.3±0.7 (2)	-3.3±1.8 (7)

[a] Mean of measurements at 8:00, 12:00 and 16:00.
If both eyes are study eyes the mean of both eyes is used in the analysis.

IOP-response in patients with different eye color (per protocol)

There were no differences in IOP-response to latanoprost nor Timoptic based on eye color. The diurnal IOP-response ranged from 6.6 to 6.9 mmHg (p>0.05; Ancova)

Diurnal[a] intraocular pressure (mmHg) at baseline, visit 6 (6 months of treatment) and change from baseline to visit 6 in patients with different eye color.

Eye color	Visit	Intraocular pressure mean±SD (No. of patients)	
		Latanoprost	Timolol
Blue/Green/Grey	Baseline	24.4±3.3 (42)	24.5±3.7 (50)
	Visit 6	17.1±2.8 (35)	18.7±3.0 (41)
	Change	-6.9±3.5 (35)	-5.1±2.9 (41)
Hazel	Baseline	24.4±2.3 (16)	24.2±3.1 (17)
	Visit 6	18.0±2.4 (11)	18.4±2.6 (12)
	Change	-6.9±2.4 (11)	-5.6±4.2 (12)
Brown	Baseline	24.4±3.3 (67)	23.8±3.7 (71)
	Visit 6	17.8±3.5 (50)	19.1±3.1 (57)
	Change	-6.6±3.6 (50)	-4.6±2.7 (57)

[a] Mean of measurements at 8:00, 12:00 and 16:00.
If both eyes are study eyes the mean of both eyes is used in the analysis.

IOP-response in different subgroups of ocular disease (per protocol)

There was no significant difference in IOP reduction in patients with primary open angle glaucoma or patients with ocular hypertension in either the Latanaprost nor the Timolol group. (p>0.05, Ancova)

IOP-response in patients previously treated with -adrenergic antagonists (per protocol)

There was no difference in the response pattern to Latanaprost between patients who had previously received topical -adrenergic antagonists and patients who never previously had been treated with antiglaucoma drugs to latanoprost

There was no difference in the response pattern between the latanoprost and the timolol groups (p>0.05; Ancova)

IOP-response in patients with variable duration of ocular disease (per protocol)

There were no indications in neither group that the IOP-reduction was dependent on the duration of the ocular condition.

Efficacy conclusions

Latanoprost administered once daily in the evening reduced IOP at least equally well as timolol administered twice daily at the time points measured. Even though the sponsor reported that the IOP-reducing effect of latanoprost was superior to that of timolol, in reality this conclusion is not supported by the data presented. The timepoints chosen by the sponsor in this trial did not include the peak effect of the active control timolol, which occurs between 1 and 2 hours after drug administration.

Safety:

Systemic (non-ocular) safety variables

Blood pressure

The systolic and diastolic blood pressures were measured in the morning at baseline, and at two weeks, three months and six months of treatment. No significant ($p>0.05$, paired t-test) changes occurred in mean systolic and diastolic blood pressures .

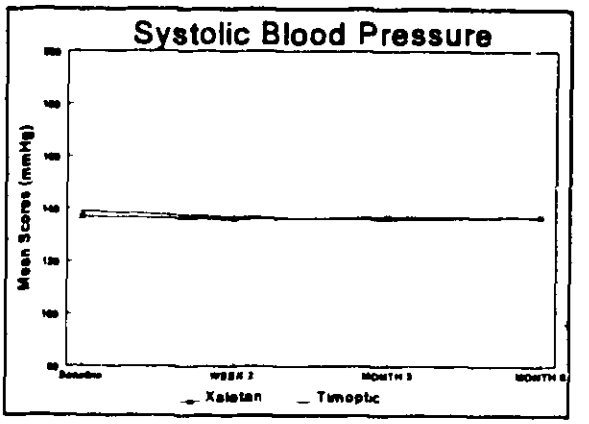
Heart rate

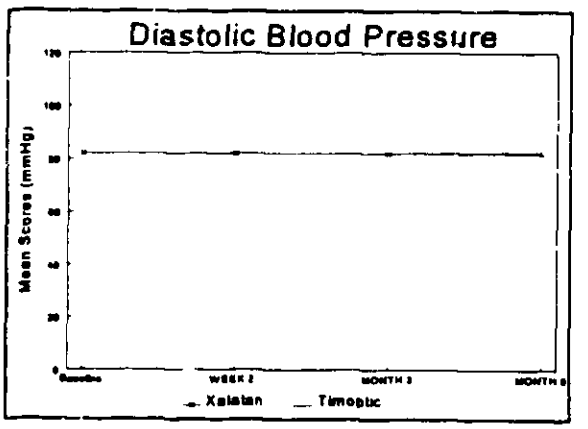
The heart rate was determined at the same occasions as the blood pressure. There was no significant ($p>0.05$, paired t-test) change in the latanoprost, but a significant ($p<0.001$; paired t-test) reduction of 3.1 beats/min. in the timolol group at Month 6.

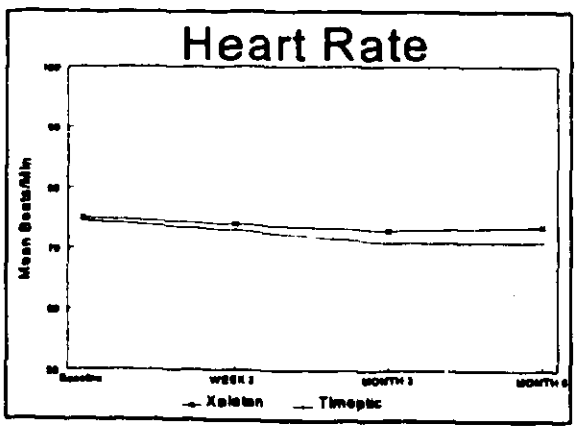
Arterial blood pressure (mmHg) and heart rate (beats/min.) at scheduled examinations.

Visit	Blood pressure/Heart rate	Mean±SD (No. of patients)	
		Latanoprost	Timolol
Baseline	Systolic BP	137.4±17.6 (126)	138.6±19.0 (140)
	Diastolic BP	81.7±9.7 (126)	82.2±9.8 (140)
	Heart rate	74.8±10.7 (126)	74.5±9.7 (140)
2 weeks	Systolic BP	136.0±16.2 (125)	136.7±18.0 (139)
	Diastolic BP	81.6±10.9 (125)	82.0±10.0 (139)
	Heart rate	73.6±9.6 (125)	73.0±9.0 (138)
3 months	Systolic BP	136.9±17.1 (120)	135.6±18.6 (132)
	Diastolic BP	82.1±9.9 (120)	81.9±9.5 (133)
	Heart rate	73.0±9.8 (120)	71.0±9.9 (133)
6 months	Systolic BP	137.0±18.3 (117)	136.6±19.4 (124)
	Diastolic BP	82.2±10.8 (117)	82.5±12.0 (124)
	Heart rate	73.5±9.6 (117)	71.2±10.0 (124)

BP = Blood pressure


Systolic Blood Pressure
Mean Scores (mmHg)
Xalatan
Timoptic


Diastolic Blood Pressure
Mean Scores (mmHg)
Xalatan
Timoptic


Heart Rate
Mean Beats/Min
Xalatan
Timoptic

Ocular safety variables

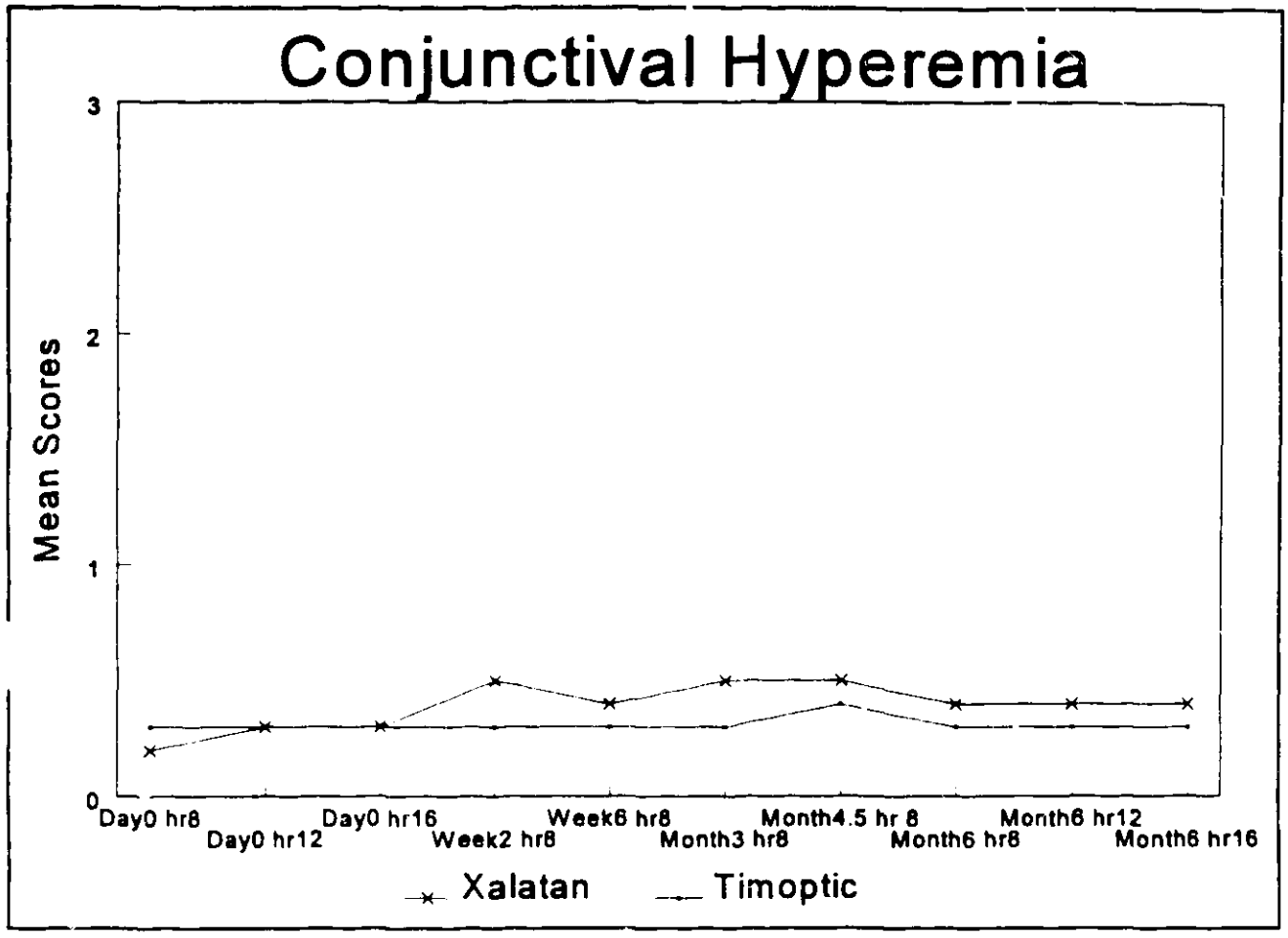
Conjunctival hyperaemia

At Month 6 only 1 patient in the latanoprost group exhibited hyperaemia graded as moderate. One hundred nine (92 %) of the patients in the latanoprost group and 126 (97 %) of those treated with timolol had no increase of hyperaemia or a barely detectable increase, i.e. 0.5 units, at Month 6 compared to baseline. The development of hyperaemia was significant in the latanoprost group ($p<0.001$)

Conjunctival hyperaemia at each scheduled examination.

Treatment group	Statistics	Visit and time									
		1			2	3	4	5	6		
		8:00	12:00	16:00	8:00	8:00	8:00	8:00	8:00	12:00	16:00
Latanoprost	MEAN	0.2	0.3	0.3	0.5	0.4	0.5	0.5	0.4	0.4	0.4
	STD	0.4	0.4	0.4	0.5	0.5	0.5	0.4	0.4	0.4	0.4
	N	128	128	128	126	124	121	120	118	118	118
	MIN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	MAX	1.5	1.5	1.5	2.0	2.0	2.0	1.5	2.0	2.0	2.0
Timolol	MEAN	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.3
	STD	0.4	0.3	0.4	0.3	0.4	0.4	0.4	0.3	0.3	0.3
	N	140	140	140	140	138	133	130	130	129	128
	MIN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	MAX	1.5	1.5	1.5	1.5	1.5	1.5	2.0	1.0	1.5	1.5

* If both eyes treated the worse eye is used in the analysis.


Conjunctival Hyperemia
Mean Scores
3
2
1
0
Day0 hr8
Day0 hr12
Day0 hr16
Week2 hr8
Week6 hr8
Month3 hr8
Month4.5 hr 8
Month6 hr8
Month6 hr12
Month6 hr16
Xalatan
Timoptic

Aqueous flare

A slight aqueous flare was detected during the course of the study in two patients of each treatment group.

Flare in aqueous humor in individual patients. Flare was absent in all other patients.

Treatment	Pat. No.	Visit a	Flare score[b]
Latanoprost	102	3	
		4	
		5	
		6	
	1022	1	
Timolol	1016	3	
	1018	2	

Visit 1 is baseline before the study drug has been instituted.

Flare is graded slight, moderate or severe.

If both eyes are study eyes the worse eye is listed.

Cells in the aqueous humor

One patients treated with latanoprost had a few cells in the aqueous humor at visit 2, 3 and 4, which increased to 10 cells in each eye at Month 6 visit. In addition to this patient, a few cells were occasionally detected in seven other patients on latanoprost and four patients on timolol.

Number of cells in aqueous humor in individual patients. Cells were absent in all other patients.

Treatment	Pat. No.	Visit[a]	Examination time	No. of cells[b]
Latanoprost	102	2	8:00	
		3	8:00	
		4	8:00	
		5	8:00	
		6	8:00	
			12:00	
			16:00	
	109	2	8:00	
	119	5	8:00	
	510	1	12:00	
	813	6	16:00	
	1013	3	8:00	
	1022	1	8:00	
			12:00	
			16:00	
	1202	2	8:00	
Timolol	108	4	8:00	
		6	8:00	
			12:00	
			16:00	
	514	1	16:00	
	814	6	16:00	
	1016	3	8:00	

[a] Visit 1 is baseline; i.e. before any study drug has been instilled. [b] If both eyes are study eyes the sum of both eyes is listed.

Visual acuity and refractive error

The mean visual acuity was 0.88 at baseline in the latanoprost group and 0.87 in the timolol group, and did not change significantly ($p>0.05$, paired t-test) during the study period. Neither did the refractive error change during the study.

Best corrected visual acuity[a] and refractive error[b].

Visit	Variable	Mean±SD (No. of patients)	
		Latanoprost	Timolol
Baseline	Visual acuity	0.88±0.18 (128)	0.87±0.18 (140)
	Spherical equivalent	-0.28±2.58 (127)	-0.18±2.58 (138)
2 weeks	Visual acuity	0.88±0.17 (126)	0.88±0.17 (140)
1.5 months	Visual acuity	0.88±0.19 (124)	0.89±0.17 (138)
3 months	Visual acuity	0.88±0.19 (121)	0.88±0.16 (133)
4.5 months	Visual acuity	0.88±0.19 (120)	0.89±0.17 (131)
6 months	Visual acuity	0.88±0.18 (118)	0.89±0.18 (130)
	Spherical equivalent	-0.36±2.69 (112)	-0.15±2.42 (126)

[a] Visual acuity is measured as 20/X, where 20 denotes the distance and X the line on the chart. In the table the decimal value of 20/X has been used in the calculations.

[b] Refractive error is expressed as spherical equivalents; refractive error +0.5 x cylinder

Visual fields

In one patient (911) treated with latanoprost and in one patient (1106) treated with timolol, a deterioration in the visual field was reported as an adverse event. In the other patients, either no change or only minor changes were observed.

Optic nerve head

In 8 patients treated with latanoprost and 7 patients treated with timolol, the cup-disc ratio increased 0.3 or more. In 3 patients from each of the 2 treatment groups, the ratios decreased by 0.3 or more. For 5 patients the classification of the optic nerve changed from normal to glaucomatous, and for 1 patient it changed from glaucomatous to normal, in the group treated with latanoprost. Corresponding figures for timolol were 3 and 1, respectively. In none of these cases the change was regarded as being of clinical importance, but was most likely explained by different examiners.

General examination of the eye

The eye lids, the conjunctiva, the cornea, the iris and the anterior chamber were examined at each visit, while the lens, the vitreous body and the retina were examined pre- and post-study. Except for findings included in the adverse events and/or ocular signs and symptoms, no pathological findings compared to baseline were made in these tissues.

LABORATORY SAFETY VARIABLES

There were no gross differences between the treatment groups.

ADVERSE EVENTS:

Comparison of ocular symptoms and findings between latanoprost and timolol.

Part of eye	Ocular symptom/finding*	Number of patients (%)	
		Latanoprost	Timolol
Discomfort	Stinging	8 (6%)	17 (12%)
	Itching	7 (5%)	15 (11%)
	Foreign body sensation	5 (3%)	17 (12%)
	Eye pain	3 (2%)	6 (4%)
	Eye irritation	3 (2%)	2 (1.4%)
	Burning	15 (12%)	18 (13%)
	Dry eye	10 (7%)	6 (4%)
	Tearing	4 (3%)	13 (9%)
	Mattering	3 (2%)	--
	Ophthalmic migraine	1(.8%)	1 (.7%)
Vision	Blurred vision	15 (12%)	9 (6%)
	Vision disturbances (Flashing lights, Flickering vision, glare)	4 (3%)	5 (3.5%)
	Photophobia	4 (3%)	5 (3.5%)
	Floaters	2 (1.6%)	2 (1.4%)
	Diplopia	1 (.8%)	1 (.7%)
	Visual field changes	1 (.8%)	1 (.7%)
Lid	Pain/discomfort	9 (7%)	4 (2.8%)
	Oedema	4 (3%)	6 (4%)
	Erythema	9 (7%)	7 (5%)
	Blepharitis	7 (5%)	7 (5%)
	Ptosis	-	2 (1.4%)
	Angular injection	-	2 (1.4%)
	Hemangioma	-	1 (.7%)
	Ecchymosis	1 (.8%)	-
	Meibomian inspissation/chalazion/Hordeolum	2 (1.6%)	5 (3.5%

Part of eye	Ocular symptom/finding*	Number of patients ((reports))	
		Latanoprost	Timolol
Co junctiva	Redness/injection	7 (5%)	3 (2.1%)
	Punctate Epithelial erosions	14 (12%)	23 (16%)
	Subconjunctival hemorrhage	4 (3%)	2 (1.4%)
	Mild film over the eye/watery boggy	2 (1.6%)	1 (.7%)
	Chemosis	1 (.8%)	1 (.7%)
	Oedema	-	1 (.7%)
	Concretion	-	2 (1.4%)
	Pinguecula	1 (.8%)	-
	Follicles	1 (.8%)	1 (.7%)
	Pterygium	-	1 (.7%)
	Conjunctivitis	-	4 (2.8%)
is	Darker color	4 (3%)	-
Cornea	Oedema	-	1 (.7%)
	Whitish infiltrate/epithelial plaque	-	2 (1.4%)
	Abrasion	-	
	Increased tear break up time	1 (.8%)	-
	Endothelial pigments	4 (3%)	4 (2.8%)
	Krukenberg spindle	1 (.8%)	1 (.7%)
	Gutattae	1 (.8%)	-

* Adverse events, punctate epithelial erosions, and symptoms/findings reported at baseline, before treatment, are not included.

Comparison of non-ocular adverse events between latanoprost and timolol

Site	Description	No. of: Patients (reports)	
		Latanoprost	Timolol
Respiration	Bronchitis	2 (2)	1 (2)
	Upper respiratory infection	5 (5)	3 (3)
	Shortness of breath	--	2 (2)
	Cough	1	2
	Total	7 (7)	6 (7)
Cardiovascular	Palpitations	1 (1)	1 (1)
	Arrhythmia/Bradycardia	1	1
	Hypertension	-	1
	Chest Pain	1	-
Skin	Eczema/dermatitis/Rash	4	2 (5)
	Itching	2	--
	Total	6 (13)	2 (6)
Female reproduction	Cervicitis	1 (1)	--
	Intermenstrual bleeding	--	1 (1)
	Total	1 (1)	1 (1)
CNS	Memory loss	--	1 (2)
	Headache	--	1 (2)
	Dizziness/Weakness	--	2 (2)
	Anxiety	--	1 (1)
	Total	--	5 (7)
Urinary tract	Urinary tract infection	1 (1)	4 (4)
	Hematuria	1 (1)	--
	Total	2 (2)	4 (4)
Gastrointestinal	Stomach ulcer/pain	--	2 (4)
	Gall bladder attack	--	1 (1)
	Total	--	3 (5)

Continued.

Site	Description	No. of: Patients (reports)	
		Latanoprost	Timolol
Laboratory values	Anaemia	1 (1)	--
	Hypopotassemia	--	1 (1)
	Abnormal liver function values	--	1 (1)
	Hypertriglycerides	--	1 (1)
	Eosinophilia	--	1 (1)
	Total	1 (1)	4 (4)
Skeleto-muscle	Pain neck/shoulder	1 (2)	--
	Bunion surgery	1 (1)	--
	Total	2 (3)	--
Various	Nipples; red and swollen	--	1 (1)
	Tooth ache	--	2 (4)
	Ear disorders	--	2 (2)
	Accident	--	1 (1)
	Total	--	6 (8)

Reviewer's Comment: *This reviewer incorporated the total number of patients with ocular symptoms or findings irrespective whether reported as adverse events or not.*

Increase in iridial pigmentation.

Patient No.	Treatment	Visit*	Iris color according to:		Degree of pigmentation**	Type of pigmentation
			Pharmacia	Investigator		
115	Latanoprost	Month 4.5	Green-brown	Brown		
908	Latanoprost	Month 4.5	Green-brown	Brown		
1501	Latanoprost	Month 6	Yellow-brown	Brown		
1602	Latanoprost	Month 4.5	Yellow-brown	Brown		

* Visit when first sign/suspicion was observed on photos.

Safety Conclusions:

The most significant side-effect of latanoprost (which differentiate it from Timolol) during this six month study was an creased pigmentation of the iris in 4 patients

Apart from local symptoms from the eye , the other significant and drug related sign was punctate epithelial erosion in the cornea (which occurred in 12% of the patients). Latanoprost had no clear-cut effect on blood pressure or heart rate.

Study #2

Protocol	#9200PG005
Title:	A 6-month, randomized, double-masked comparison of latanoprost (PhXA41) with timolol in patients with open angle glaucoma or ocular hypertension. A multicenter study in the Great Britain.
Objectives:	The primary objective was to demonstrate that the IOP-reducing effect of latanoprost was comparable to that of timolol at the end of 6 months of treatment. The extreme limit for this comparison was defined as a difference in IOP-reduction between the two treatments not exceeding 1.5 mmHg in favor of timolol. The secondary objectives were to describe the IOP-reduction throughout the study period, and to follow the safety variables in the two treatment groups. Study design: Same as study #9200PG004
Study population:	Two hundred and fifty to three hundred patients were planned to be included, 125-150 patients per treatment group.
Inclusion criteria	Same as study #9200PG004
Exclusion Criteria:	Same as study #9200PG004
Efficacy assessments	Same as study #9200PG004
Safety assessments	Same as study #9200PG004
Laboratory safety assessments	Same as study #9200PG004

INVESTIGATORS

Study center 1: Addenbrooke's Hospital	Cambridge		
Principal Investigator:	Mr. Peter Watson		
Treatment initiated:	Dec. 11, 1992	Treatment completed:	Nov. 5, 1993
Study center 2: University Hospital of Wales	Cardiff		
Principal Investigator: Co-Investigator:	Mrs. Lyn Beck Dr. Michael Blackmore		
Treatment initiated:	Feb. 24, 1993	Treatment completed:	Nov. 23, 1993
Study center 3: King's College Hospital	London		
Principal Investigator: Co-Investigator:	Mr. Roger Coakes Dr. Patricia Reynolds		
Treatment initiated:	Jan. 6, 1993	Treatment completed:	Dec. 1, 1993
Study center 4: Royal Free Hospital	London		
Principal Investigator: Co-Investigator:	Miss Clare Davey Mr. Julian Hickman-Casey		
Treatment initiated:	Feb. 5, 1993	Treatment completed:	Dec. 3, 1993
Study center 5: Southampton Eye Hospital	Southampton		
Principal Investigator: Co-Investigator:	Prof. Andrew Elkington Mr. Andrew Luff		
Treatment initiated:	Feb. 24, 1993	Treatment completed:	Dec. 10, 1993
Study center 6: Aberdeen Royal Infirmary	Aberdeen		
Principal Investigator: Co-Investigator:	Mr. Frank Green Dr. Fernando Valenzuela		
Treatment initiated:	Mar. 23, 1993	Treatment completed:	Dec. 14, 1993
Study center 7: Royal Hallamshire Hospital	Sheffield		
Principal Investigator: Co-Investigator:	Mr. Simon Longstaff Dr. Zana Currie		
Treatment initiated:	Feb. 23, 1993	Treatment completed:	Dec. 7, 1993

Study center 9:
Manchester Royal Eye Hospital — Manchester

Principal Investigator: Mr. Barry Mills
Co-Investigator: Mr. Anupam Chatterjee

Treatment initiated: Jan. 20, 1993 — Treatment completed: Dec. 1, 1993

Study center 10:
The Royal Alexandra Hospital — Paisley

Principal Investigator: Dr. Stephen Murray

Treatment initiated: Feb. 3, 1993 — Treatment completed: Nov. 24, 1993

Study center 11:
Moorfields Eye Hospital — London

Principal Investigator: Dr. Suryanarayanan Nagasubramanian

Treatment initiated: Mar. 16, 1993 — Treatment completed: Dec. 7, 1993

Study center 12:
Bristol Eye Hospital — Bristol

Principal Investigator: Mr. Michael Potts
Co-Investigator: Dr. Ian Spencer

eatment initiated: Jan. 12, 1993 — Treatment completed: Dec. 14, 1993

Study center 13:
Ninewells Hospital and Medical School — Dundee

Principal Investigator: Dr. Stuart Roxburgh
Co-Investigators: Dr. Roshini Sanders
Dr. Michael Bailey

Treatment initiated: Jan. 8, 1993 — Treatment completed: Dec. 3, 1993

Study center 14:
Queens Medical Center — Nottingham

Principal Investigator: Mr. Stephen Vernon
Co-Investigator: Mrs. Myra Sloper

Treatment initiated: Mar. 4, 1993 — Treatment completed: Dec. 10, 1993

Study center 15:
Royal Liverpool University Hospital — Liverpool

Principal Investigator: Mr. Peter Wishart

Treatment initiated: Mar. 2, 1993 — Treatment completed: Dec. 7, 1993

RESULTS:

Study population
Number of patients

A total of 294 patients were included in the study. All 294 patients were included in the intention to treat analysis. The number of patients who completed the last visit according to the protocol was 262, (133 in the latanoprost group and 129 in the timolol group). The number of evaluable patients in the per-protocol analysis changed per visit according to the following:

Treatment	Visit					
	1 (Day 0)	2 (2 weeks)	3 (6 weeks)	4 (12 weeks)	5 (18 weeks)	6 (26 weeks)
Latanoprost	149	127	128	130	130	133
Timolol	145	119	120	125	128	129

Study centers, and number of patients per treatment group and study center. Number of patients included in the per-protocol analysis indicated in parenthesis.

Study center	Latanoprost	Timolol	All
Cambridge	13 (11)	14 (12)	27 (23)
Cardiff	12 (12)	10 (8)	22 (20)
King's College	5 (3)	4 (3)	9 (6)
Royal Free*	9 (7)	7 (6)	16 (13)
Southampton	9 (8)	9 (7)	18 (15)
Aberdeen	9 (9)	9 (9)	18 (18)
Sheffield	15 (10)	15 (14)	30 (24)
Manchester	15 (14)	15 (12)	30 (26)
Paisley	5 (5)	4 (4)	9 (9)
Moorfields*	15 (15)	15 (14)	30 (29)
Bristol	12 (12)	12 (12)	24 (24)
Dundee	10 (10)	11 (11)	21 (21)
Nottingham	10 (9)	10 (8)	20 (17)
Liverpool	10 (8)	10 (9)	20 (17)
Total	149 (133)	145 (129)	294 (262)

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Patient characteristics (demography)

Variable		Latanoprost	Timolol	All
Number of patients		149	145	294
Age (mean ±SD) (min-max)		64.7±9.5 (41-85)	65.3±10.5 (39-88)	65.0±10.0 (39-88)
Sex	Males	98	93	191
	Females	51	52	103
Ethnic origin	Caucasians	143	142	285
	Blacks	6	3	9
Family history of glaucoma/ocular hypertension		39	47	86

Distribution of patients between treatment groups according to diagnosis.

Ocular diagnosis	Latanoprost	Timolol	All
Primary open angle glaucoma	59	62	121
Exfoliation glaucoma	3	2	5
Pigmentary glaucoma	2	1	3
Ocular hypertension	80	68	148
Primary open angle glaucoma/Exfoliation glaucoma*)	0	1	1
Primary open angle glaucoma/Ocular hypertension*)	5	11	16

* Different diagnoses in study eyes.

Eye (iris) color of the patients as judged by investigators during examination and by Pharmacia staff from color photographs of the eyes.

Eye color (Evaluated by investigators)	Latanoprost	Timolol	All	% of total population
Blue/Green/Grey	83	96	179	61
Hazel	36	30	66	22
Brown	30	19	49	17
Eye color (Evaluated by Pharmacia staff)				
Blue/Grey	15	13	28	9
Blue/grey with slightly brown	39	41	80	27
Blue/grey and brown	36	49	85	29
Green	0	0	0	0
Green with slightly brown	0	2	2	1
Green-brown	43	30	73	25
Brown (Caucasian)	8	4	12	4
Yellow-brown (Caucasian)	2	2	4	2
Brown (Black)	6	3	9	3
Brown (Asian)	0	0	0	0

Clinical efficacy variables

The primary objective of the study was to compare the IOP-reducing effect of latanoprost with that of timolol at the end of six month treatment. The secondary objective was to describe the IOP-reduction throughout the treatment period.

Reviewer's Comments: *This reviewer will examined primarily the IOP-reduction throughout the treatment period.*

The IOP values throughout the study period of both treatment groups and differences in mean IOP-reduction from baseline per visit and examination and p-values calculated by Ancova between the latanoprost group and the timolol group the are given the tables below.

IOP* (mmHg) at all scheduled examinations.

Treatment group		Visit and time									
		1			2	3	4	5	6		
		9:00	13:00	17:00	9:00	9:00	9:00	9:00	9:00	13:00	17:00
Latanoprost	MEAN	26.2	24.9	24.6	17.4	17.2	17.1	16.7	17.1	16.5	16.5
	STD	3.6	3.8	3.8	2.9	3.2	2.9	2.5	2.8	2.8	2.7
	N	149	149	149	127	128	130	130	137	133	133
	MIN	16.7	14.8	14.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
	MAX	39.5	37.0	39.3	23.5	32.0	27.3	23.0	28.3	25.5	25.5
Timolol	MEAN	26.5	24.9	24.8	17.8	17.5	17.8	17.7	17.7	16.6	17.1
	STD	3.9	3.9	4.0	2.6	2.7	2.8	2.8	2.8	2.8	3.0
	N	145	145	145	119	120	125	128	131	129	129
	MIN	18.3	13.8	15.0	12.0	11.3	10.8	12.0	10.0	10.0	12.0
	MAX	40.2	37.0	36.0	25.0	27.5	27.2	26.0	26.2	26.2	27.5

* If both eyes are study eyes, then the IOP is represented by the mean of both eyes.

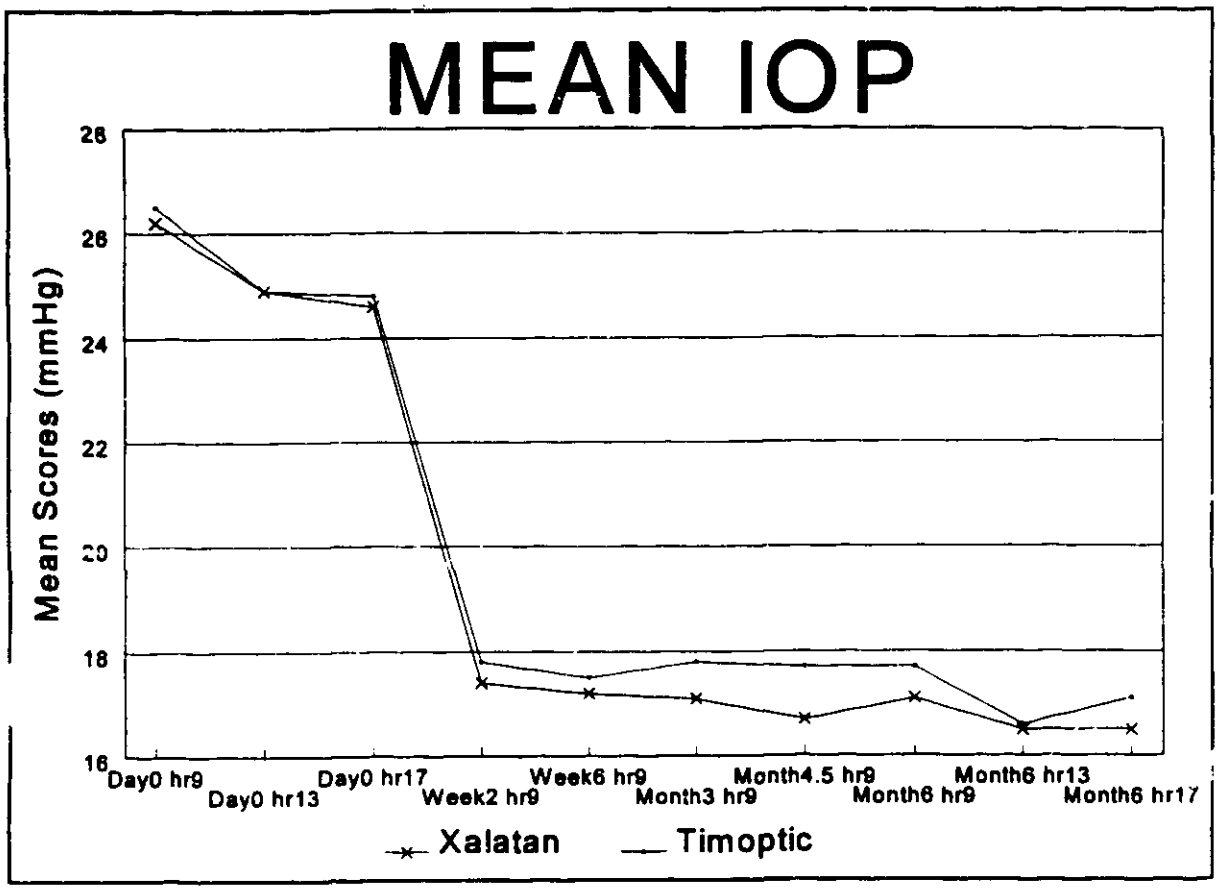
Differences in mean IOP reduction (mmHg) from baseline between the latanoprost group and the timolol group and Ancova p-values.

Week	Visit	Time	IOP-differences* Latanoprost compared to Timolol	Ancova p-values
2	2	9:00	0.0	p=0.36
6	3	9:00	0.0	p=0.57
12	4	9:00	-0.4	p=0.04
18	5	9:00	-0.9	p<0.001
26	6	9:00	-0.2	p=0.12
26	6	13:00	-0.1	p=0.63
26	6	17:00	-0.2	p=0.14

* **A negative value indicates that the mean IOP reduction larger with latanoprost than with timolol.**

Sponsor's Report: At visit 4 and 5 (3 and 4.5 months of treatment) there was a significantly better pressure reduction with latanoprost than with timolol (p=0.04 and p<0.001, respectively; Ancova).

Reviewer's Comments: These comparisons are not adequate since the timepoints selected by the sponsor are not matched with the corresponding peaks and troughs of the compared drugs. Latanaprost pharmacologic action peaks between 8 and 12 hour after administration while Timolol action peaks between 1- 2 hrs after administration.



The IOP-profiles throughout the study period of both treatment groups are depicted in the fig above.

Reviewer's Comments: *At the timepoints measured there are no clinical significant differences between the two drug treatments. The peaks and troughs of the tested drug (Xalatan) are below the troughs of Timolol. At month 6 hr 13 we see that 2 hr after the peak of Timolol the IOP reduction is more than the month 6 hr 9 measurement of Latanaprost which is 1 hr after its peak.*

SUBGROUP ANALYSES:

IOP-response at individual study centers (per-protocol)

Diurnal IOP** (mmHg) at baseline and at visit 6 (six months of treatment) and change from baseline at visit 6 of the latanoprost group. (Mean±SD; number of patients in parenthesis).

Study center	Baseline	6 months	Change
Cambridge	26.2±2.7 (13)	17.6±1.4 (11)	-8.8±3.0 (11)
Cardiff	26.1±1.7 (12)	17.0±1.8 (12)	-9.2±1.5 (12)
Kings College*	22.6±1.8 (5)	17.1±2.1 (3)	-5.4±1.4 (3)
Royal Free*	25.3±3.4 (9)	14.5±2.2 (7)	-10.0±1.5 (7)
Southampton	21.7±2.2 (9)	14.5±2.4 (8)	-7.6±2.0 (8)
Aberdeen	27.1±2.8 (9)	16.9±1.5 (9)	-10.1±2.5 (9)
Sheffield	25.5±3.0 (15)	15.9±2.0 (10)	-8.3±2.8 (10)
Manchester	26.1±2.9 (15)	18.2±2.1 (14)	-8.3±2.1 (14)
Paisley	27.6±3.7 (5)	19.9±3.1 (5)	-7.7±1.2 (5)
Moorfields*	25.3±2.1 (15)	16.0±2.9 (15)	-9.3±3.0 (15)
Bristol	25.1±4.8 (12)	17.5±2.7 (12)	-7.6±3.0 (12)
Dundee	27.4±4.1 (10)	17.6±2.3 (10)	-9.8±3.7 (10)
Nottingham	24.4±2.9 (10)	16.4±2.3 (9)	-7.6±2.5 (9)
Liverpool	20.9±2.9 (10)	15.0±3.5 (8)	-6.7±4.0 (8)

* Hospital situated in London.
** Mean of measurements at 9:00 h., 13:00 h., 17:00 h.

Diurnal IOP** (mmHg) at baseline and at visit 6 (six months of treatment) and change from baseline at visit 6 of the timolol group (Mean±SD; number of patients in parenthesis).

Study center	Baseline	6 months	Change
Cambridge	26.3±2.6 (14)	16.6±2.2 (12)	-9.8±2.9 (12)
Cardiff	24.4±2.0 (10)	16.6±1.0 (8)	-8.1±2.5 (8)
King's College*	23.7±7.2 (4)	19.2±5.8 (3)	-5.1±3.8 (3)
Royal Free*	22.7±1.5 (7)	14.8±1.8 (6)	-7.6±2.3 (6)
Southampton	23.3±5.5 (9)	17.9±3.7 (7)	-5.3±3.6 (7)
Aberdeen	25.8±1.9 (9)	16.7±1.9 (9)	-9.1±2.4 (9)
Sheffield	26.8±4.0 (15)	17.7±1.7 (14)	-9.3±3.7 (14)
Manchester	27.2±3.5 (15)	18.8±2.8 (12)	-8.1±3.5 (12)
Paisley	26.0±3.9 (4)	17.5±3.0 (4)	-8.5±5.1 (4)
Moorfields*	26.0±2.1 (15)	16.8±3.6 (14)	-9.4±3.6 (14)
Bristol	24.6±3.3 (12)	17.1±2.4 (12)	-7.5±3.0 (12)
Dundee	28.2±4.4 (11)	17.2±1.7 (11)	-11.0±3.7 (11)
Nottingham	24.3±2.2 (10)	16.9±3.2 (8)	-7.5±2.7 (8)
Liverpool	22.5±3.0 (10)	16.1±0.8 (9)	-5.9±3.0 (9)

* Hospital situated in London
** Mean of measurements at 9:00 h., 13:00 h., 17:00 h.

Reviewer's Comments: *There was a similar response with respect to pressure reduction between latanoprost and timolol in all study centers.*

IOP-response in males and females (per-protocol)

Diurnal IOP* (mmHg) at baseline and at visit 6 (six months of treatment) and change from baseline at visit 6 in males and females. (Mean±SD; number of patients in parenthesis).

Sex	Visit	Latanoprost	Timolol
Males	Baseline	25.7±3.7 (98)	25.7±3.7 (93)
	6 months	17.1±2.8 (87)	16.8±2.5 (85)
	Change	-8.6±2.9 (87)	-9.0±3.5 (85)
Females	Baseline	24.2±2.5 (51)	24.8±3.4 (52)
	6 months	16.1±2.1 (46)	17.6±2.7 (44)
	Change	-8.3±2.5 (46)	-7.1±3.0 (44)

Sponsor's Report: There was a statistically significant difference in response between females and males in the timolol group, the males exhibiting a better IOP-reduction (p=0.008; Ancova). In the latanoprost group there was no statistical significance in IOP-reduction between males and females (p=0.30; Ancova).

Reviewer's Comments: The difference between males and females in the Timolol group is not clinically significant was not seen in the US study.

IOP-response in different age groups (per-protocol)

Diurnal IOP* (mmHg) at baseline and at visit 6 (six months of treatment) and change from baseline at visit 6 in different age groups. (Mean±SD; number of patients in parenthesis).

Age group	Visit	Latanoprost	Timolol
<50 years	Baseline	25.0±3.4 (15)	23.0±2.5 (13)
	6 months	16.7±2.3 (13)	16.7±1.3 (12)
	Change	-8.6±2.5 (13)	-6.1±2.6 (12)
50-<60	Baseline	24.9±3.4 (27)	25.7±4.1 (32)
	6 months	16.5±2.2 (25)	17.5±2.7 (27)
	Change	-8.7±3.0 (25)	-8.7±3.7 (27)
60-<70	Baseline	25.3±3.2 (58)	25.0±3.7 (48)
	6 months	16.9±2.9 (51)	17.1±3.1 (45)
	Change	-8.3±2.7 (51)	-8.0±3.6 (45)
70-<80	Baseline	25.4±3.7 (45)	26.2±3.5 (42)
	6 months	16.6±2.5 (41)	17.1±2.1 (37)
	Change	-8.6±3.0 (41)	-9.0±3.3 (37)
80 years	Baseline	25.2±4.5 (4)	26.0±2.1 (10)
	6 months	17.3±0.7 (3)	16.5±2.9 (8)
	Change	-10.0±2.1 (3)	-10.1±2.5 (8)

* Mean of measurements at 9:00 h., 13:00 h., 17:00 h.

Reviewer's Comments: *There were no clinically significant differences in response to latanoprost or timolol when comparing patients in age groups when the baseline values are considered.*

IOP-response in different subgroups of disease (per-protocol)

Diurnal IOP* (mmHg) at baseline and at visit 6 (six months of treatment) and change from baseline at visit 6 in patients with different ocular disease. (Mean±SD; number of patients in parenthesis).

Diagnosis	Visit	Latanoprost	Timolol
Primary open angle glaucoma	Baseline	25.7±3.5 (59)	26.0±4.0 (62)
	6 months	16.6±3.0 (53)	16.8±3.0 (55)
	Change	-9.1±2.4 (53)	-9.4±3.8 (55)
Exfoliation glaucoma	Baseline	30.7±6.0 (3)	27.8±0.8 (2)
	6 months	16.4±1.5 (2)	17.1±1.8 (2)
	Change	-13.0±6.4 (2)	-10.7±0.9 (2)
Pigmentary glaucoma	Baseline	26.5±2.2 (2)	20.9 (1)
	6 months	--	13.8 (1)
	Change	--	-7.1 (1)
Ocular hypertension	Baseline	24.6±3.1 (80)	24.6±3.2 (68)
	6 months	16.7±2.3 (74)	17.5±2.1 (61)
	Change	-8.1±2.6 (74)	-7.1±2.8 (61)
Primary open angle glaucoma/Exfoliation glaucoma**	Baseline	--	28.8 (1)
	6 months	--	19.3 (1)
	Change	--	-9.5 (1)
Primary open angle glaucoma/Ocular hypertension**	Baseline	24.5±2.9 (5)	26.2±3.4 (11)
	6 months	17.3±3.9 (4)	16.0±2.2 (9)
	Change	-5.9±4.8 (4)	-10.5±2.9 (9)

* Mean of measurements at 9:00 h., 13:00 h., 17:00 h.
If both eyes are study eyes, then the IOP is represented by the mean of both eyes

Sponsor's Report: "Patients with primary open angle glaucoma of the timolol group responded significantly better (p=0.006; Ancova) than the ocular hypertensive patients in the same group. No significant difference was seen in the latanoprost group (p=0.13; Ancova)."

Reviewer's Comments: *The baselines of the two groups were also different and may explain this finding. This was not seen in the US study.*

IOP-response in patients with variable duration of ocular disease (per-protocol)
No statistically significant difference in the response could be detected in the latanoprost group or the timolol group.

IOP-response in patients previously treated with glaucoma medication (per-protocol)
The IOP-response was comparable to that in the whole population out of which most had not received glaucoma medication prior to the study.

IOP-response in patients with different eye color (per-protocol)
There was a statistically significant difference in the reduction of IOP between patients with different eye colors in the latanoprost group (p=0.02; Ancova). Patients with hazel irides had slightly but statistically significantly (p=0.006; Ancova) better IOP-reduction than patients with blue/green/grey irides. No difference between different eye colors was seen in the timolol group. The difference in the latanaprost was not clinically significant.

EFFICACY CONCLUSIONS:

At the timepoints measured Latanoprost administered once daily in the evening reduced IOP as well as timolol administered twice daily. There were no signs of long-term drift with latanoprost or timolol when comparing the IOP-profiles throughout the study period. There were no clinically significant differences in IOP reduction in any subpopulation in either treatment group.

SAFETY

Systemic (non-ocular) safety variables:

Blood pressure

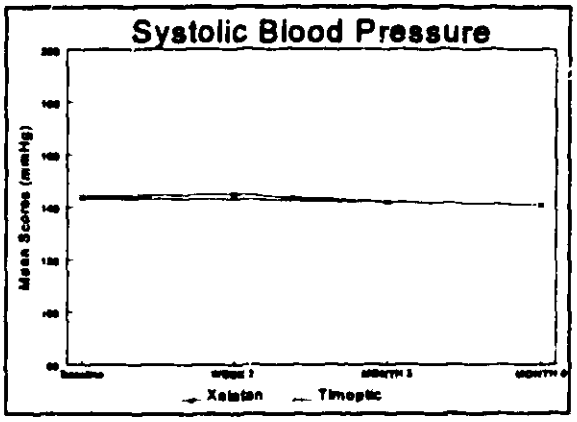
The systolic and diastolic blood pressures were measured in the morning at baseline, and at two weeks, three months and six months of treatment. There was a slight decrease both in systolic and diastolic blood pressure in both groups, a phenomenon that reached statistical significance at 6 months. The differences in reduction of blood pressures between the treatment groups were not statistically significant.

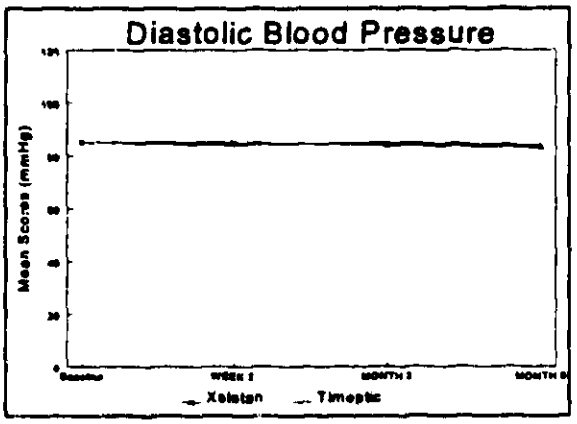
Reviewer's Comments: *The effect on arterial blood is clinically insignificant. See the following graphs.*

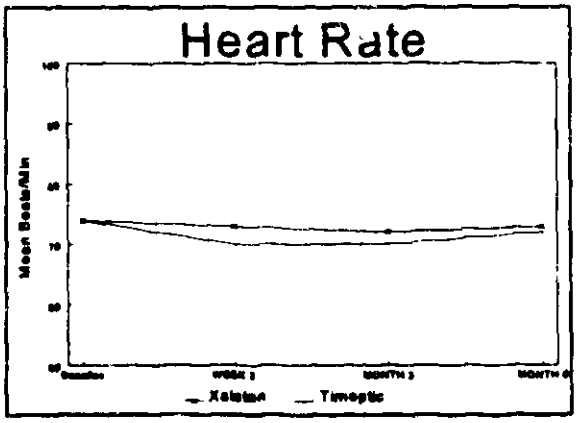
Heart rate

The heart rate was determined at the same occasions as the blood pressure. There was a tendency towards a slight reduction in heart rate in both treatment groups. The reduction in heart rate was most marked in the timolol group. At 6 month treatment the reduction from baseline was statistically significant in the timolol group ($p=0.02$; paired t-test), albeit being less than 5 % of the mean heart rate value at baseline. The reduction in heart rate at six months was not statistically significant in the latanoprost group. The difference in reduction of heart rate between the treatment groups was not statistically significant.

Reviewer's Comments: *The above findings in the Timolol group are expected. The overall effect on heart rate is clinically insignificant. See the following graphs.*

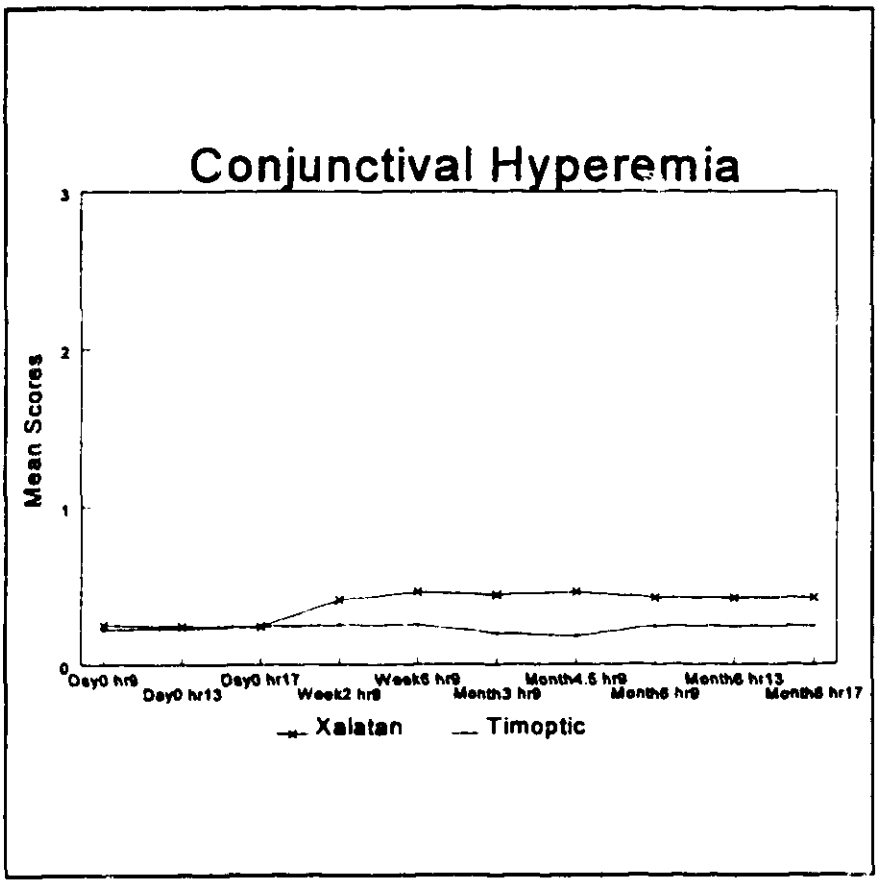

Systolic Blood Pressure
Mean Scores (mmHg)
Xalatan
Timoptic


Diastolic Blood Pressure
Mean Scores (mmHg)
Xalatan
Timoptic


Heart Rate
Mean Beats/Min
Xalatan
Timoptic

Ocular safety variables

Conjunctival hyperaemia



Reviewer's Comments: *Timolol caused less hyperaemia than latanoprost, but it should be emphasized that the mean increase in hyperemia was less than the one unit considered clinically significant.*

Aqueous flare

Slight aqueous flare was detected only in one patient in the latanoprost group. No flare was detected in the timolol group.

Cells in the aqueous humor

A few cells in the aqueous humor were detected in two patients treated with latanoprost and in one patient treated with timolol.

Visual acuity and refractive error

There was no clinically significant change in visual acuity or refractive error (calculated as spherical equivalents) during the treatment period in either group.

Visual fields

The visual fields were determined twice before the start of the treatment and once at the end of the treatment. In the timolol group one patient (#309) was reported having a deterioration in the visual field of the left eye at the end of the study compared to baseline (see adverse events). No clear-cut changes were observed in any of the other patients.

Optic nerve head

The horizontal and vertical cup-disc ratio was estimated at baseline and the end of the treatment period. No clinically significant change was observed in any of the patients.

General examination of the eye

The lids, iris, conjunctiva, cornea and anterior chamber were examined on each visit day. Before entering the study and at the six month visit the lens, vitreous and the retina were examined in addition to the examinations mentioned above. Except for findings included in the adverse events and/or ocular signs and symptoms, no pathological findings compared to baseline were made in these tissues.

LABORATORY SAFETY VARIABLES

There were no apparent differences between the treatment groups.

ADVERSE EVENTS, SIGNS AND SYMPTOMS

Reviewer's Comment: *This reviewer will incorporate the total number of patients with ocular symptoms or findings irrespective whether reported as adverse events or not.*

Comparison of number of patients with adverse events (not including serious adverse events) between the latanoprost group and the timolol group. Total number of adverse events indicated in parenthesis.

Adverse event	Latanoprost	Timolol
OCULAR		
Punctate epithelial erosions	19 (13%)	10 (7%)
Hyperaemia/redness	25 (17%)	9 (6%)
Foreign body sensation	34 (22%)	11 (8%)
Blurred vision	16 (11%)	17 (12%)
Stinging/burning/irritation	36 (24%)	27 (19%)
Eye lid inflammation/discomfort	29 (19%)	27 (19%)
Conjunctivitis	3 (2%)	1 (.7%)
Discharge	5 (3.3%)	2 (1.4%)
Eye lid oedema/erythema	3 (2%)	3 (2%)
Itching	15 (10%)	11 (8%)
Eye pain	16 (11%)	10 (7%)
Tearing	9 (6%)	7 (5%)
Increased iris pigmentation	**15 (10%)**	**0**
Dry eyes	4(2.7%)	4 (2.7%)
Allergic conjunctivitis	0	2 (1.4%)
The Following ADR occurred in less than 2 patients .		
Corneal limbal infiltrates	**1 (1)**	**0**
Corneal microcysts	1 (1)	0
Photophobia	1 (1)	0
Visual disturbance	1 (1)	0
Vitreous detachment	1 (1)	0
Keratic precipitates	0	1 (1)
Cells in anterior chamber	0	1 (1)
Photopsia	0	1 (1)
Retinal neovascularization	0	1 (1)
Visual field deterioration	0	1 (1)
Periorbital oedema/irritation	0	1 (1)

Adverse event	Latanoprost	Timolol
NON-OCULAR		
Influenza/Upper resp. infection/cold	35 (23%)	26 (18%)
Headache	9 (6%)	14 (10%)
Breathing problems	2 (1.3%)	6 (4%)
Pain (muscle, joint, back)	6 (4%)	11 (8%)
Gastric flu/diarrhoea	2 (1.3%)	2 (1.4%)
Chest infection/bronchitis	2 (1.3%)	3 (2%)
Cough	1 (.7%)	2 (1.4%)
Ear infection/discomfort	3 (2%)	2 (1.4%)
Lethargy/lassitude	1 (1)	1 (.7%)
Abdominal discomfort/pain	0	2 (1.4%)
Low blood pressure	0	2 (1.4%)
Oedema (lip, finger)	0	2 (1.4%)
The following ADR occurred in less than 2 patients.		
Angina pectoris	1 (1)	0
Couplet beats on pulse	1 (1)	0
Blackouts	1 (1)	0
Insomnia	1 (1)	0
Impotence	1 (1)	0
Dyspepsia	1 (1)	0
Inguinal hernia	1 (1)	0
Urinary tract infection	1 (1)	0
Wheezing	0	1 (1)
Palpitations	0	1 (1)
Atrial fibrillation	0	1 (1)
Claudication	0	1 (1)
Transient loss of vision, inferior hemifield	0	1 (1)
Vertigo	0	1 (1)
Cramp in legs	0	1 (1)
Shaking/Sweating	0	1 (1)
Acute jaundice	0	1 (1)
Menopause symptoms	0	1 (1)
Fracture of radius	0	1 (1)

Serious adverse events

Treatment group	Patient No.	Description of Adverse Event	Severity	Action taken	Patient outcome
Latanoprost	104				
	701				
	908				
	1210				
Timolol	504				
	1304				
	1304				
	1209				
	1520				

Sponsor's Report: "Although a causal relationship to the study drugs can not be excluded it seems unlikely that the adverse events would have been caused by latanoprost or timolol."

Reviewer's Comment: *Agree.*

Increased pigmentation of the iris:

Increased pigmentation of the iris was diagnosed or suspected in 15 patients out of 149 (10.1 %) in the latanoprost group. There were no cases in the timolol group with suspected or diagnosed increased pigmentation of the iris.

It is interesting that all patients exhibiting increased pigmentation had green-brown or blue/grey-brown irides (as assessed by Pharmacia staff). No patients with other color of the iris exhibited increased pigmentation. The increase in pigmentation became manifest at visits 4-6 (3-6 months of treatment). There was no consistent pattern of the increase in pigmentation. In some individuals the pigmentation spread concentrically from a more pigmented ring around the pupil while in others greenish patches peripherally became pigmented and turned brown. The patients exhibiting manifest increased pigmentation of the iris were not allowed to continue in the open-label study but entered a follow-up program to investigate whether the increase in pigmentation is reversible or not.

Patients exhibiting increased iridial pigmentation as judged from photographs. The visit at which the first sign or suspicion of increased pigmentation occurred is also indicated. Eye color in parenthesis as assessed by investigator.

Patient No.	Treatment group	Visit	Eye color
117	Latanoprost	4	
118	Latanoprost	5	)
120	Latanoprost	5	
212	Latanoprost	6	
213	Latanoprost	4	
219	Latanoprost	4	
501	Latanoprost	6	
510	Latanoprost	4	
610	Latanoprost	5	
611	Latanoprost	5	
725	Latanoprost	4	
1207	Latanoprost	6	
1406	Latanoprost	4	
1503	Latanoprost	6	
1519	Latanoprost	6	
1202	Timolol	6	)
1208	Timolol	6	

Safety conclusions

Both latanoprost and timolol were generally well tolerated in the eye and systemically. The most significant side-effects were increased pigmentation of the iris in patients with green-brown or blue-brown irides. Punctate epithelial erosions of the cornea, conjunctival hyperaemia as well as local symptoms (burning, stinging, foreign body sensation, itching) in the eye were the most common ocular adverse events.

Study #3
Protocol # 9200PG006

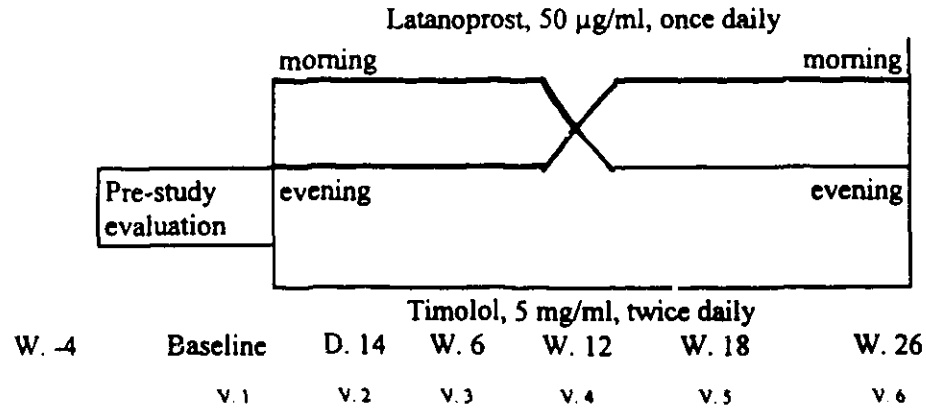
Title: A 6-month, randomized, double-masked comparison of latanoprost (PhXA41) with timolol in patients with open angle glaucoma or ocular hypertension. A multicenter study in Scandinavia.

Objectives: The primary objective was to demonstrate that the IOP-reducing effect of latanoprost was comparable to that of timolol at the end of 6 months of treatment. The extreme limit for this comparison was defined as a difference in IOP-reduction between the two treatments not exceeding 1.5 mmHg in favor of timolol.

To demonstrate that the IOP-reducing effect of latanoprost administered in the morning was equivalent to the effect of latanoprost administered in the evening.

Study Design:

The study was designed as a randomized, three-group double-masked comparison of latanoprost and timolol over six months. Two groups received latanoprost once daily and one group received timolol twice daily. The groups that received latanoprost once daily shifted between morning and evening administration half-way through the study after three months: one group starting with morning administration (latanoprost group 1), the other group starting with evening administration (latanoprost group 2).
To obtain complete masking of the treatments all patients received one morning and one evening bottle for a treatment period of one month: Timolol patients received two timolol bottles and latanoprost patients one latanoprost - and one vehicle bottle.



D = Day, W= Week, V = Visit

Table of investigational events.

Examination	Pre-study		Visit 1			Visit 2	Visit 3	Visit 4			Visit 5	Visit 6		
	-4 w		Day 0			Day 14 ±4 days	W 6 ±1 week	W 12 ±1 week			W 18 ±1 week	W 26 ±1 week		
			8	12	16	8	8	8	12	16	8	8	12	16
Medical and ocular history	X													
Gonioscopy[1]	X													
Visual fields[2]	X	X											X	
Symptomatology	X		X		X	X	X	X		X	X	X		X
Visual acuity	X		X			X	X	X			X	X		
Refraction[3]			X			(X)	(X)	X			(X)	X		
Slitlamp examination[4]	X		X	X	X	X	X	X	X	X	X	X	X	X
Conjunctival hyperaemia	X		X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmoscopy	X													X
IOP	X		X	X	X	X	X	X	X	X	X	X	X	X
Iris photography	X							X			X	X		
External photography	X											X		
Blood Pressure	X		X			X		X				X		
Heart Rate	X		X			X		X				X		
Blood sample[5]	X												X	
Urine sample[5]	X												X	

1) If information about the phakoba angle was previously documented in the case notes gonioscopy was not required

2) Two pre-study visual fields had to be obtained At least one had to be performed during the month prior to the start of the study The other was acceptable if obtained within six months prior to the start of the study

3) Refraction was determined at visit 2, 3 and 5 only if visual acuity had changed from baseline

4) Aqueous flare was assessed only in the morning at each visit

5) Blood and urine samples could be taken within one week of visit 6

Study population

This study was designed to include at total of 260-300 patients, with 130-150 patients in the timolol group and 65-75 in each latanoprost group. As expressed in the protocol, the sample size was based on the assumption that the diurnal IOP-reducing effect of latanoprost could be considered as "at least equivalent to" that of timolol if the reduction in the combined latanoprost groups were no more than 1.5 mmHg less than that of timolol. This was to be assessed by constructing a two-sided 90 % confidence interval for difference in diurnal IOP-reduction (latanoprost minus timolol). If the upper limit of that confidence interval was less than 1.5 mmHg, then latanoprost would be at least equivalent to timolol. Assuming that the "true" diurnal IOP-reducing effect of timolol is no more than 0.5 mmHg better than that of latanoprost and that the standard deviation for the mean reduction in diurnal IOP is 3 mmHg, the upper limit of the 90 % confidence interval for the latanoprost-timolol difference will be less than 1.5 mmHg with a probability of 0.80 if 111 patients were enrolled in each treatment group. In order to allow for withdrawals, it was targeted that at least 130 patients were to be enrolled in the timolol group and at least 65 patients in each latanoprost group.

Number of patients recruited

By mistake, the randomization was not performed according to the procedure stated in the protocol. It was detected in January 1994, after the randomization code was broken, that the randomization had allocated patients in equal number to the three treatment groups (latanoprost group 1, latanoprost group 2 and the timolol group) instead of allocating half of the patients to the timolol group and one fourth of the patients to each of the two latanoprost groups. As a consequence of this fault in randomization, the power of the statistical testing of latanoprost morning versus evening administration was increased whereas the power of the comparison of latanoprost versus timolol was decreased, but was not less than anticipated in the protocol because more patients were valid for the per-protocol analysis than expected in the protocol.

Inclusion criteria:	Same as study #9200PG004
Exclusion Criteria:	Same as study #9200PG004
Efficacy assessments	Same as study #9200PG004
Safety assessments	Same as study #9200PG004
Laboratory safety assessments	Same as study #9200PG004

RESULTS:

Major protocol deviations.

Pat. No.	Treatment group	Specification of protocol deviation	Statistical analysis	
			Per protocol	Week 26 Intention to treat
		Unauthorized concomitant therapy		
	Latanoprost 2	Systemic b-adrenergic medication initiated between w. 18 and w. 26.	Exclude w. 26	X
	Latanoprost 2	Systemic b-adrenergic medication initiated 2 weeks before w. 18. Discontinued treatment with systemic -adrenergic medication two days after w. 18. Morning drop not administered w.12.	Exclude w. 12, noon, afternoon and w. 18	X
		Broken code		
	Latanoprost 1	Code broken 14 days after completion of the study due to nausea.	X	X
	Latanoprost 1	Code broken due to IOP not controlled. Withdrawn d. 14.	Exclude all visits after day 14	Give 0 as response
		Discontinuation of study medication		
	Latanoprost 2	Cornea erosion. Treatment temporarily discontinued.	Exclude w. 26	Give 0 as response
	Timolol	Skin rash in face. Treatment temporarily discontinued	Exclude day 14	X
	Latanoprost 1	Treatment temporarily discontinued. Did not instil morning drops after examination w. 12.	Exclude w. 6, w. 12 noon and afternoon	X
	Latanoprost 2	Did not instil morning drops after examination w. 12. Withdrawn w. 18 due to cancer mammae, metastatic spreading.	Exclude w. 12 noon and afternoon and w. 26	Give 0 as response
	Latanoprost 1	Did not instil morning drops after examination w. 12.	Exclude w. 12 noon and afternoon	X
	Latanoprost 1	Did not instil morning drops after examination w. 12 and w. 26.	Exclude w. 12 noon and afternoon, w. 26 noon and afternoon	X
	Latanoprost 2	Did not instil morning drops after examination w. 12 and w. 26.	Exclude w. 12 noon and afternoon, w. 26 noon and afternoon	X
	Timolol	Did not instil morning drops after examination w. 12	Exclude w. 12 noon and afternoon	X
	Timolol	Did not instil morning drops after examination w. 12	Exclude w. 12 noon and afternoon	X
	Latanoprost 1	Did not instil morning drops after examination w. 12	Exclude w. 12 noon and afternoon	X
	Latanoprost 1	Did not instil morning drops after examination w. 12.	Exclude w. 12 noon and afternoon	X
	Latanoprost 2	Did not instil morning drops after examination w. 12.	Exclude w. 12 noon and afternoon	X
	Latanoprost 2	Did not instil morning drops after examination w. 12. Withdrawn due to decrease in visual acuity w. 12.	Exclude w. 12 noon and afternoon, w. 18 and w. 26	Give 0 as response
		Administration from wrong bottle		
	Latanoprost 1	Instilled eye drops from the wrong bottle in the morning W. 12.	Exclude w. 12 noon and afternoon	X
	Timolol	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
	Timolol	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
	Latanoprost 2	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
	Latanoprost 1	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
	Latanoprost 2	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X

Timolol	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
Latanoprost 2	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
Latanoprost 1	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
Latanoprost 2	Instilled eye drops from the wrong bottle in the morning W. 12	Exclude w. 12 noon and afternoon	X
	Timing error		
Latanoprost 2	Completed study too early.	Exclude w. 26	X
Timolol	Completed study too early.	Exclude w. 26	X
	Visits not performed		
Latanoprost 2	W. 18 not performed.	Exclude w. 18	X
Latanoprost 2	Day 14 not performed	Exclude d. 14	X
	Withdrawals		
Latanoprost 1	Due to erosion, the patient was withdrawn after w.18 visit.	Exclude w.26.	Give 0 as response
Latanoprost 1	Due to iris pigmentation, the patient was withdrawn after w.18.	Exclude w.26.	Give 0 as response
Latanoprost 1	Due to IOP not controlled, the patient was withdrawn on day 14	Exclude all visits after d.14.	Give 0 as response
Latanoprost 1	Due to burning sensation in tongue, the patient was withdrawn shortly after w.12	Exclude all visits after w.12	Give 0 as response
Timolol	Due to information about iris pigmentation, the patient was withdrawn on w.18.	Exclude w.26.	X
Latanoprost 1	Due to information about iris pigmentation, the patient was withdrawn on w.26.	Exclude w.26.	X
Latanoprost 2	Due to information about iris pigmentation, the patient was withdrawn on w.26.	Exclude w.26.	X
Timolol	Due to information about iris pigmentation, the patient was withdrawn on w.26.	Exclude w.26.	X
Latanoprost 1	Due to embolus of ophthalmic artery, after w.12, the patient was withdrawn.	Exclude w.18 and w.26.	Give 0 as response
Latanoprost 2	Due to central retinal vein thrombosis after w.6 patient was withdrawn.	Exclude w.12, w.18 and w.26	Give 0 as response
Timolol	Due to headache the patient was withdrawn after w.6.	Exclude w.12, w.18, and w.26	Give 0 as response
Timolol	Due to IOP not controlled the patients was withdrawn on w.18	Exclude w.26	Give 0 as response
Latanoprost 2	Due to cancer mammae metastatic spreading, the patient was withdrawn after w.18	Exclude w.26.	Give 0 as response
Latanoprost 2	Due to decrease in visual acuity because of diabetes also involving CNS, the patient was withdrawn on w.12.	Exclude w.18 and w.26.	Give 0 as response

Study population

Number of patients

A total of 267 patients were included in the study. The distribution of the patients between the treatment groups is presented in Table 3. All 267 patients were included in the "intention to treat" analysis. Of the 267 patients, 248 completed the study according to the protocol. The number of evaluable patients in the per-protocol analysis decreased per visit according to the following:

Treatment	Visit					
	1 (Day 0)	2 (2 weeks)	3 (1.5 months)	4* (3 months)	5 (4.5 months)	6 (6 months)
Latanoprost 1	89	89	87	80	87	84
Latanoprost 2	94	93	94	85	88	85
Timolol	84	83	84	78	80	79

* All values at 3 month visit at Hellerup are missing (see 9.1 protocol deviations).

Patient characteristics.

Variable		Latanoprost 1	Latanoprost 2	Timolol	All
Number of patients		89	94	84	267
Age (mean ±SD) (min-max)		66.9±9.8 (40-84)	66.6±9.1 (44-85)	65.8±9.4 (42-84)	66.5±9.4 (40-85)
Sex	Males	39	43	34	116
	Females	50	51	50	151
Ethnic origin	Caucasians	89	93	84	266
	Indian	0	1	0	1
Family history of glaucoma/ocular hypertension		30	26	37	93

Slightly more females than males were included, but the male/female ratio was similar between the treatment groups. The age distribution between the groups was very even, resulting in mean ages of 66.9, 66.6 and 65.8 years for the three treatment groups. All patients, except for one of Indian origin, were Caucasians. Approximately 35 % of the patients reported a family history of glaucoma.

Patients withdrawn from treatment.

Patient No.	Visit	Treatment group	Reason
106	W. 6	Latanoprost 2	
116	W. 24	Latanoprost 1	
209	D. 14	Latanoprost 1	
311	W. 12	Latanoprost 2	
411	W. 24	Timolol	
412	W. 18	Timolol	
413	W. 23	Latanoprost 1	
414	W. 19	Latanoprost 2	
415	W. 19	Timolol	
515	W. 12	Latanoprost 1	
625	W. 6	Latanoprost 2	
702	W. 6	Timolol	
710	W. 18	Timolol	
1201	W. 18	Latanoprost 2	
1210	W. 12	Latanoprost 2	

Study centers, and number of patients per treatment group and study center. Number of patients analyzed per protocol in parenthesis.

Study center	Latanoprost 1	Latanoprost 2	Timolol	All
Gothenburg (S)	6 (5)	8 (7)	6 (6)	20 (18)
Huddinge (S)	9 (8)	9 (8)	9 (8)	27 (24)
Linköping (S)	11 (11)	10 (9)	10 (10)	31 (30)
Lund (S)	5 (4)	5 (4)	5 (3)	15 (11)
Malmö (S)	7 (6)	8 (8)	7 (7)	22 (21)
Umeå (S)	11 (11)	12 (11)	10 (10)	33 (32)
Uppsala (S)	7 (7)	7 (6)	6 (4)	20 (17)
Bergen (N)	7 (7)	7 (7)	7 (7)	21 (21)
Oslo (N)	7 (7)	8 (8)	6 (6)	21 (21)
Trondheim (N)	6 (6)	7 (7)	7 (7)	20 (20)
Hellerup (D)	4 (3)	4 (1)	2 (2)	10 (6)
Vejle (D)	1 (1)	2 (2)	2 (2)	5 (5)
Oulu (F)	8 (8)	7 (7)	7 (7)	22 (22)
Total	**89 (84)**	**94 (85)**	**84 (79)**	**267 (248)**

Distribution of patients between treatment groups according to diagnosis.

Disease	Latanoprost 1	Latanoprost 2	Timolol	All
Primary open angle glaucoma	27	31	33	91
Capsular glaucoma	15	14	14	43
Pigmentary glaucoma	0	1	0	1
Ocular hypertension	43	44	36	123
Different diagnosis in study eyes	4	4	1	9

Duration (months) of glaucoma/ocular hypertension in study eyes prior to study start (Mean±SD; min-max.).

Ocular diagnosis	Latanoprost 1	Latanoprost 2	Timolol	All
POAG	12.5±24.7 (0-120)	17.0±43.8 (0-230)	19.3±43.7 (0-170)	16.5±38.7 (0-230)
Capsular glaucoma	12.5±23.2 (0-72)	3.7±5.1 (0-14)	9.6±25.2 (0-96)	8.8±20.0 (0-96)
Pigmentary glaucoma	--	200.0[1)]	--	200.0
Ocular hypertension	30.3±47.0 (1-276)	41.9±61.8 (0-253)	24.4±32.7 (1-144)	32.7±49.7 (0-276)
Different diagnosis in LE and RE	2.5±1.9 (1-5)	74.5±29.6 (31-97)	24.0[1)]	36.9±40.6 (1-97)

1) One patient.

Eye (iris) color of the patients, as judged by the investigators during the examination and by Pharmacia staff from color photographs of the eyes.

Eye color (Evaluated by investigators)	**Latanoprost 1**	**Latanoprost 2**	**Timolol**	**All**	**% of total population**
Blue/green/grey	73	78	77	228	85.4
Hazel	8	6	4	18	6.7
Brown	8	10	3	21	7.9
Eye color (Evaluated by Pharmacia staff)					
Blue/grey	34	31	27	92	34.4
Blue/grey with slightly brown	25	33	37	95	35.6
Blue/grey with brown	11	11	12	34	12.7
Green	1	0	0	1	0.4
Green with slightly brown	2	0	0	2	0.7
Green with brown	14	12	8	34	12.7
Brown (Caucasians)	2	5	0	7	2.6
Yellow-Brown (Caucasians)	0	1	0	1	0.4
Brown (blacks)[1]	0	1	0	1	0.4
Brown (Asians)	0	0	0	0	0

1) Including Indian

The distribution of iris color according to this classification by the Pharmacia staff, is also presented in the table above. It should be noted that approximately 13 % of the patients exhibited green-brown irides and another 13 % exhibited blue-brown irides. The vast majority of patients, however, exhibited blue/grey or blue/grey irides with some diffuse brown pigmentation mostly in the pupillary zone.

Efficacy:

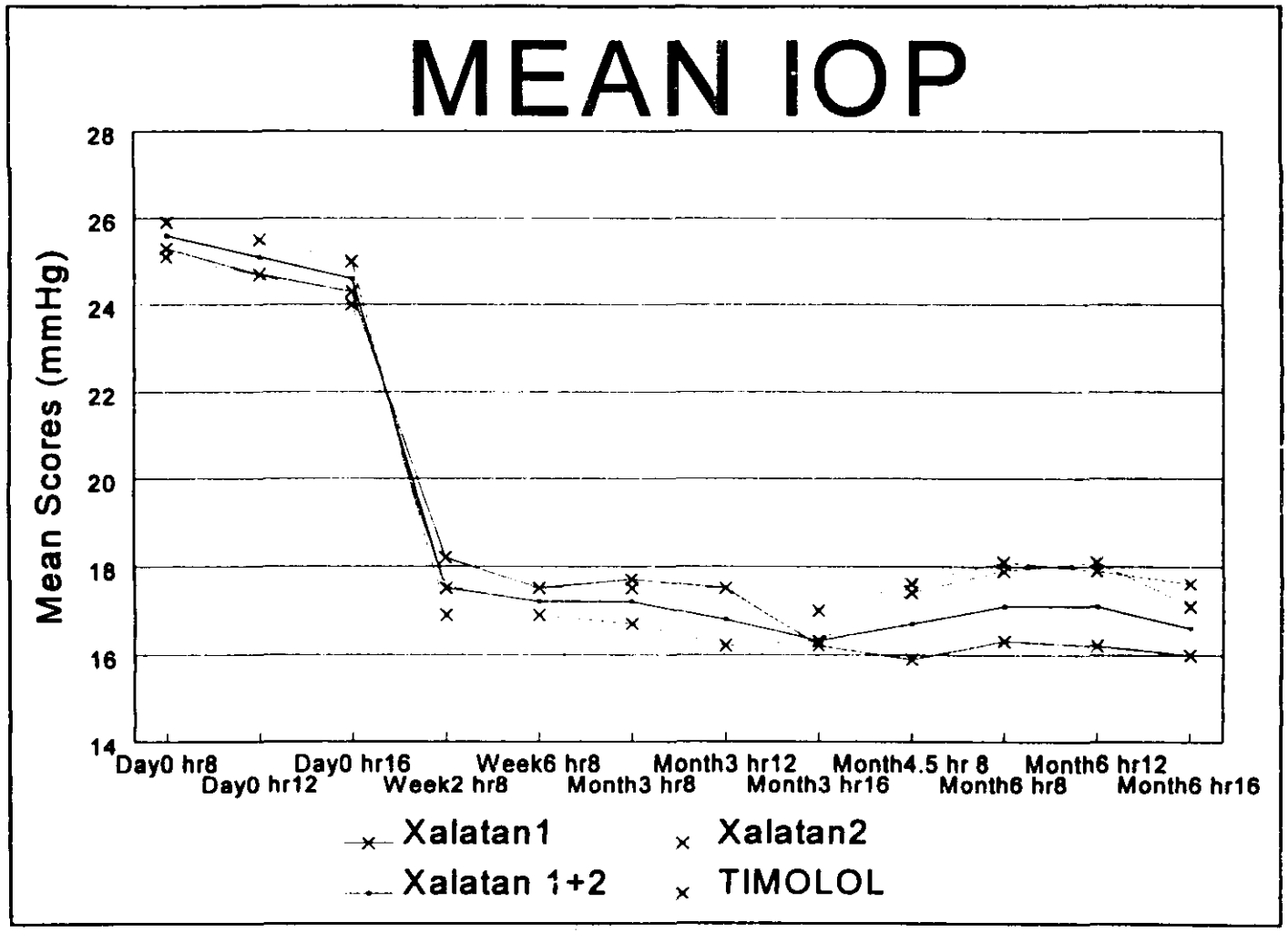
The primary objective of the study was to compare the IOP-reducing effect of latanoprost with that of timolol at the end of six months of treatment. The secondary objective was to compare morning with evening administration of latanoprost.

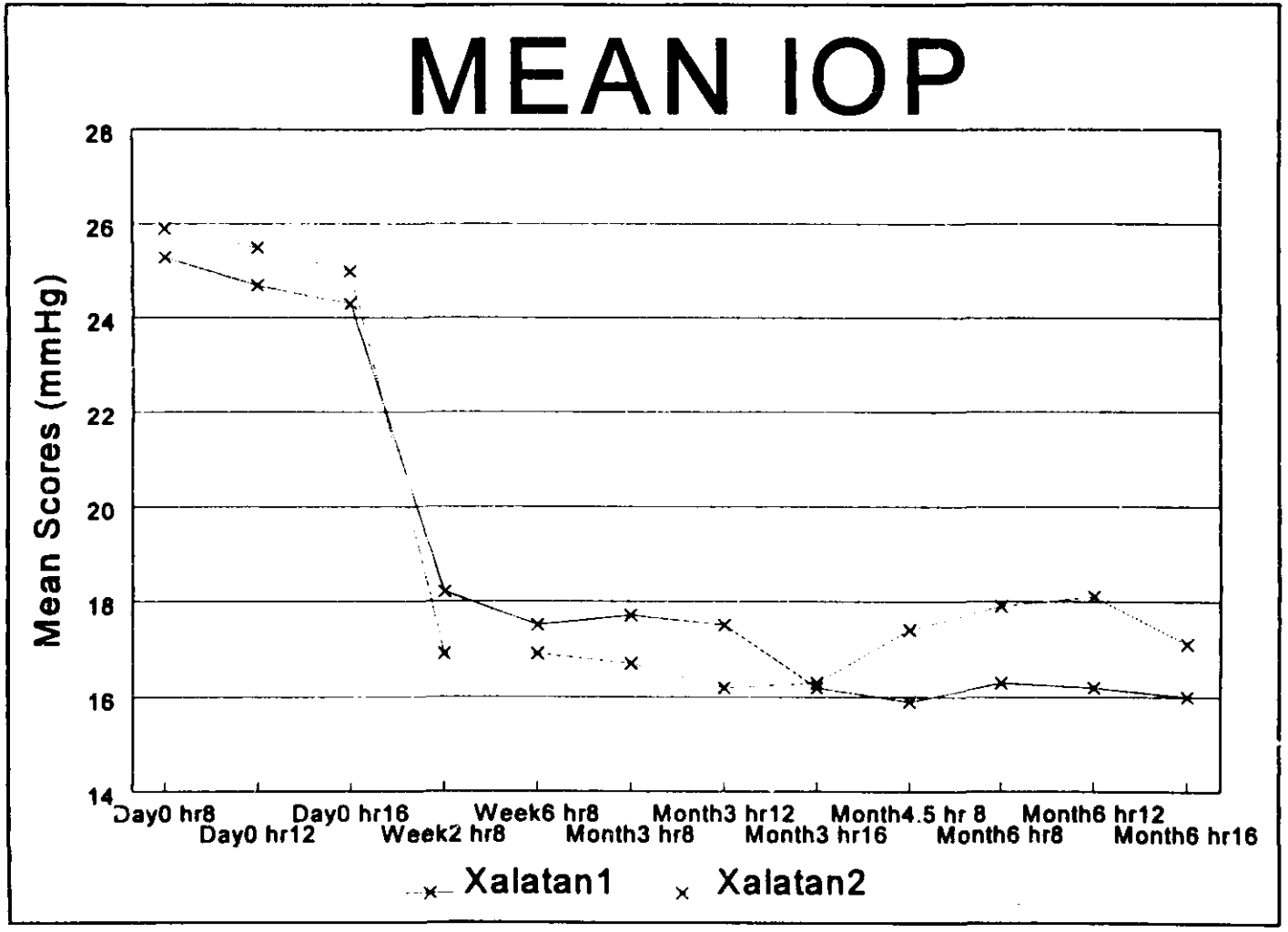
Reviewer's Comments: *This reviewer will examine IOP at every timepoint during the study in the per protocol analysis since only those patients have complete diurnal IOP-values at the 6-month visit. The number of patients in the analysis was 248; 169 in the pooled latanoprost treatment groups and 79 in the timolol treatment group.*

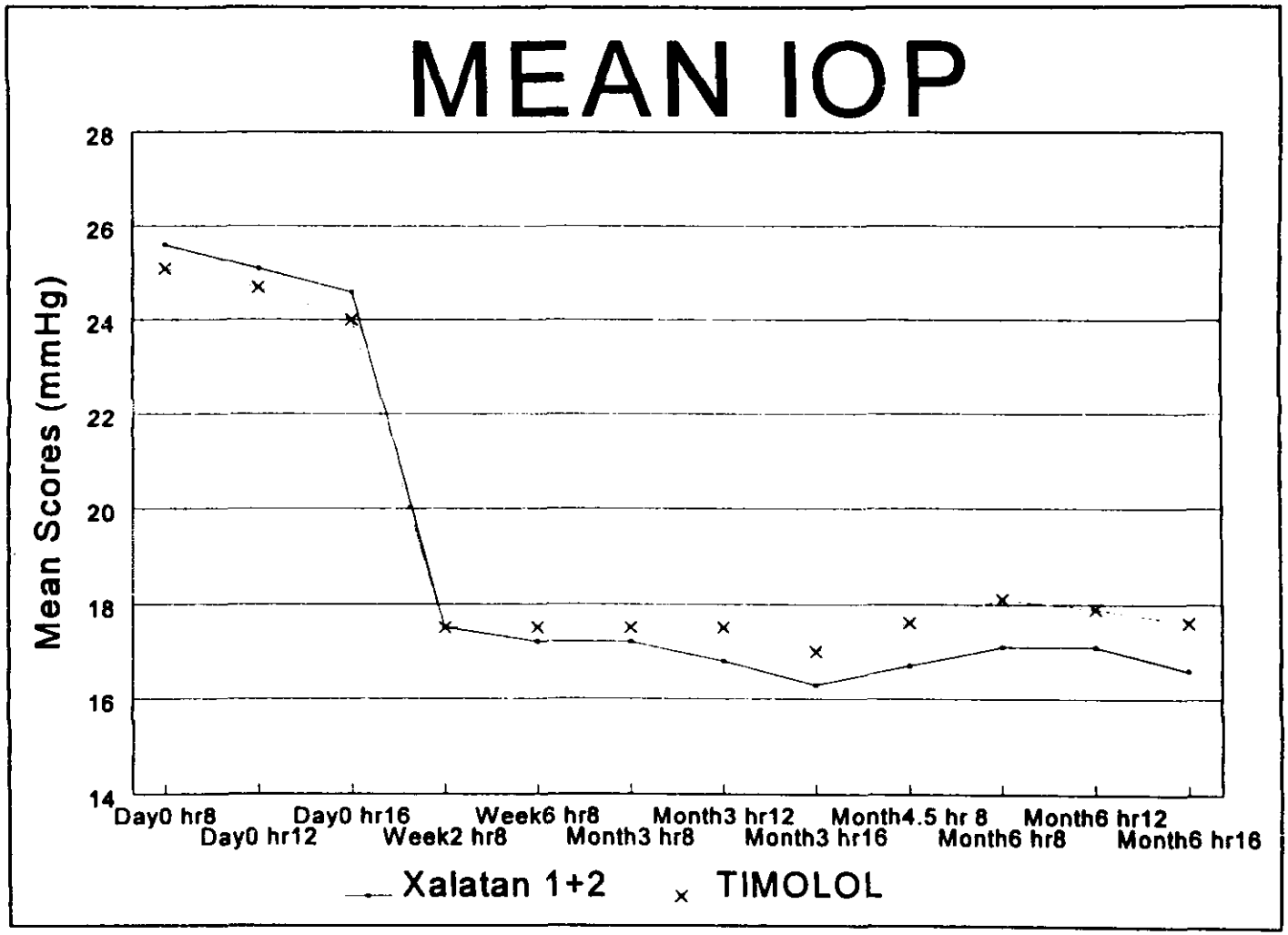
IOP (mmHg) at each scheduled examination.

Treatment group	Variable	Visit and time											
		1			2	3	4			5	6		
		8:00	12:00	16:00	8:00	8:00	8:00	12:00	16:00	8:00	8:00	12:00	16:00
Latanoprost 1	MEAN	25.3	24.7	24.3	18.2	17.5	17.7	17.5	16.2	15.9	16.3	16.2	16.0
	STD	4.6	3.9	3.8	3.9	2.9	3.0	2.9	2.6	2.8	2.6	2.7	2.8
	N	87	89	89	89	87	88	80	80	87	85	84	84
	MIN	16	16	17	12	13	10	13	10	10	12	12	11
	MAX	45	42	38	43	29	28	28	23	25	25	29	28
Latanoprost 2	MEAN	25.9	25.5	25.0	16.9	16.9	16.7	16.2	16.3	17.4	17.9	18.1	17.1
	STD	3.7	3.2	3.5	3.2	3.3	3.0	3.1	3.2	3.3	3.2	3.0	3.0
	N	94	94	94	93	94	93	85	85	88	86	85	85
	MIN	19	19	16	9	16	10	9	8	9	12	12	9
	MAX	37	36	37	30	27	27	26	23	27	27	28	25
Latanoprost 1+2	MEAN	25.6	25.1	24.6	17.5	17.2	17.2	16.8	16.3	16.7	17.1	17.1	16.6
	STD	4.2	3.6	3.7	3.6	3.1	3.0	3.1	2.9	3.1	3.0	3.0	2.9
	N	183	183	183	182	181	181	165	165	175	171	169	169
	MIN	16.0	16.0	16.2	9.0	10.0	9.7	9.3	8.3	9.3	11.5	11.5	9.0
	MAX	44.7	42.0	38.3	42.7	29.3	28.0	27.7	23.3	27.0	27.0	29.0	28.0
Timolol	MEAN	25.1	24.7	24.0	17.5	17.5	17.5	17.5	17.0	17.6	18.1	17.9	17.6
	STD	4.0	3.5	3.2	3.5	3.4	3.3	3.2	3.0	3.8	3.9	3.1	2.9
	N	84	84	84	83	84	83	78	78	80	79	79	79
	MIN	16	18	17	11	11	10	10	10	10	11	10	11
	MAX	41	45	39	28	26	26	25	25	32	39	30	26

*) If both eyes are study eyes, then the IOP is represented by the mean of both eyes.


MEAN IOP
Mean Scores (mmHg)
28
26
24
22
20
18
16
14
Day0 hr8
Day0 hr12
Day0 hr16
Week2 hr8
Week6 hr8
Month3 hr8
Month3 hr12
Month3 hr16
Month4.5 hr 8
Month6 hr8
Month6 hr12
Month6 hr16
Xalatan1
Xalatan2
Xalatan 1+2
TIMOLOL


MEAN IOP
Mean Scores (mmHg)
28
26
24
22
20
18
16
14
Day0 hr8
Day0 hr12
Day0 hr16
Week2 hr8
Week6 hr8
Month3 hr8
Month3 hr12
Month3 hr16
Month4.5 hr 8
Month6 hr8
Month6 hr12
Month6 hr16
Xalatan1
Xalatan2


MEAN IOP
Mean Scores (mmHg)
28
26
24
22
20
18
16
14
Day0 hr8
Day0 hr12
Day0 hr16
Week2 hr8
Week6 hr8
Month3 hr8
Month3 hr12
Month3 hr16
Month4.5 hr 8
Month6 hr8
Month6 hr12
Month6 hr16
Xalatan 1+2
TIMOLOL

SUBGROUP ANALYSES:

IOP-response at individual study centers (per-protocol)

Both drugs gave a similar pressure reduction at all study centers.

Change in diurnal IOP (mmHg) from baseline to visits 4 and 6 (3 and 6 month treatment) of the timolol group. (Mean±SD; number of patients in parenthesis.)

Study center	Change from baseline	
	Visit 4	Visit 6
Gothenburg (S)	-4.2±2.0 (6)	-2.6±2.5 (6)
Huddinge (S)	-10.0±2.3 (9)	-9.6±3.0 (8)
Linköping (S)	-7.1±2.4 (10)	-6.6±3.3 (10)
Lund (S)	-9.1±2.4 (5)	-7.6±3.2 (3)
Malmö (S)	-7.2±3.2 (7)	-6.7±2.6 (7)
Umeå (S)	-5.5±3.2 (10)	-4.7±2.1 (10)
Uppsala (S)	-9.7±4.4 (5)	-8.8±1.1 (4)
Bergen (N)	-8.6±1.9 (7)	-7.6±2.7 (7)
Oslo (N)	-6.6±1.6 (6)	-6.0±1.2 (6)
Trondheim (N)	-6.5±3.5 (7)	-6.2±2.7 (7)
Hellerup (D)[1]	--	-8.3±0 (2)
Vejle (D)	-9.7±3.0 (2)	-9.8±3.1 (2)
Oulu (F)	-5.0±1.9 (4)	-4.0±2.4 (7)

1) All values of 3 month visit at Hellerup are missing.

IOP-response in males and females (per protocol)

No statistically significant difference between the IOP-response of females and males was observed with either drug.

Diurnal IOP (mmHg) at baseline, visits 4 and 6 (3 and 6 month treatment) in males and females. (Mean±SD; number of patients in parenthesis.)

Sex	Visit	Latanoprost 1	Latanoprost 2	Timolol
Males	Baseline	24.6±3.5 (39)	25.2±3.3 (43)	24.9±3.7 (34)
	4 months	17.1±2.7 (34)	15.5±2.3 (41)	16.2±2.8 (34)
	6 months	16.4±2.6 (36)	17.1±2.4 (39)	17.1±3.2 (32)
Females	Baseline	24.9±4.1 (50)	25.6±2.8 (51)	24.4±2.7 (50)
	4 months	17.1±2.6 (46)	17.2±3.2 (44)	18.2±2.7 (44)
	6 months	16.0±2.4 (48)	18.3±3.1 (46)	18.4±2.7 (47)

IOP-response in different age groups (per protocol)

The difference in IOP-reducing effect between age groups was significant in the latanoprost group 2 (p=0.03; Ancova). In the age group 60-<70 years the IOP-reduction was less compared to that of the IOP-reduction in the age group <60 years and the age group 70 years.

There were no significant differences in IOP-reducing effect between age groups in the other treatment groups (latanoprost group 1, p=0.95, pooled latanoprost groups, p=0.13, timolol group, p=0.71; Ancova).

Diurnal IOP[1)] (mmHg) at baseline, visits 4 and 6 (3 and 6 month treatment) in different age groups. (Mean±SD; number of patients in parenthesis.)

Age	Visit	Latanoprost 1 (mmHg)	Latanoprost 2 (mmHg)	Timolol (mmHg)
<50 years	Baseline	23.0±1.7 (8)	26.1±2.1 (5)	23.8±1.8 (6)
	3 months	17.1±1.6 (8)	17.7±2.3 (4)	17.8±1.2 (5)
	6 months	15.9±1.9 (8)	17.0±2.0 (5)	19.1±2.1 (6)
50-<60	Baseline	24.4±1.7 (8)	25.0±2.3 (13)	24.3±2.0 (15)
	3 months	16.2±1.7 (5)	16.1±3.1 (11)	17.7±3.1 (14)
	6 months	15.8±1.3 (8)	17.1±3.1 (12)	17.7±2.9 (14)
60-<70	Baseline	25.5±4.8 (37)	25.5±3.1 (40)	24.5±4.2 (31)
	3 months	16.9±3.0 (31)	16.8±3.2 (35)	17.1±3.2 (29)
	6 months	16.5±3.1 (35)	18.5±2.4 (34)	17.5±2.8 (10.6)
70-<80	Baseline	23.9±2.9 (29)	25.7±3.6 (30)	25.1±2.6 (30)
	3 months	17.3±2.5 (29)	15.9±2.7 (29)	17.4±2.7 (28)
	6 months	15.9±2.3 (27)	17.2±3.3 (28)	18.2±3.4 (29)
80-	Baseline	26.8±3.1 (7)	24.5±3.2 (6)	23.1±1.7 (2)
	3 months	18.0±2.8 (7)	16.3±3.1 (6)	15.7±1.6 (2)
	6 months	16.7±1.9 (6)	17.0±2.0 (6)	16.6±3.1 (2)

1)Mean of measurements at 8:00 h., 12:00 h., 16:00 h.

IOP-response in different subgroups of disease (per protocol)

There was no significant difference in IOP-reducing effect between patients with different ocular diagnosis in any of the treatment groups.

IOP-response in patients with variable duration of ocular disease (per protocol)

No statistically significant difference in the IOP-response between ocular disease of different duration was seen in the latanoprost groups or the timolol group.

IOP-response in patients previously treated with glaucoma medication (per protocol)

There were no significant differences in IOP-reduction between the groups.

IOP-response in patients with different color of the iris (per-protocol)

There was no statistically significant difference in IOP-response between individuals with blue/grey/green, hazel or brown irides in the pooled latanoprost groups. Due to the small number of patients with brown and hazel eyes the analysis was not performed in the timolol group.

Eye color	Visit	Latanoprost 1	Latanoprost 2	Timolol
Blue/Green/Grey	Baseline	24.9±3.9 (73)	25.3±3.1 (78)	24.7±3.2 (77)
	3 months	17.1±2.5 (65)	16.3±3.1 (70)	17.4±2.9 (73)
	6 months	16.3±2.6 (70)	17.6±2.9 (70)	18.0±3.0 (73)
Hazel	Baseline	24.4±4.1 (8)	27.4±2.8 (6)	22.1±2.8 (4)
	3 months	17.2±3.8 (7)	17.6±1.8 (6)	18.3±0.6 (3)
	6 months	15.7±2.1 (7)	18.4±2.3 (6)	18.5±0.6 (3)
Brown	Baseline	23.6±1.7 (8)	25.1±2.9 (10)	25.2±1.8 (3)
	3 months	17.4±2.7 (8)	16.5±2.4 (9)	14.6±1.8 (2)
	6 months	16.0±1.4 (7)	18.2±2.1 (9)	15.1±2.1 (3)

1) Mean of measurements at 8:00 h., 12:00 h., 16:00 h.

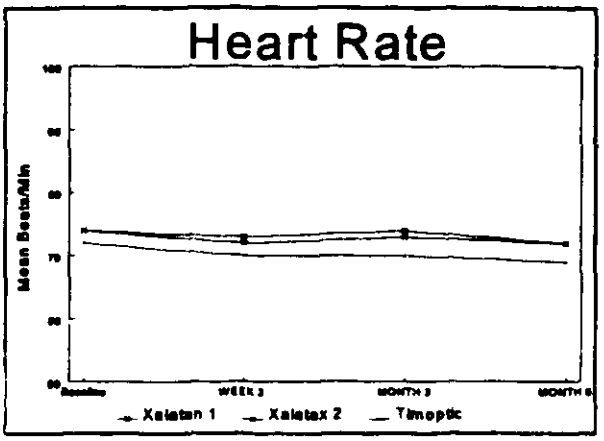
Reviewer's Efficacy Conclusions

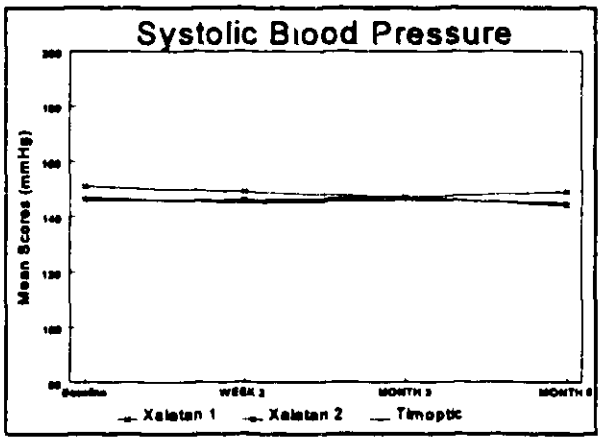
The IOP-reducing effect of latanoprost (pooled groups), administered once daily, was clinically as effective as timolol, administered twice daily, at the time points measured.

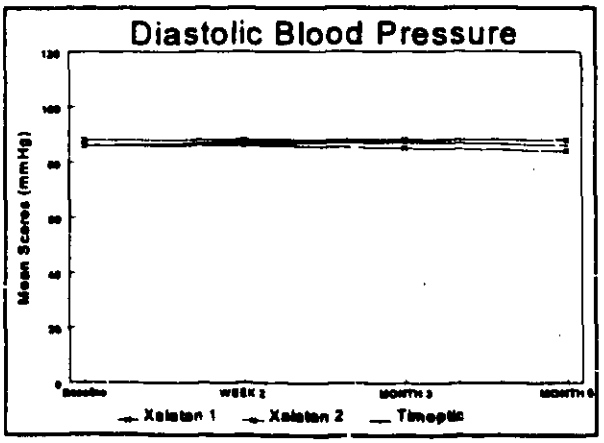
The sponsor's conclusion that "Latanoprost administered once daily in the evening, resulted in a significantly larger reduction of diurnal IOP when compared latanaprost administered once daily in the morning (p=0.008, p=0.002, respectively; Ancova) after 3 and 6 months of treatment." is not supported by the above study. These differences are only reflecting the timepoints at which the IOP was measured in relation to the time of drug administration. We can not compare IOP 24 hours after drug administration with IOP 12 hours after drug administration in a once a day regimen.

SAFETY:

Systemic (non-ocular) safety variables: There were no clinically significant differences between groups.



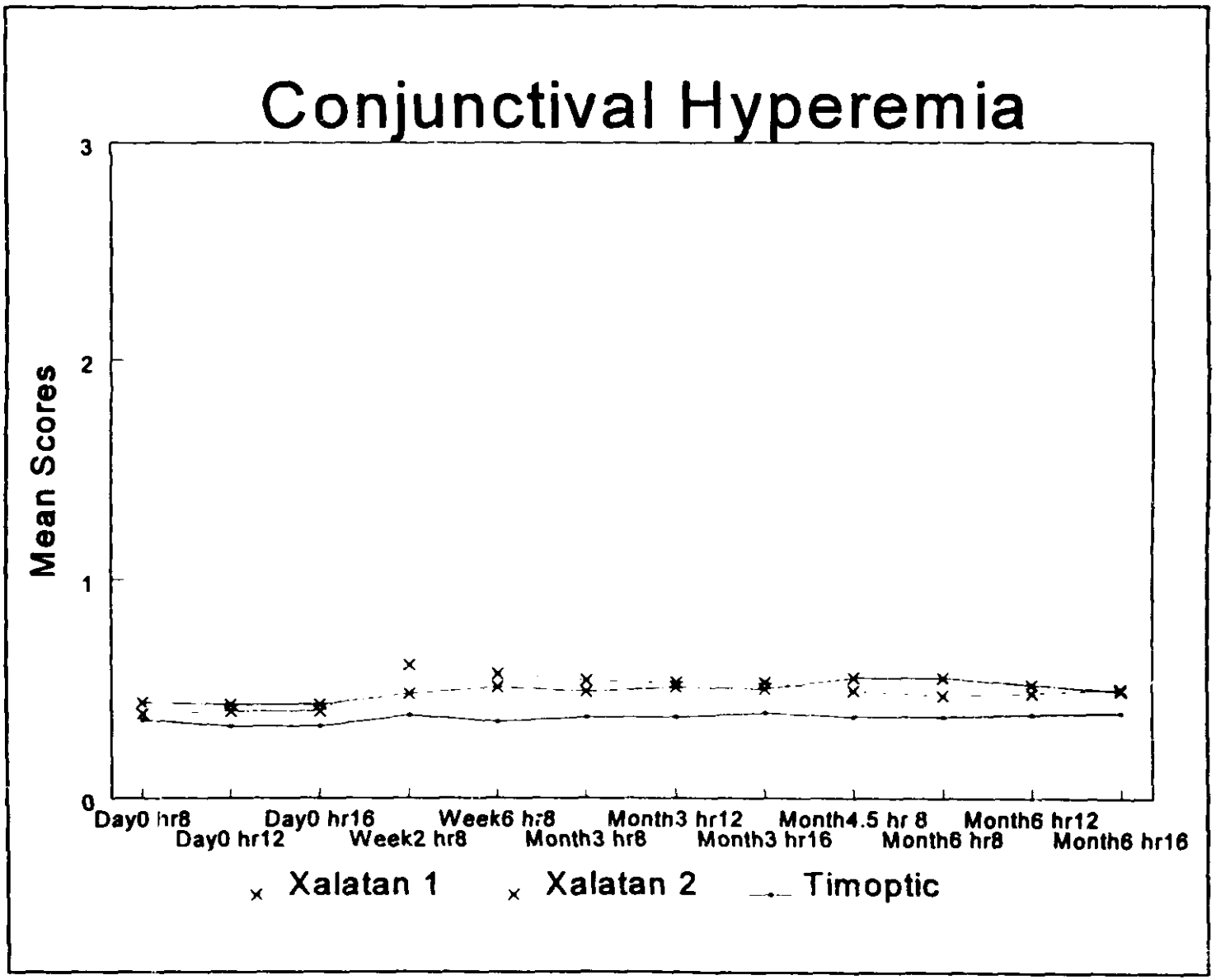




Conjunctival hyperaemia at all scheduled examinations.

Treatment group	Variable	Visit and time											
		1			2	3	4			5	6		
		8:00	12:00	16:00	8:00	8:00	8:00	12:00	16:00	8:00	8:00	12:00	16:00
Latanoprost 1	MEAN	0.44	0.43	0.43	0.48	0.51	0.49	0.51	0.50	0.55	0.55	0.52	0.49
	STD	0.39	0.37	0.36	0.38	0.40	0.41	0.44	0.45	0.44	0.43	0.41	0.40
	N	89	89	89	89	88	88	88	88	87	86	86	86
	MIN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	MAX	1.5	1.5	1.5	2.5	2.0	1.5	1.5	2.0	2.0	2.0	2.0	2.0
Latanoprost 2	MEAN	0.39	0.40	0.40	0.61	0.57	0.54	0.53	0.53	0.49	0.47	0.48	0.50
	STD	0.33	0.34	0.33	0.44	0.47	0.43	0.46	0.47	0.34	0.36	0.38	0.38
	N	94	94	94	93	94	93	92	92	89	89	89	89
	MIN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	MAX	1.0	1.5	1.0	2.0	2.0	2.0	2.0	2.0	1.5	1.5	1.5	1.5
Timolol	MEAN	0.36	0.33	0.33	0.38	0.35	0.37	0.37	0.39	0.37	0.37	0.38	0.39
	STD	0.29	0.27	0.28	0.28	0.25	0.30	0.30	0.31	0.29	0.30	0.31	0.31
	N	84	84	84	84	84	83	83	83	81	82	82	82
	MIN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	MAX	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

1) The highest score of the study eyes registered at the respective examination.


Conjunctival Hyperemia
Mean Scores
3
2
1
0
Day0 hr8
Day0 hr12
Day0 hr16
Week2 hr8
Week6 hr8
Month3 hr8
Month3 hr12
Month3 hr16
Month4.5 hr 8
Month6 hr8
Month6 hr12
Month6 hr16
Xalatan 1
Xalatan 2
Timoptic

Aqueous flare:

The aqueous humor was examined for flare only in the morning at each examination day to avoid flare caused by the fluorescein used for the tonometry. No aqueous flare was detected in any patient in the latanoprost groups or the timolol group.

Cells in the aqueous humor:

Cells were detected in the aqueous humor of only one patient in the latanoprost group 1, in whom one cell was observed at the 16.00 h. examination of the 3-month visit.

Visual acuity and refractive error:

Visual acuity was determined at each visit throughout the study period. Refractive error was determined at baseline, visits 4 and 6, unless a change in visual acuity had occurred. There were no clinically significant changes in visual acuity or spherical equivalence in any of the treatment groups.

Visual fields:

The visual fields were determined twice before the start of the treatment and once at the end of the treatment. One patient (#710) developed a marked deterioration in the visual field of the study eye (timolol group). No clinically significant changes were observed in any other patient.

Optic nerve head:

The horizontal and vertical cup-disc ratios were estimated at baseline and at the end of the treatment period. No clinically significant change of these ratios was observed in any of the patients.

General examination of the eye:

The lids, iris, conjunctiva, cornea and anterior chamber were examined on each visit day. Before entering the study and at the 6-month visit the lens, vitreous and the retina were examined in addition to the above-mentioned examinations. Except for findings included in the adverse events and/or ocular signs and symptoms, no pathological changes were seen in these tissues.

Laboratory safety variables

The laboratory safety variables were assessed at preinclusion and at the 6-month visit. No clinically significant differences were seen between the treatment groups.

Adverse events:

Comparison of number of patients with adverse events (not including serious adverse events) between the pooled latanoprost groups and the timolol group. Total number of adverse events in parenthesis.

Adverse event	**Latanoprost 183 treated patients**	**Timolol 84 treated patients**
OCULAR		
Increased iris pigmentation	12 (6.6%)	0
Itching	13 (7%)	4 (5%)
Burning/stinging	24 (13%)	15 (18%)
Hyperaemia/redness	6 (3.3%)	0
Foreign body sensation	10 (5.5%)	4 (4%)
Blurred vision	6 (3.3%)	6 (7%)
Vision disturbance	2 (1%)	0
Subconjunctival bleeding	0	1 (1.2%)
Disc hemorrhage	3 (1.6%)	3 (3.5%)
Corneal erosion/epithelial defects	11 (6%)	2 (2.4%)
Deep stromal opacities in cornea	1 (.5%)	0
Tearing	4 (2%)	1 (1.2%)
Vitreous detachment	1 (.5%)	1 (1.2%)
Vitreous hemorrhage	0	1 (1.2%)
Follicles in lower fornix	0	1 (1.2%)
Keratoconjunctivitis	1 (.5%)	0
Epithelial haze	1 (.5%)	0
Eye pain	1 (.5%)	0
Allergic reaction	1 (.5%)	1 (1.2%)
NON-OCULAR		
Allergic reaction/eczema	6 (3.3%)	1 (1.2%)
Influenza/Common cold	14 (8%)	13 (15%)
Bronchitis	2(1%)	1 (1.2%)
Sinusitis	2 (1%)	0
Nose flow/sneezing after instilling eye drops	1 (.5%)	1 (1)
Sneezing	0	1 (1)
Headache/Migraine	3(1.6%)	6 (7%)

Adverse event	Latanoprost 183 treated patients	Timolol 84 treated patients
Sleeping problems	1 (.5%)	0
Angina pectoris/Chest pain	2 (1%)	0
Arterial hypertension	2 (1%)	0
Urinary infection	2 (1%)	0
Thrombophlebitis	0	1 (1.2%)
Nocturia	1 (.5%)	0
Reduced sexual libido	0	1 (1.2%)
Mild diarrhea	0	1 (1.2%)
LABORATORY		
Increase in liver enzymes	2 (1%)	0
Asymptomatic bacteriuria	0	1 (1.2%)

Serious adverse events.

Treatment group	Patient No.	Visit	Description of Adverse Event	Severity	Action taken	Causal relationship with study drug Investigator's opinion	Patient outcome
Latanoprost 1	101	5					
	101	5, 6					
	108	6					
	117	91					
	313	5, 6					
	313	5, 6					
	313	6					
	505	5, 6					
	515	91					
	619	4					
Latanoprost 2	208	5, 6					
	625	3, 91					
	709	4					
	1201	4, 5					
Timolol	516	6	K				
	710	5	V				

Increased pigmentation of iris:

Increased pigmentation of the iris occurred in 12 of the 183 (6.6%) patients who received latanoprost. There were no cases of increased pigmentation in the timolol group.

Patients exhibiting increased iridial pigmentation as judged from photographs. The visit at which the first sign or suspicion of pigmentation occurred is also indicated. Eye color in parenthesis as assessed by investigator.

Patient No.	Treatment group	Visit	Eye color
	Latanoprost 1	4	Blue/grey-brown (Hazel)
	Latanoprost 1	4	Green-brown (Hazel)
	Latanoprost 1	5	Green-brown (Brown)
	Latanoprost 2	5	Green-brown (Brown)
	Latanoprost 2	5	Green-brown (Blue/green/grey)
	Latanoprost 1	6	Blue/grey-brown (Blue/green/grey)
	Latanoprost 1	6	Green-brown (Hazel)
	Latanoprost 1	4	Green-brown (Brown)
	Latanoprost 1	4	Green-brown (Brown)
	Latanoprost 2	5	Green-brown (Blue/green/grey)
	Latanoprost 2	6	Green-brown (Hazel)
	Latanoprost 2	6	Blue/grey-brown (Hazel)

All patients exhibiting increased pigmentation had green-brown or blue/grey-brown irides (as assessed by the Pharmacia staff). Patients with other colors of the iris did not exhibit any increase in pigmentation. The increase in pigmentation was seen between the visits 4 and 6 (after 3-6 months of treatment). There was no consistent pattern of the increase in pigmentation. In some individuals the pigmentation spread concentrically from a more pigmented ring around the pupil while in others the increase in pigmentation was rather uniform. The patients exhibiting increased pigmentation of the iris were not allowed to continue in the open-label continuation of the study, and entered a follow-up program to investigate whether the increase in pigmentation is reversible or not.

Safety Conclusions:

In general, latanoprost was well tolerated, and caused only minor side-effects with the exception of the increase in iris pigmentation which occurred in 6.6% of the patients in this study. It is unknown at present whether the increase in pigmentation has any negative consequences other than cosmetic.

Latanoprost had only minor or no effects on blood pressure and heart rate. There was no indication that latanoprost had any negative effects on the respiratory, gastrointestinal, central nervous or any other of the organ systems of the body.

Latanaprost caused conjunctival hyperaemia, burning and stinging, punctate epithelial erosions, foreing body sensation, itching and blurred vision in a significant number of patients.

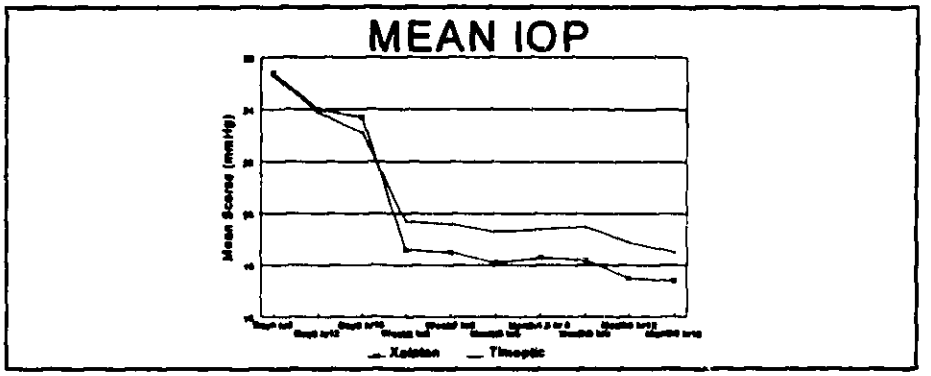
OVERALL STUDY RESULTS: EFFICACY

Effectiveness data of latanoprost. IOP reduction at the end-point compared to baseline. IOPs represent diurnal IOP based on at least 3 measurements (morning, noon, afternoon). (M=morning; E=evening)

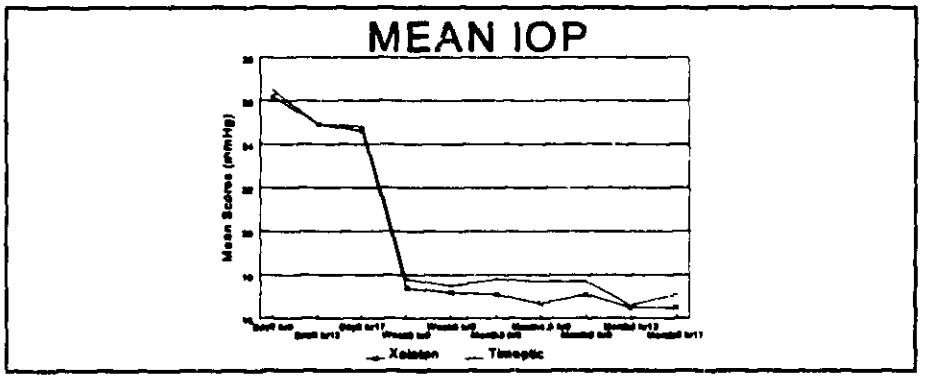
Paragraph in report	Study No./ Report No.	Study design	Objective	Treatment Latanoprost/ placebo	Number of patients enrolled	Withdrawals/ exclusions	Treat-ment time	Baseline IOP (mmHg) (Mean±SD)	Change in IOP (mmHg)	95% confidence interval (mmHg)
3.1.1	90PG09/ L411 G015	Fellow eye control	Dose-response	35 µg/ml x 1	12 HV *	0	1 day	—	-2.5±2.0 #	—
				115 µg/ml x 1	12 HV *	0	1 day	—	-3.9±1.3 #	—
				350 µg/ml x 1	12 HV *	0	1 day	—	-4.1±1.7 #	—
3.1.2	91PG02/ L411 G017	Fellow eye control	Pharmacodynamic study	60 µg/ml x 2*	20 HV	0	5 days	12.8±3.1	-2.3	-2.9: -1.5
				60 µg/ml x 2*	20	0	5 days	20.1±2.7	-4.7	-6.5: -2.9
3.1.3	91PG03/ L411 G018	Parallel groups	Dose-response	Placebo x 2	15	0	28 days	22.7±3.9	-0.3	-1.7: 1.1
				35 µg/ml x 2	15	0	28 days	21.6±4.6	-4.2	-6.4: -2.1
				60 µg/ml x 2	15	0	28 days	22.2±2.4	-4.5	-5.8: -3.2
				115 µg/ml x 2	15	0	28 days	22.0±1.8	-4.8	-6.1: -3.6
3.1.4	91PG01/ 9300175	Parallel groups	Dose-regimen	Placebo x 2	10	0	14 days	25.3±2.0	-1.7	-3.4: 0.0
				60 µg/ml x 1	20	1	14 days	24.8±2.3	-8.9	-9.8: -8.0
				60 µg/ml x 2	20	1	14 days	25.0±2.4	-7.0	-8.6: -5.4
3.1.5	90PG05/ L411 G023	Parallel groups	Dose-regimen	Placebo x 1	6	0	5 days	25.2±2.3	-1.7	-3.1:-0.2
				60 µg/ml x 1	9	0	5 days	25.4±3.0	-6.4	-7.9:-4.9
3.1.6	9200PG003/L 411 G025	Parallel groups	Dose-response	Placebo x 1	11	1	14 days	23.6±2.8	-1.3	-3.5:0.8
				12.5 µg/ml x1	12	0	14 days	23.2±4.7	-3.8	-5.5:-2.1
				25 µg/ml x 1	11	0	14 days	23.6±3.8	-4.6	-6.9:-2.3
				50 µg/ml x 1	12	0	14 days	23.8±2.9	-6.2	-7.7:-4.7
3.1.7	91PG06/ 9300148	Parallel groups	Low tension glaucoma	Placebo x 2	10	0	14 days	18.3±1.7	-1.0	-1.9: -0.1
				60 µg/ml x 2	10	0	14 days	16.8±1.8	-2.6	-3.6: -1.6
3.1.8	9200PG001/9 400215	Parallel groups	Pseudophakic patients	Placebo x 2	10	2	28 days	20.0±2.4	-1.9	-5.6: 1.8
				60 µg/ml x 2	22	6	28 days	21.2±3.4	-4.4	-5.9: -2.9
3.1.9	9300PG012/9 400648	Fellow eye control	Nocturnal IOP, Group 1. Patients on timolol	Placebo x 1	9	0	10 days	22.9±2.6	-1.3	-2.5: -0.1
				50µg/ml x 1	9	0	10 days	23.0±3.1	-3.6	-4.9: -2.3
			Nocturnal IOP, Group 2	Placebo x 1	10	0	10 days	22.0±2.6	-0.9	-2.4: 0.6
				50 µg/ml x 1	10	0	10 days	22.0±2.2	-4.4	-5.8: -3.0
3.1.10	9300PG023/9 400307	Parallel groups	Additivity to acetazolamide	Placebo x 1	12	1	14 days	21.5±4.2	+1.3	-0.5: 3.1
				50 µg/ml x 1	12	1	14 days	19.5±2.9	-2.9	-4.8: -1.0
3.1.11	9300PG014/9 400305	Cross-over	Normal (low) tension glaucoma	Placebo	30	1	21 days	16.9±2.1	-0.4	-1.1: 0.3
				15 µg/ml x 2	30	1	21 days	16.9±2.1	-2.4	-3.0: -1.8
				50 µg/ml x 1	30	1	21 days	16.9±2.1	-3.6	-4.3: -2.9

Paragraph in report	Study No./ Report No.	Study design	Objective	Treatment	Number of patients enrolled	Withdrawals/ exclusions	Treatment time	Baseline IOP (mmHg) (Mean±SD)	Change in IOP (mmHg)	95% confidence interval (mmHg)
3.2.1	9200PG002 L411 G024	Parallel groups	Dose-regimen in patients on timolol	60 µg/ml x 1	25	2	3 months	24.8±3.6	-8.7	-9.9: -7.5
				60 µg/ml x 2	25	0	3 months	24.9±2.9	-6.9	-8.4: -5.4
3.2.2	9300PG013 9400370	Cross-over	Dose-regimen	15 µg/ml x 2	50	0	21 days	24.7±3.7	-6.1	-7.1: -5.1
				50 µg/ml x 1	50	0	21 days	24.7±3.7	-7.5	-8.6: -6.4
3.2.3	9300PG015/9 400306	Cross-over with timolol as control group (3 groups)	Dose-regimen	50 µg/ml x1	10	0	21 days	29.2±6.1	-9.7	-11.6: -7.8
				15 µg/ml x 2	10	0	21 days	29.2±6.1	-6.8	-9.4: -4.2
				15 µg/ml x 2	10	2	21 days	27.2±5.1	-6.6	-9.9: -3.3
				50 µg/ml x 1	10	2	21 days	27.2±5.1	-10.0	-14.1: -5.9
				timolol 0,5% x 2	10	0	21 days	27.2±4.3	-4.8	-7.5: -2.1
3.2.4	91PG07 L411 G022	Parallel groups	Additivity to timolol	60 µg/ml x 2	10	1 ****	7 days	26.2±4.7	-8.0	-9.2: -6.8
				timolol 0.5% x 2	10	0	7 days	26.2±4.7	-4.8	-8.0: -5.6
3.2.5	91PG09 L411 G021	Parallel groups	Additivity to dipivefrine	60 µg/ml x 2	10	0 **	7 days	24.7±4.1	-7.8	-10.1: -5.5
				dipivefrine 0.1% x 2	10	0	7 days	26.3±4.6	-7.2	-8.2: -6.2
3.3.1	9200PG004/9 400369	Parallel groups	Comparison with timolol (pivotal study)	50 µg/ml x 1	128	32 ***	6 months	24.4±3.2	-6.7	-7.1: -6.0
				timolol 0.5% x 2	140	30 ***	6 months	24.1±3.6	-4.9	-5.5: -4.4
3.3.2	9200PG005/9 400243	Parallel groups	Comparison with timolol (pivotal study)	50 µg/ml x 1	149	16	6 months	25.2±3.4	-8.5	-9.0: -8.0
				timolol 0.5% x 2	145	16	6 months	25.4±3.6	-8.4	-9.0: -7.8
3.3.3	9200PG006/9 400194	Cross-over and parallel group	Comparison with timolol (pivotal study)	50 µg/mlx1E	89	5	6 months	24.8±3.8	-8.4	-9.1: -7.7
				50 µg/mlx1M	94	9	6 months	25.5±3.1	-7.7	-8.4: -7.0
				timolol 0.5% x 2	84	5	6 months	24.6±3.1	-6.4	-7.1: -5.7

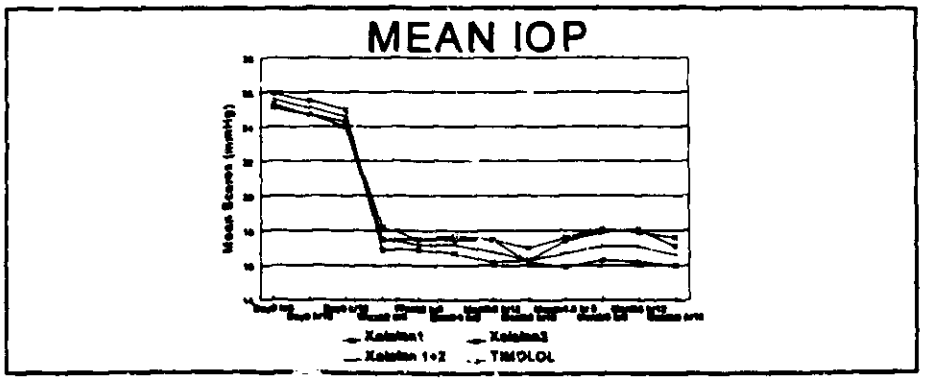
U.S. STUDY



Great Britain Study



Scandinavian Study



OVERALL STUDY RESULTS: SAFETY

Rate of increased pigmentation during 6 month treatment with latanoprost

Sponsor's Report:

The total number of patients exhibiting increased pigmentation of the iris in the phase III clinical trials (6 month double-masked study) is presented in Table 23. It can be seen that the rate of pigmentation varied among different countries, being highest in Great Britain and lowest in U.S.A. The reason for this is partly explained by the number of patients with irides predisposed to the change, the frequency of these being highest in Great Britain. However, the frequency of irides in the U.S. study population predisposed to increased pigmentation clearly exceeded that in the Scandinavian study population, and in spite of this more cases of increased pigmentation were detected in the Scandinavian study. Thus, there seems to be an underestimation of the rate in the U.S. study population for some unknown reason. Alternatively, there may be a genetic difference in the predisposition to increased pigmentation between the population in USA and England/Scandinavia. In the pooled phase III clinical trials the rate of increased pigmentation was 7.2% during 6 month treatment with latanoprost. Two patients on timolol in the phase III clinical trial in Great Britain also exhibited suspected increase in iridial pigmentation. Later, these were confirmed to be false positives, which may indicate that some of the suspect cases in the latanoprost groups may be false positives, and thus it is likely that the total rate is somewhat exaggerated.

Number of patients with increased iridial pigmentation and incidence of increased iridial pigmentation during 6 months of treatment with latanoprost 50 μg/ml x 1

Report No./Country	Number of patients with increased pigmentation	Number of patients predisposed*	Total number of treated patients*	Incidence of pigmentation in predisposed patients (%)	Incidence of pigmentation in all patients (%)
9400369/USA	4	60	118	6.7	3.4
9400243/GB	15	81	137	18.5	10.9
9400194/Scand	12	49	174	24.5	6.9
All	31	190	429	16.3	7.2

Breakdown of cases with increased iridial pigmentation, definite or suspect, in phase III clinical trials with latanoprost. Description of increase as "other" indicates undefined, neither concentric nor diffuse.

Country/ Patient No.	Sex	Age (years)	Iris color (Pharmacia)	Iris color (Invest)	When * detected (months)	Definite / Suspect	Description of increased pigmentation

Country/ Patient No.	Sex	Age (years)	Iris color (Pharmacia)	Iris color (Invest)	When * detected (months)	Definite / Suspect	Description of increased pigmentation

* Indicates month when the increased pigmentation first was detected or suspected.

** Patients in whom increased pigmentation was detected or suspected during the period of 6-12 months of treatment.

\# There may be a discrepancy between the number of definite/suspect cases of increased pigmentation compared to the study reports as some cases have been re-evaluated.

*** Investigator insists that increased pigmentation has not occurred.

Frequency of increased iris pigmentation during treatment with latanoprost for 1 year. Patients who were withdrawn prior to 12 months due to increased pigmentation have been included. For each color the number of patients affected/the number of patients treated and the frequency (%) are given. **

Iris color	9200PG005/ 9200PG008 (Great Britain) n=60+6 withdr. =66	9200PG006/ 9200PG009 (Scandinavia) n=88+6 withdr. =94	9200PG004/ 9200PG010 (USA) n=50+3 withdr. =53	All n=198+15 withdr. =213
Blue/gray	0/10 0%	0/39 0%	0/3 0%	0/52 0%
Blue/gray, some brown	0/14	0/29 0%	0/8 0%	0/51 0%
Blue/gray and brown	3/20 15%	3*/11 27.3%	1/7 14.3%	7/38 18.4%
Green				
Green, some brown (slightly)		0/1 0%		0/1 0%
Green-brown	12/18 66.7%	8/11 72.7%	2/9 22.2%	22/38 57.9%
Brown (Caucasian)	0/2 0%	0/3 0%	0/8 0%	0/13 0%
Yellow-brown (Caucasian)	2/2100%		1/6 16.7%	3/8 37.5%
Brown (Black)			0/12 0%	0/12 0%
Brown (Asian)				
All, irrespective of color	17/66 25.8%	11/94 11.7%	4/53 7.5%	32/213 15.0%

* Out of which 2 probably false positives

** Note that not all patients in Table 24 are included in this Table. This Table consists of patients who entered the study by April 30, 1993 and were found to have increased pigmentation of the iris a) during the first 6 months (double-masked treatment), or b) during the 6-12 month treatment (open label)

Patients exhibiting flare and cells iu the aqueous humor simultaneously. Dose in µg/ml. (Flare: ±; cells: absolute numbers)

Patient No./ Dose (Tx)	Report No./ Phase/Country	Cells/ Flare	0		2 W		1.5 M		3 M		4.5 M		6 M		6.5 M		8 M		10 M		12M	
			RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE

* Not determined
** Dosing first 3 weeks 50x1, last 3 weeks 15x2

Number of patients exhibiting punctate epithelial erosions (P.E.E.) in the cornea during treatment with latanoprost/timolol in the phase III clinical trials (TESS). (latanoprost = 460; timolol = 369)

Study/Report	P.E.E. reported as symptom and finding		P.E.E. reported as adverse event		P.E.E. Total	
	Lat.	Tim.	Lat.	Tim.	Lat.	Tim.
9400369 (USA)	14	21	0	0	14	21
9400243 (GB)	7	5	12	4	19	9
9400194 (Scand.)	10	1	1	1	11	2
All	31 (6.7%)	27 (7.3%)	13 (2.8%)	5 (1.4%)	44 (9.6%)	32 (8.7%)

Sponsor interim report:

The rate of punctate epithelial erosions during one year of treatment with latanoprost in 198 patients is presented in the table below. None of the patients belonging to the same cohort was withdrawn because of punctate epithelial erosions between month 6 and 12. It can be seen that the total rate of punctate epithelial erosions during the first six months was 7.1% whereas it was 6.1% during the last six months. Thus there was a tendency towards somewhat fewer punctate epithelial erosions during the last 6 months when latanoprost was administered once daily without a placebo drop, but the study population is too small to allow a firm conclusion. During the open label period, actually more punctate epithelial erosions were reported as adverse events than had been reported during the double-masked period.

Number of patients with punctate epithelial erosions of the cornea detected during 1 year treatment with latanoprost. During the first 6 months a vehicle drop was also instilled daily. During the last 6 months only latanoprost was administered (once daily).

Study No./Country	First 6 months (double-masked)		Last 6 months (open label)	
9200PG005/9200PG008 (Great Britain) (n=60)				
Total	5	8.3 %	5	8.3 %
Reported as AE	2	3.3 %	4	6.7 %
9200PG006/9200PG009 (Scandinavia) (n=88)				
Total	4	4.6 %	2	2.3 %
Reported as AE	0	0 %	0	0 %
9200PG004/9200PG010 (USA) (n=50)				
Total	5	10.0 %	5	10.0 %
Reported as AE	0	0 %	0	0 %
All studies (n=198)				
Total	14	7.1 %	12	6.1 %
Reported as AE	2	1.0 %	4	2.0 %

Total number of patients with ocular symptoms and/or findings in the phase III clinical trials irrespective of whether reported as adverse events or not.

Symptom/Finding	ALL Lat. = 460	ALL Tim. = 369
Subjective symptoms		
Foreign body sensation	49 (13.3%)	31 (8.4%)
Stinging	43 (9.3%)	45 (12.2%)
Itching	35 (7.6%)	30 (8.1%)
Burning	34 (7.4%)	28 (7.6%)
Tearing	19 (4.1%)	22 (6.0%)
Dry eye	15 (3.3%)	10 (2.7%)
Eye pain	14 (3.0%)	12 (3.3%)
Eye irritation/ocular discomfort	6 (1.3%)	5 (1.4%)
Tiredness of eyes	1 (0.2%)	2 (0.5%)
Ophthalmic migraine	1 (0.2%)	0 (0%)
	217 (47.2%)	185 (50.1%)
Functional symptoms		
Blurred vision	35 (7.6%)	30 (8.1%)
Vision disturbances/variable vision	10 (2.2%)	12 (3.3%)
Photophobia	8 (1.7%)	5 (1.4%)
Floaters	3 (0.7%)	3 (0.8%)
Diplopia	3 (0.7%)	1 (0.3%)
Visual field deterioration	1 (0.2%)	2 (0.5%)
	60 (13.0%)	53 (14.4%)
Lids		
Lid pain/discomfort	17 (3.7%)	8 (2.2%)
Erythema	14 (3.0%)	8 (2.2%)
Blepharitis/crusting	14 (3.0%)	12 (3.3%)
Edema	7 (1.5%)	12 (3.3%)
Hordeolum	4 (0.9%	2 (0.5%)
Trauma/lid operation post op. st./lid tic	2 (0.4%)	1 (0.3%)
Angular injection	0 (0%)	2 (0.5%)
Hemangioma	0 (0%)	1 (0.3%)
Ptosis/droopy eyelid	0 (0%)	2 (0.5%)
Cyst	0 (0%)	1 (0.3%)
Meibomian inspissation/chalazion	2 (0.4%)	4 (1.1%)

continued

Symptom/Finding	ALL Lat. = 460	ALL Tim. = 369
Conjunctiva		
Conjunctival hyperemia/inj./redness	37 (8.0%)	12 (3.3%)
Subconjunctival hemorrhage	5 (1.1%)	4 (1.1%)
Conjunctivitis	4 (0.9%)	4 (1.1%)
Film over the eye/watery eyes	2 (0.4%)	1 (0.3%)
Pinguecula	2 (0.4%)	0 (0%)
Follicles/cyst	2 (0.4%)	3 (0.8%)
Mattering	2 (0.4%)	0 (0%)
Discharge	1 (0.2%)	1 (0.3%)
Chemosis	1 (0.2%)	3 (0.8%)
Concretion/scar	1 (0.2%)	3 (0.8%)
Keratoconjunctivitis	1 (0.2%)	0 (0%)
Allergic conjunctivitis	1 (0.2%)	3 (0.8%)
Pterygium	0 (0%)	1 (0.3%)
Conj./scleral jaundice	0 (0%)	1 (0.2%)
Cornea		
Endothelial pigment	6 (1.3%)	5 (1.4%)
Infiltrates/epithelial plaque/haze/microcysts	3 (0.7%)	3 (0.8%)
Increased tear break-up time	1 (0.2%)	0 (0%)
Endothelial dystrophy	1 (0.2%)	0 (0%)
Guttatae	0 (0%)	1 (0.3%)
Abrasion	0 (0%)	1 (0.3%)
Corneal edema	0 (0%)	1 (0.3%)
Keratic precipitates	0 (0%)	1 (0.3%)
Various findings		
Disc hemorrhage	3 (0.7%)	3 (0.8%)
Vitreous detachment	3 (0.7%)	2 (0.5%)
Vasodilation of the iris	1 (0.2%)	0 (0%)
Pigment clump on iris	1 (0.2%)	0 (0%)
Ingrown eye lash	1 (0.2%)	1 (0.3%)
Darker eye lashes	1 (0.2%)	0 (0%)
Retinoschisis	1 (0.2%)	0 (0%)
Retinal pigmentary degeneration	1 (0.2%)	0 (0%)
Retinal neovascularization	0 (0%)	1 (0.3%)
Ciliary artery dilated	0 (0%)	1 (0.3%)
Periorbital edema	0 (0%)	1 (0.3%)

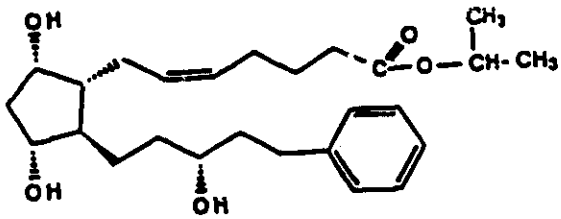
Labeling Review *Reviewer recommended additions are identified by* [redacted]. *Reviewer recommended deletions are identified by* ~~*single strikeout lines.*~~

XALATAN™
(latanoprost[redacted]tion) Sterile Ophthalmic Solution
0.005% (50μ g/mL)

DESCRIPTION

XALATAN™ (latanoprost~~solution~~) Sterile Ophthalmic Solution, ~~a novel~~ prostaglandin F_2 analogue, is a selective FP receptor agonist. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its structural formula is:

Chemical structure:



M.W. 432.58

~~The active substance is an isopropyl ester pro-drug which is hydrolyzed in the cornea to the acid form to become biologically active.~~

Latanoprost is a colorless to slightly yellow, oil which is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.

XALATAN Ophthalmic Solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7. Each mL of XALATAN, contains 50 micrograms of latanoprost. The inactive ingredients are: sodium chloride, monosodium phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. Benzalkonium chloride, 0.02% is added as a preservative.
One drop contains approximately 1.5 μg of latanoprost.

CLINICAL PHARMACOLOGY

Mechanism of Action

Latanoprost, a ~~novel~~ prostaglandin F_2 α analogue, is a ~~selective~~ prostanoid FP receptor agonist which~~this~~ [redacted] reduces ~~the~~ intraocular pressure by increasing the outflow of aqueous humor. Studies in animals and man ~~indicate~~[redacted]~~gest~~ that the main mechanism of action is increased uveoscleral outflow.

Pharmacokinetics/Pharmacodynamics

[redacted]

~~Latanoprost is well absorbed through the cornea and all of the drug which enters the aqueous humor is hydrolyzed to the biologically active acid form during passage through the cornea.~~

Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

~~Following topical administration, latanoprost is primarily distributed in the anterior segment, conjunctiva and eyelids with only minute quantities reaching the posterior segment.~~ Reduction of intraocular pressure following a single dose in man starts about 3 to 4 hours after topical administration and the maximum effect is reached after 8 to 12 hours. ~~Pressure reduction is maintained for at least 24 hours.~~

~~There is practically no metabolism of the acid of latanoprost in the eye.~~ Primary metabolism of latanoprost occurs in the liver. ~~In man, the~~ The half-life of the biologically active acid in plasma is approximately 17 minutes. ~~In animal studies, the main metabolites, the 1,2 - dinor and 1,2,3,4 - tetranor exert no or only weak biologic activity and were excreted primarily in the urine.~~

~~nical trials have shown that latanoprost has no significant effect on the production of aqueous humor and no ect on the blood-aqueous barrier. Latanoprost, at clinical dose levels, has no or negligible effects on intraocular blood circulation. However, mild to moderate conjunctival hyperemia may occur as a result of topical administration. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short term treatment.~~

Animal Studies
~~The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Latanoprost was well-tolerated at intravenous doses of 1 μg/kg/day in the dog and 35 μg/kg/day in the rat for 13 weeks. These doses are approximately 16 and 560 times the recommended human dose given ocularly. In animal studies latanoprost has not been found to have sensitizing properties.~~

~~In the eye, no toxic effects have been detected with doses of up to 100 μg/eye/day in rabbits or monkeys.~~ In monkeys, ~~however,~~ latanoprost has been shown to induce increased pigmentation of the iris. Increased pigmentation of the iris has also been reported in humans ~~with hazel eyes~~ during chronic treatment with latanoprost. The results from ~~a large~~ the pre-clinical program demonstrated that the effect is unlikely to be associated with proliferation of melanocytes, and neither naevi nor freckles in the eye have changed during chronic treatment with latanoprost. It appears that the mechanism of increased pigmentation is due to stimulation of melanin production in melanocytes of the iris. The change in iris color occurs slowly~~,~~ ~~and~~ may not be noticeable for several months and may be irreversible.

In ~~chronic ocular~~ ocular toxicity studies of [redacted], administration of latanoprost at a dose of 6μg/eye/day (4 times the daily human dose) has also been shown to induce increased palpebral fissures. This effect is reversible and occurs at doses above the clinical dose level. ~~This effect has not been observed in humans.~~

~~Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction did not effect the retinal blood vessels as determined by fluorescein angiography.~~

INDICATIONS AND USAGE

XALATAN is indicated for the reduction of elevated intraocular pressure in patients with open-angle

glaucoma and ocular hypertension [redacted] ~~intraocular pressure-lowering~~ [redacted]~~ications~~.

CLINICAL STUDIES

~~Clinical trials show that latanoprost is effective both as monotherapy and in combination with other anti-glaucoma drug therapy. XALATAN is even effective in patients who respond inadequately to other single or multiple anti-glaucoma drug therapy. The trials also show that the intraocular pressure reducing effect of latanoprost is additive to that of beta-adrenergic antagonists (timolol), adrenergic antagonists (dipivalyl epinephrine), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide).~~

~~Results of placebo-controlled and active-treatment controlled studies demonstrated that latanoprost used at 50 to 60 μg/ml once daily has the intended effect of reducing intraocular pressure in patients with open-angle glaucoma or ocular hypertension.~~ Patients [redacted]~~24-25~~ were treated for 6 ~~or more~~ months in ~~the Phase III~~ multi-center, randomized, ~~double-blind,~~ controlled trials [redacted]~~reductions in intraocular pressure; results of these trials showed the sustained benefit of long-term latanoprost therapy.~~

~~TABLE 1~~
~~IOP (mmHg) RESPONSE TO LATANOPROST IN PATIENTS~~
~~TREATED FOR 6 MONTHS IN THE PHASE III CLINICAL TRIALS~~

	~~U. S. Study (9400369)~~	~~GB Study (9400243)~~	~~Scandinavian Study (9400194)~~
~~Baseline IOP~~	~~24.4 ± 3.2 (n=125)~~	~~25.2 ± 3.4 (n=149)~~	~~25.1 ± 3.5 (n=183)~~
~~IOP at 6 months~~	~~17.6 ± 3.1 (n=96)~~	~~16.7 ± 2.6 (n=133)~~	~~17.0 ± 2.8 (n=169)~~
~~ΔIOP at 6 months~~	~~6.7 ± 3.4 (n=96)~~	~~8.5 ± 2.8 (n=133)~~	~~8.0 ± 3.1 (n=169)~~

CONTRAINDICATIONS

Known hypersensitivity to [redacted]~~aprost~~, benzalkonium chloride or any other ingredients in this product.

WARNINGS

[redacted]~~may cause increased pigmentation of the iris in patients.~~ ~~XALATAN may cause increased pigmentation of the iris in patients with blue-brown, gray-brown, green-brown or yellow-brown irides where brown areas are seen against the otherwise blue, gray, green and yellow irides (i.e. mixed color irides). When treating patients with mixed colored irides it is recommended that the patients are informed of the possibility of increased pigmentation. Until further long-term experience is gained it is furthermore recommended that gonioscopy be performed twice yearly if pigmentation occurs. Accumulation of pigment in the trabecular meshwork and chamber angle has not been observed in clinical trials, but withdrawal of treatment may be considered if marked accumulation of pigment is observed in these structures.~~

PRECAUTIONS

General

[redacted]

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 *Information for Patients*)

Patients ~~with hazel colored eyes~~ may slowly develop increased pigmentation of the iris. This change may not be noticeable for several months. ~~Commonly, hazel colored eyes are brown around the pupil and green, gray, blue or yellow towards the periphery of the iris.~~ 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 darker. ~~Increased iris pigmentation has not been noted in pure blue, gray, green or brown eyes.~~ Until more information about increased pigmentation is available, patients ~~predisposed to iris pigmentation (hazel eyes)~~ should be examined ~~more~~ frequently and, depending on the clinical situation, treatment may be stopped if cosmetically disturbing increased pigmentation ensues. The increase in iris pigmentation does not progress further upon discontinuation of treatment but may be permanent.

There is no experience with XALATAN in the treatment of angle closure, inflammatory or neovascular glaucoma and only limited experience in pseudophakic patients. ~~Latanoprost has no effect on the pupil but has not been died in acute attacks of closed angle glaucoma. Therefore, it is recommended that XALATAN be used with tion in these conditions until more experience is obtained.~~

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

~~Benzalkonium chloride, the preservative in XALATAN, may be absorbed by contact lenses. Thus,~~ XALATAN should not be administered while wearing contact lenses.

Information for Patients

Patients ~~with mixed colored irides~~ should be informed about the possibility of increased pigmentation and heterochromia between eyes.

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

Patients also should be instructed that ocular solutions, ~~if handled improperly or~~ if the tip of the dispensing container contacts the eyes 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.

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

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

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Drug Interactions

~~The intraocular pressure reducing effect of XALATAN has been shown to be additive to that of beta-adrenergic antagonists (timolol), adrenergic antagonists (dipivalyl epinephrine), cholinergic agonists (pilocarpine) and carbonic acid anhydrase inhibitors (acetazolamide).~~

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with XALATAN. If such drugs are used they should be administered with an interval of at lease five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Chromosome aberrations were observed *in vitro* with human lymphocytes.~~ Latanoprost was not carcinogenic in either mice or rats when administered at doses of up to 200 μg/Kg/day (6700 times the recommended human dose) for up to 20 and 24 months, respectively.

Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus tests. ~~Chromosome aberrations were observed *in vitro* with human lymphocytes, however, similar effects were observed with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, suggesting that this is a class effect~~. 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. ~~A systemic dose 100 times the clinical dose has been shown to induce abortion in rabbits but not in rats. No teratogenic potential has been detected.~~

Pregnancy

Teratogenic Effects:

Pregnancy Category ~~B~~C.

~~Reproduction studies have been performed in rats and rabbits at doses up to 825 times the clinical dose (based on 0.06 μg/Kg - 50 Kg human) and have revealed no evidence of impaired fertility or harm to the fetus due to latanoprost. A systemic dose of 100 times the clinical dose has been shown to induce abortion in rabbits but not in rats. There are, however, no adequate and well- controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.~~

~~XALATAN has been shown to have an embryocidal effect in rabbits when given in doses 100 times the 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, caution should be exercised when XALATAN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in ~~children~~ pediatric patients have not been established.

~~*Geriatric Use*~~

~~In clinical studies, latanoprost has been administered to a total of 890 patients and 99 healthy volunteers; almost 70% of the subjects were above age 60, and more than 1/3 were above age 70. The mean age, ±SD was 63 ± 14 years. Consequently, the majority of the clinical efficacy and safety data are from patients above age 60, and the efficacy and safety profile described in this labeling reflects this experience.~~

ADVERSE REACTIONS

~~In clinical studies, latanoprost has been administered to a total of 890 patients and 99 healthy volunteers. The adverse experiences that have occurred during treatment with latanoprost are divided into local adverse events and systemic adverse events.~~ The rates of local ocular adverse events reported in more than ~~1%~~ [redacted]% of the 460 patients in the ~~Phase III~~ multi-center trials treated for 6 months are provided below:

Reported Local/Ocular Adverse Events	Rate (n=460)
Foreign body sensation	[redacted]
Punctate epithelial erosions	[redacted]
Stinging	[redacted]
Conjunctival hyperemia	[redacted]
Blurred vision	[redacted]
Itching	[redacted]
Burning	[redacted]
Increased pigmentation of the iris	[redacted]
Dry eye	[redacted]
Lid discomfort/pain	[redacted]
Excessive tearing	[redacted]
~~Increased pigmentation of iris~~	~~31 (6.7%)~~
~~Conjunctival hyperemia~~	~~18 (3.9%)~~
~~Punctate epithelial erosions~~	~~13 (2.8%)~~
~~Foreign body sensation~~	~~12 (2.6%)~~
~~Blurred vision~~	~~9 (2.0%)~~
~~Itching~~	~~8 (1.7%)~~
~~Burning~~	~~5 (1.1%)~~
~~Excessive tearing~~	~~5 (1.1%)~~

~~*Local Ocular Adverse Events:*~~

In addition to the above listed local ocular adverse events, ~~minor local ocular symptoms and signs of no clinical consequence were observed in less than 0.5% of the patients. These symptoms and signs included~~ [redacted] ~~following were reported in less than 0.5% of the patients:~~ [redacted] ~~edema. The following ocular events were reported in less than 0.5% of patients:~~ conjunctivitis, diplopi[illegible] ~~scharge from eye, eye discomfort, eye pain, lid edema, ophthalmic migraine and visual disturbance~~ [illegible] ~~ese minor signs and symptoms involving either eyelid, conjunctiva, cornea, or visual acuity were of r[illegible] little clinical consequence.~~

Local conjunctival hyperemia was frequently observed, [redacted] ~~this was well tolerated and~~ less than 1% of the patients required discontinuation of therapy because of intolerance to conjunctival hyperemia.

~~The effect of latanoprost on the integrity of the blood-aqueous barrier was evaluated with laser flare meter, as well as other techniques. Latanoprost was shown to have no clinically significant effect on the blood-aqueous barrier in healthy volunteers or in patients. Latanoprost had no clinically significant effect on "flare/cells" in the aqueous humor. This indicates that latanoprost does not induce clinically significant leakage of proteins into the aqueous humor.~~

~~Only two patients were withdrawn due to punctate epithelial erosions out of 460 (0.4%) during latanoprost treatment for 6 months.~~

Increased Iris Pigmentation:

Latanoprost caused increased pigmentation of the iris in certain individuals. The results from a large pre-clinical program demonstrated that the effect is unlikely to be associated with proliferation of melanocytes, and neither naevi nor freckles in the eye have changed during chronic treatment with latanoprost. Individuals with mixed colored irides seem to be predisposed to this change. Typically individuals with green-brown, blue/gray-brown or yellow-brown irides are affected, but not individuals with homogeneously blue/gray, green or brown irides. The actual clinical consequence of this side effect is unknown; however, so far there are no indications to suggest that increased pigmentation of the iris would have clinically detrimental consequences.

Systemic Adverse Events:

The most common systemic adverse events were upper respiratory tract infection/cold/flu which occurred at a rate of [redacted] ~~approximately~~ 4% ~~4.3%, pain~~ [redacted] in muscle/joint/back; ~~(1.5%) and~~ chest pain/angina pectoris as well as rash/allergic skin reaction, each ~~occurring~~ occurred at a rate of ~~1.1%. The rest of the systemic adverse events occur at a rate below 1%~~1-2%.

~~Latanoprost is administered topically at such a low concentration (50 μg/ml) that theoretical systemic side effects should not occur, except for possible immunogenic reactions. The results of a study in patients with asthma show that latanoprost, even when used at a concentration seven times higher than the intended clinical concentration, had no effect on pulmonary or cardiovascular functions. The majority of the systemic adverse events observed during the Phase III trials involving six months of treatment were similar to those one would observe in the general population of people above age 60.~~

OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, [redacted] ~~the ocular effects of latanoprost administered at high doses are not known. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. there are no known ocular effects when latanoprost is administered at high doses.~~ One bottle of XALATAN contains 125 micrograms of latanoprost. More than 90% of topically administered latanoprost is metabolized during the first pass through the liver. Intravenous infusion of up to 3 μg/kg in healthy volunteers induced no symptoms but a dose of 5.5 to 10 μg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

The half-life of the biologically active acid of latanoprost in plasma is about 10 minutes.

~~In monkeys, latanoprost has been infused intravenously in doses of up to 500 μg/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically to the eye at a dose of seven times the recommended clinical dose.~~

If overdosage with XALATAN occurs, treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

The ~~usual~~ recommended dosage ~~for adults (including those over 60 years of age)~~ is one drop in the affected eye(s) once daily. ~~Optimal effect is obtained if XALATAN is administered~~ in the evening.

The dosage of XALATAN should not exceed once daily since it has been shown that more frequent administration decreases the intraocular pressure lowering effect.

~~If one dose is missed, continue with the next dose the following evening.~~

~~While XALATAN is effective as monotherapy, it can also be used in combination with beta-adrenergic antagonists (timolol), adrenergic antagonists (dipivalyl epinephrine), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide) to achieve an additive effect. If combined therapy is used, allow an interval of at least five (5) minutes between administration of the different eye drops.~~

Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours. ~~Pressure reduction is maintained for at least 24 hours.~~

HOW SUPPLIED

\LATAN™ (latanoprost solution) Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless ution supplied in plastic ophthalmic dispenser bottles with a dropper tip and tamper evident overcap.

NDC 0013-8303-04, 0.005% (50 μg/mL), 2.5 mL fill.

Storage: Store unopened bottle under refrigeration at 2° to 8° C (36° to 46° F).
Protect from light.
Do Not Freeze.

Once opened the container may be stored at room temperature up to 25° C (77° F) for one month.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
Automatic Liquid Packaging, Inc.
Woodstock, Illinois 60098

Distributed by:
Pharmacia Inc.
Columbus, Ohio 43216
124000695 June 7, 1995

124000695

Xalatan Ophthalmic Solution NDA 20-597, was presented on December 8,1995 to the Ophtnalmology Advisory Subcommittee for recommendations regarding safety issues.

The following issues were raised during the review and the following questions were presented to the Panel:

Iris Pigmentation

Committee Recommendations: The committee recommended approval of this product with post marketing studies to continue to evaluate iridial pigmentation. Gonioscopy was not recommended as a routine examination to assess the pigmentation of the iris and angle. It was recommended that the labeling should reflect the lack of total understanding of the mechanism and consequences of this iridial pigmentation and because of this, it was suggested that the product should be used in patients who are intolerant to other medication or were other therapies have failed, until the iridial pigmentation has been further investigated and characterized.

Lack of Endothelial Cell Count Studies:

Committee Recommendations: The drug was recommended for approval with post marketing endothelial cell count studies.

Inflammation:

Committee Recommendations: The panel concur that further studies were not required.

Regulatory Recommendations:

Xalatan Ophthalmic Solution, NDA 20-597 is recommended for approval for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are intolerant or unresponsive to other intraocular pressure lowering medications under the following conditions:

1. The labeling should be revised as recommended in this review.

2. The applicant should agree to conduct a Phase 4 study to evaluate the effect of lantaprost on endothelial cell counts.

3. The applicant should continue their investigations into the effects of iris pigmentation changes caused by latanaprost.

For

Jose A. Carreras, M.D.

: NDA 20-597
HFD-550
HFD-550/Chem/Tso
HFD-540/Pharm/Shriver
HFD-550/MO/Carreras
HFD-550/ProjManager/Holmes
HFD-550/Acting Director/Chambers mac 3/2/96

STATISTICAL REVIEW AND EVALUATION

NOV 28 1995

NDA#:	20-597
Applicant:	Pharmacia, Inc.
Name of Drug:	XALATAN™ (latanoprost) sterile ophthalmic solution, 0.005%
Drug Class:	1-P
Indication(s):	Reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension.
Type of Review:	Clinical.
Documents Reviewed:	Volumes 1.87 though 1.112, stamp dated June 16, 1995.
Medical Officer:	Dr. Tony Carreras, HFD-540

I. INTRODUCTION

In 1983, Pharmacia embarked in collaboration with on a project to develop a new intraocular pressure-reducing drug for glaucoma utilizing naturally occurring prostaglandins. Current therapy for glaucoma includes β-adrenergic blocking agents such as timolol, carbonic anhydrase inhibitors such as acetazolamide, miotics, and sympathomimetic agents. Latanoprost, a prostaglandin analogue (naturally occurring prostaglandins caused too many side-effects, mainly conjunctival hyperemia and irritation), is a new class of antiglaucoma agent with a different mechanism of action. It reduces intraocular pressure (IOP) by increasing uveoscleral outflow of aqueous humor.

Based on Phase I and II studies, once daily administration of one drop per affected eye of 50 μg/ml concentration latanoprost (0.005%) was chosen as the optimal concentration and dose regimen, and is used in all Phase III trials. This regimen was found to have the greatest IOP lowering effect and the least amount of conjunctival hyperemia as a side effect.

A total of 25 studies were conducted. Of these, 19 are controlled clinical trials (11 Phase I or II placebo controlled, 5 Phase II active treatment controlled, and 3 Phase III active treatment controlled). This review focuses on the 3 Phase III active treatment-controlled clinical trials (Protocol 9200PG004 in the U.S., Protocol 9200PG005 in Great Britain, and Protocol 9200PG006 in Scandinavia), as the company considers them to be the pivotal studies. Since the Phase III studies are very similar, Section II describes the common study design and statistical plan of analysis. Section III discusses any deviations/differences in methods and presents the results for each trial. At the end of each Phase III study, patients had the option to continue in an open-label study of latanoprost for up to 1 additional year (Protocol 9200PG008 in Great Britain, Protocol 9200PG009 in Scandinavia, and Protocol 9200PG010 in the U.S.). The interim results from these three extra protocols are discussed in Section III, as is the company's integrated summary of safety. Section IV

provides conclusions which may be conveyed to the sponsor.

II. COMMON STUDY DESIGN AND STATISTICAL PLAN OF ANALYSIS

Each of the 3 Phase III studies was a six-month, randomized, double blind, active controlled (timolol, 0.5%, administered twice daily), multi-center clinical trial in patients with open angle glaucoma or ocular hypertension. Protocol 9200PG004 was conducted in the United States at 17 different centers, protocol 9200PG005 was conducted in Great Britain at 14 centers, and protocol 9200PG006 was conducted in Scandinavia at 13 centers (7 in Sweden, 3 in Norway, 2 in Denmark, and 1 in Finland). Since timolol was administered twice daily (once in the morning and once in the evening), while latanoprost was administered only once a day, placebo drops were used to maintain the blind. Each patient received two bottles of eye drops, one marked for morning administration (1 drop per affected eye at 8:00am) and one marked for evening administration (1 drop per affected eye at 8:00pm). In the timolol groups, both bottles were active drug. In the latanoprost groups, one bottle was active drug while the other was placebo. All three solutions (timolol, latanoprost, and placebo) were identical to one another in appearance.

Compliance was not specifically determined, although the sponsor did collect study medication bottles and keep track of unreturned medication. The analysis performed by the sponsor assumes that patients were taking medication daily, and that compliance was equal between the two groups (note: this was not tested statistically). Since latanoprost needs to be taken only once a day, compared to twice a day for timolol, compliance on latanoprost should be better than on timolol in practice, assuming side-effects on latanoprost are no worse than on timolol. However, in the study the sponsor was not able to compare compliance, in terms of taking medication once- versus twice-a-day, due to the requirement that the study treatment be double-blind which meant that all patients were administering drops twice-a-day. Note that the sponsor could still have compared compliance, in terms of side-effects which would cause one to discontinue drug, if they had had the patients keep study diaries.

Patients were checked for eligibility one month prior to study start. They were to be of either sex, 40 years or older, with IOP of 22 mmHg or higher measured during the pre-study period, and with unilateral or bilateral primary open angle glaucoma, exfoliation (capsular) glaucoma, pigmentary glaucoma, or ocular hypertension. Patients previously not treated or on single drug treatment for elevated IOP were eligible after a wash-out period of 3 weeks for β-adrenergic antagonists, 2 weeks for adrenergic agonists, 5 days for cholinergic agonists, or 5 days for oral carbonic anhydrase inhibitors. Patients requiring treatment bilaterally had to fulfill eligibility criteria for both eyes. For exclusion criteria, please refer to the medical officer's review.

During the six month treatment period there were six scheduled visits: (1) at baseline (full day visit with 3 exams: 8:00am, 12:00pm, and 4:00pm); (2) 2 weeks (8:00am exam); (3) 1.5 months (8:00am exam); (4) 3 months (8:00am exam); (5) 4.5 months (8:00am exam); and (6) 6 months (full day visit with 3 exams: 8:00am, 12:00pm, and 4:00pm). Patients were randomized to treatment groups at baseline using a computer generated randomization scheme. Randomization was stratified for center, and performed in blocks of 6 (within each center). A deviation of 4 days for visit 2 (2 weeks) and one week for

subsequent visits was accepted. On visit days, patients were instructed not to instill the morning drop and it was given after the 8:00am exam. IOP was measured, if possible by the same investigator using the same Goldmann applanation tonometer throughout the study period, three times during each exam and the average was used as the response. Diurnal IOP, defined as the mean of the 3 IOP measurements taken during the morning, noon, and afternoon exams, was measured at baseline and again at the final visit (month 6). During the other visits, only morning IOP was measured. If both eyes were study eyes, the average response was used. IOP was the only efficacy variable measured.

There were several safety variables that were assessed throughout the study. The present dose regimen of latanoprost was chosen to maximize IOP reduction while minimizing the occurrence/severity of conjunctival hyperemia, thus conjunctival hyperemia is one of the major safety variables followed throughout the study. In addition, in a chronic toxicity study performed in cynomolgus monkeys it was demonstrated that latanoprost may cause increased pigmentation of the iris and an increase in the palpebral fissure. The latter effect was reversible and occurred only at doses significantly above the clinical dose. However, the darkening of the iris was observed to occur at clinical doses, and furthermore was not reversible. Neither effect had been observed in any of the pre-Phase III clinical trials in humans (the longest trial lasted 3 months), but these two variables were to be followed closely during the Phase III trials. External (en face) photography was used pre-study and at month 6 for evaluation of the palpebral fissure and eyelids. Color photographs of the irides were taken at pre-inclusion and months 3, 4.5, and 6 (visits 4, 5, and 6) for evaluation of iris color, which was classified by the investigator as blue/green/grey, hazel, or brown. During the course of all 3 Phase III studies, increased iris pigmentation was observed in several patients. In order to investigate this phenomenon more fully, iris color was classified according to the following scheme by Pharmacia staff (using the color photographs):

1 = Blue/grey iris
2 = Blue/grey iris with slightly brown, usually around the pupil
3 = Blue/grey and brown iris (mixed color iris, i.e. hazel)
4 = Green iris
5 = Green iris with slightly brown, usually around the pupil
6 = Green-brown iris (mixed color iris -- hazel)
7 = Brown iris (Caucasian)
8 = Yellow-brown iris (Caucasian; mixed color iris -- hazel)
9 = Brown iris (Black)
10 = Brown iris (Asian).

All patients with increased iris pigmentation were to be withdrawn from the study and followed up at least twice yearly for a minimum of 2 years to investigate whether the increase in iris pigmentation was reversible or not.

Other safety variables which were followed throughout the study include ocular and non-ocular symptoms, slit lamp examination with special emphasis on aqueous flare and presence of any cells in the aqueous humor, visual acuity and refraction, blood pressure and heart rate, visual field, urine and blood samples to test hematology, blood chemistry, kidney and liver function, electrolyte and fluid balance, and urinalysis, and ophthalmoscopy

to examine the lens, vitreous, retina, and optic nerve head.

The primary objective was to demonstrate that the IOP-reducing effect of latanoprost was equivalent to that of timolol at the end of 6 months of treatment. This was assessed using both an intent-to-treat (ITT) and a per-protocol (PP) analysis of the difference in reduction of diurnal IOP from baseline for latanoprost minus timolol. A positive difference indicates that timolol is performing better than latanoprost, while a negative difference indicates that latanoprost is performing better. The ITT analysis was based on all randomized patients (patients were randomized at visit 1). For patients with missing data at month 6, the baseline IOP measurement was carried forward to month 6. Thus, for those patients IOP reduction was defined to be 0. This approach differed from that stated in the protocol that the last observed value would be carried forward. How/whether this affects conclusions is discussed in Section III. The PP analysis was restricted to patients who completed the study with no major protocol deviations and who were present at month 6. In both approaches, the difference in reduction of diurnal IOP was estimated using analysis of covariance with treatment group and center as factors, and baseline IOP as covariate (all 3 variables are highly significant). Interaction terms were also considered, but removed from all models due to lack of significance. A two-sided 90% confidence interval was then constructed for the difference in diurnal IOP reduction from baseline between latanoprost and timolol. If the upper limit of that confidence interval was less than 1.5 mmHg, then latanoprost was to be considered equivalent to timolol. In Section III, 95% confidence intervals are constructed and compared to the 90% confidence intervals provided by the sponsor.

Although unplanned in the protocol, the diurnal IOP-reducing effect of latanoprost was summarized for the following subgroups to determine if any differences exist: sex, age (<60 years, 60-<70, and ≥70), race (caucasian and black, although only the U.S. study had enough data to test for racial differences), color of study eye (blue/green/grey, hazel, and brown), study eye diagnosis (primary open angle glaucoma, exfoliation glaucoma, pigmentary glaucoma, and ocular hypertension), and duration of study eye diagnosis (<6 months, 6-36, 37-100, and >100 months). Assessment of the change in diurnal IOP from baseline to month 6 within each subgroup was performed using analysis of covariance with the subgroup variable as the factor and baseline IOP as a covariate. The sponsor states that "center" was included in the initial analysis, and then deleted due to the number of empty (or near empty) cells.

The other unplanned analysis examined change in diurnal IOP in the untreated fellow eye in patients with unilateral disease. Change in diurnal IOP from baseline to month 6 was tested within and between the latanoprost and timolol groups using analysis of covariance with treatment group as factor and baseline IOP as covariate. Again, an analysis with "center" included was performed and found to be inappropriate due to the number of empty cells.

The secondary objectives were to describe the IOP reduction at each visit/time point and to follow the safety variables in each treatment group. Reduction in IOP from baseline at each visit and time point for latanoprost minus timolol was assessed using a PP analysis and analysis of covariance, with treatment group and center as factors, and baseline IOP as the covariate. Safety analyses were based upon all patients who received study drug

(i.e., ITT). Conjunctival hyperemia was rated on a scale from 0 to 3 (in steps of 0.5), where 0 equals absence and 3 indicates severe conjunctival hyperemia, and measured at each of the three exams during the baseline and month 6 visit. The difference in the maximum conjunctival hyperemia score at month 6 minus baseline is used for analysis (if both eyes are study eyes, then the maximum score at baseline and month six is over both the 3 exams and right and left eyes). The sign test is used to determine whether the change is significant within each treatment group, and the Wilcoxon rank sum test is used to test for differences between treatment groups. Change from baseline to month 6 in systolic and diastolic blood pressure, heart rate, and visual acuity and refractive error is tested within each treatment group using a paired t-test, and between treatment groups using a two-sample t-test. Laboratory safety variables (blood chemistries and hematologies) were assessed pre-study and at month 6. Due to differences in methodology and reference values employed by the laboratories, all values were normalized using the following scheme:

$$\text{relative value} = (\text{measured value} - \text{limit}_{min}) / (\text{limit}_{max} - \text{limit}_{min}),$$

where limit_{min} and limit_{max} refer to the lower and upper limit of the reference range, respectively. Thus, relative values less than 0 correspond to measured values below the reference range, relative values greater than 1 correspond to measured values above the reference range, and relative values between 0 and 1 correspond to measured values within the reference range. For each laboratory variable, a scatterplot of the pre-inclusion versus the month 6 relative values was generated and visually interpreted. Finally, symptom and adverse event data are summarized within each treatment group.

All statistical tests are two-sided and performed at the 5% significance level, unless stated otherwise. No adjustments are made for multiple comparisons.

III. EVALUATION

A. Protocol No. 9200PG004 (U.S. Study)

Methods

On baseline day, patients were randomly allocated to receive either timolol, 0.5%, twice daily, or latanoprost, 0.005%, once daily (latanoprost patients received placebo/vehicle in the morning and latanoprost in the evening).

An additional subgroup analysis was performed in this study to examine the diurnal IOP response in patients treated with topical β-adrenergic antagonists (e.g., timolol) prior to study enrollment. Patients were divided into two categories of pre-study therapy: (1) had no ocular medication within 6 months of the pre-study visit and no topical β-adrenergic antagonists for a duration longer than 3 months pre-study, or (2) were treated with topical β-adrenergic antagonists within 6 months of the pre-study visit and/or for a duration longer than 3 months pre-study. Analysis of covariance with pre-study therapy group as a factor and baseline IOP as a covariate was used to test for differences within the latanoprost and timolol groups. In addition, a second analysis of covariance, with pre-study and study therapy group as factors and baseline IOP as a covariate, was used to test for a difference

in response to study therapy between the latanoprost and timolol groups, controlling for pre-study treatment.

Results

A total of 268 patients were entered into the study and thus included in the ITT analysis, 128 on latanoprost and 140 on timolol. Of these patients, 206 (96, or 75%, of the latanoprost group, and 110, or 78.6%, of the timolol group) completed the final visit at month 6 according to protocol and are included in the PP analysis of the primary objective. Of the 62 patients excluded from the PP analysis, 20 were treatment withdrawals (10 in each group) and 42 had protocol violations (19 in the latanoprost group and 23 in the timolol group). Of the 10 treatment withdrawals in the latanoprost group, 4 were lost to follow-up, 2 were due to rash (in both cases, it is unclear whether or not latanoprost was the causative agent), 2 had ocular symptoms such as hyperemia and blurring of vision (the sponsor does not state whether these 2 events were considered drug-related), 1 experienced palpitations (judged by the sponsor as "unlikely" to be due to latanoprost), and 1 had a peptic ulcer. The majority of the protocol violations are due to a misunderstanding by a few of the investigators that patients should not be administered medication in the morning of the final visit. By protocol, they were to be administered medication and the absence of this final dose in the timolol group could bias results against timolol (recall that the morning drop is active drug in the timolol group). Of the 19 protocol violations in the latanoprost group, 15 were due to the reason just mentioned, 1 patient administered study drug prior to the morning exam, and 3 patients had IOP measurements taken outside the allowed time window (more than two hours late).
Of the 268 patients who entered the study, 114 were male and 154 were female, 185 were caucasian, 65 were black, 16 were hispanic, and 2 were asian, and the average age was 62.3 years. One third of the patients suffered from glaucoma, while two thirds had ocular hypertension. The mean duration of the ocular condition was approximately 5 years. Forty-one patients were treated unilaterally, the rest were treated bilaterally. Half of the patients (52%) had brown eyes, one third (36%) blue/green/grey eyes, and the remainder (12%) had hazel eyes, as judged by the investigators. According to re-classification of eye color by Pharmacia staff using the color photographs, more patients actually had hazel eyes (43%). All of the above demographic characteristics were evenly distributed among the latanoprost and timolol groups. There was a slight difference in the percentage of patients not treated with antiglaucoma medication during the 6 months prior to the study, 44% among latanoprost patients, compared to 37% of timolol patients. Among those previously treated, approximately half in each group had received either timolol or another topical β-adrenergic antagonist. Each study center contributed 9-25 patients.

In the ITT analysis of the primary objective, reduction in diurnal IOP from baseline at month 6, latanoprost was found to be superior to timolol. Diurnal IOP was reduced from an average baseline of 24.4 mmHg by an average of 6.15 mmHg (25%) in the latanoprost group, and from an average baseline of 24.1 mmHg by an average of 4.34 mmHg (18%) in the timolol group (corresponding to an average difference of -1.81 for latanoprost minus timolol). The analysis of covariance estimated that latanoprost was superior to timolol by 1.76 mmHg (i.e., the estimated difference in change from baseline for latanoprost minus timolol was -1.76). The 90% confidence interval for this difference constructed by the

company is (-2.32, -1.20). The corresponding 95% confidence interval, which is what we require, is (-2.43, -1.09). In both cases, the upper limit is well below 1.5 and hence latanoprost can be considered equivalent to timolol according to the sponsor's definition in the protocol. In fact, both intervals lie entirely below 0, indicating that the reduction in diurnal IOP is statistically greater for the latanoprost group. Whether this difference is clinically significant will have to be determined by the reviewing medical officer.

The results of the PP analysis of the primary objective are very similar. Diurnal IOP was reduced by an average of 6.71 mmHg (28%) in the latanoprost group, and by an average of 4.88 mmHg (20%) in the timolol group (corresponding to an average difference of -1.82 for latanoprost minus timolol). The analysis of covariance estimated that latanoprost was superior to timolol by 1.58 mmHg. The 90% confidence interval for this difference constructed by the company is (-2.13, -1.04). The corresponding 95% confidence interval is (-2.23, -0.93). Again, in both cases the upper limit is well below both 1.5 and 0, so latanoprost is statistically superior to timolol in terms of reduction in diurnal IOP.

No differences were found in various subgroups' responses to treatment with latanoprost. The average reduction in diurnal IOP was not statistically different for different sexes, age groups, races, eye color, ocular disease, duration of ocular disease, and whether or not patients had previously been treated with topical β-adrenergic antagonists (p-values from the analyses of covariance of 0.13, 0.34, 0.52, 0.65, 0.88, 0.12, and 0.77, respectively). The response to treatment with both latanoprost and timolol did vary somewhat from center to center. Reduction in diurnal IOP ranged from 3.9 to 10.4 mmHg in the latanoprost group, and from 2.0 to 8.3 mmHg in the timolol group. In all but 2 centers, IOP reduction was greater with latanoprost (in center 11, latanoprost reduced IOP by 7.7 mmHg while timolol reduced IOP by 8.3 mmHg, and in center 16, latanoprost reduced IOP by 6.8 mmHg while timolol reduced IOP by 7.3 mmHg).

Thirteen patients completed the study who were treated unilaterally with latanoprost, as did 17 patients treated unilaterally with timolol. The reduction in diurnal IOP at month 6 from baseline in the untreated fellow eye was significant in both the latanoprost and timolol groups ($p=0.04$ and $p=0.008$ from the analyses of covariance, respectively). Latanoprost reduced diurnal IOP in the untreated fellow eye by an average of 1.2 mmHg. The corresponding number for timolol was 1.4 mmHg. The difference between groups was not statistically significant ($p=0.78$).

Intraocular pressure was monitored throughout the study, and the reduction from baseline is examined for each visit/time point (morning visits 2, 3, 4, and 5, and three exams during visit 6). IOP is reduced an average of 7.0 mmHg in the latanoprost group by visit 2, and remains fairly stable throughout the rest of the study. The difference in reduction for latanoprost versus timolol is significant at each visit and time point, ranging from a difference of -1.3 at visit 2 to -1.9 at 8:00am during visit 6. The sponsor does not adjust for multiple comparisons, however the difference is still significant at each visit and time point when one does adjust (significance is reached if the p-value is less than 0.05 / 7 = 0.007, and the p-values are 0.002, 0.002, 0.001, <0.001, <0.001, <0.001, and <0.001, respectively for visits 2, 3, 4, 5, visit 6 at 8:00am, visit 6 at 12:00pm, and visit 6 at 4:00pm).

Several safety variables were followed throughout the study. Overall, the safety profile of latanoprost appears acceptable. Among patients treated with latanoprost, there were no significant changes in systolic or diastolic blood pressure, heart rate, visual acuity, or refractive error (p-values of 0.62, 0.50, 0.36, 0.12, and 0.80, respectively). There was a significant development of conjunctival hyperemia in the latanoprost group ($p<0.001$), which was not observed in the timolol group, and the difference in maximum conjunctival hyperemia score was significant between latanoprost and timolol ($p=0.03$). However, the mean increase in maximum conjunctival hyperemia score in the latanoprost group was only 0.2 units (recall this was measured on a 0-3 scale). Only in 2 patients treated with latanoprost was the increase in conjunctival hyperemia possibly cosmetically disturbing (≥ 1.5 units). One patient treated with latanoprost had a few cells in the aqueous humour at visits 2, 3, and 4, which increased to 10 cells in each eye at visit 6. In addition, in one patient treated with latanoprost (and one treated with timolol), a deterioration in the visual field was reported as an adverse event. Latanoprost appears to have no effect on hematological, urinary, and clinical chemistry variables.

In 4 (3.1%) of the 128 patients who received latanoprost, increased pigmentation of the iris was observed. All 4 patients who exhibited this increased iris pigmentation had either green-brown or yellow-brown irides as assessed by Pharmacia staff (however, they were classified as having brown eyes by the investigators). No increase in pigmentation was observed before 4.5 months. In two of the patients, the increase in pigmentation was concentric, spreading peripherally. In the other 2 patients, the increase in pigmentation was more scattered. In no patients could any change in palpebral fissure be detected.

Ocular adverse events were reported on 36 occasions and non-ocular adverse events on 28 occasions in 26 (20%) patients out of 128 treated with latanoprost. Of the non-ocular adverse events, three cases deserve more attention: one patient experienced palpitations, and two developed maculo-papular rashes. It is not clear whether latanoprost was the causative agent. There were 8 serious adverse events, none of which appear to be related to treatment with latanoprost. In the timolol group, 24% of the patients reported ocular and non-ocular adverse events, and there were 10 serious adverse events. Twenty-six percent of the latanoprost group and 16% of the timolol group experienced non-ocular signs and symptoms which were not regarded as adverse events. Forty-nine percent of latanoprost patients and 61% of timolol patients experienced ocular signs and symptoms not regarded as adverse events. In both groups several patients exhibited punctate erosions of the corneal epithelium (17 on latanoprost and 25 on timolol). Since these were generally mild and could have been caused by the tonometry, none were reported as adverse events.

Comments

Recall that in the ITT analysis of the primary objective, change from baseline in diurnal IOP for latanoprost minus timolol, patients with missing data were treated differently than specified in the protocol. The protocol specified that for patients with missing data at month 6, the last observed value would be carried forward to estimate IOP at month 6. Instead, the baseline value was carried forward, so that for patients with missing data at month 6, the change in diurnal IOP was always specified to be 0. There were 10 patients in the latanoprost group and 10 patients in the timolol group who had missing values at

month 6. This reviewer reanalyzed the data using the method specified in the protocol (i.e., using the last observed value rather than the baseline value to estimate IOP at month 6), and found that the results are very similar. Diurnal IOP is reduced by an average of 6.33 mmHg in the latanoprost group (the value given in the sponsor's analysis is 6.15), and 4.49 mmHg in the timolol group (previously 4.34). Thus, the new difference in change from baseline of diurnal IOP between latanoprost and timolol (sample mean) is -1.84 (previously -1.81).

B. Protocol No. 9200PG005 (U.K. Study)

Methods

In this study, patients previously treated with topical β-adrenergic antagonists such as timolol were excluded from participation. More specifically, patients were excluded if they had had "treatment of elevated IOP with a topical β-adrenergic antagonist regularly or for a period longer than 3 months and/or treatment with a β-adrenergic antagonist at any time during 6 months prior to study start".

On baseline day, patients were randomly allocated to receive either timolol, 0.5%, twice daily, or latanoprost, 0.005%, once daily (latanoprost patients received placebo/vehicle in the morning and latanoprost in the evening).

Exams during visits were scheduled one hour later than in the two other studies. At baseline and the final visit, exams were conducted at 9:00am, 1:00pm, and 5:00pm. At visits 2, 3, 4, and 5, morning exams were conducted at 9:00am.

The analysis of diurnal IOP reduction in the untreated fellow eye in patients treated unilaterally was performed using an analysis of variance rather than an analysis of covariance as in the other studies. This was due to the fact that baseline IOP (the covariate used in the other studies) was only very weakly correlated with change in IOP.

Results

A total of 294 patients were enrolled in the study, and thus included in the ITT analysis (149 in the latanoprost group and 145 in the timolol group). In addition, 262 patients completed the final visit according to protocol and were included in the PP analysis (133, or 89%, in the latanoprost group and 129, or 90%, in the timolol group). Of the 32 patients excluded from the PP analysis, 26 patients were withdrawn from treatment (12 on latanoprost and 14 on timolol) and 6 had protocol violations (4 latanoprost and 2 timolol). Of the 12 patients withdrawn from treatment on latanoprost, 5 were lost to follow-up, 2 had IOP which was not controlled, 2 had ocular symptoms such as hyperemia and blurred vision, one did not instill drops for 2 months due to a myocardial infarction, one was prescribed atenolol (a systemic β-blocker) for chest pains, and one experienced shortness of breath. Of the 4 protocol violations in the latanoprost group, one patient was prescribed atenolol prior to the final visit due to chest pains, two patients did not instill morning drops on time (one not at all due to corneal epithelial changes and one not until 3:00pm which was after the noon exam), and one patient instilled drops after the morning exam from a bottle in the open-label study (Protocol 9200PG008) dispensed by the pharmacy

incorrectly.

Each center contributed 16-30 patients, except for two centers which contributed only 9 patients. There were more males than females in the study (approximately two-thirds of the patients were male). The average age was 65 years. All patients, except for 9 blacks, were Caucasian. Roughly half of the patients suffered from primary open angle glaucoma and half from ocular hypertension. Many of the glaucoma patients were newly diagnosed, while the majority of patients with ocular hypertension had exhibited increased IOP for a longer duration. Twenty-nine percent of the patients reported a family history of glaucoma or ocular hypertension. Forty patients (13.6%) were treated unilaterally, and there were more unilaterally treated patients in the latanoprost group, 18% compared to 9% for timolol. Other demographic characteristics were distributed evenly across treatment groups, however (note: this was not tested statistically). As classified by the investigator, 61% of patients had blue/green/grey eyes, 22% had hazel eyes, and 17% had brown eyes. After reclassification by the Pharmacia staff, approximately 56% had hazel eyes (29% blue/grey-brown, 25% green-brown, and 2% yellow-brown).

In the ITT analysis of the primary objective, reduction in diurnal IOP from baseline at month 6, latanoprost was found to be equivalent to timolol. Diurnal IOP was reduced from an average baseline of 25.2 mmHg by an average of 7.84 mmHg (31%) in the latanoprost group, and from an average baseline of 25.4 mmHg by an average of 7.48 mmHg (29%) in the timolol group (corresponding to an average difference of -0.36 for latanoprost minus timolol). The analysis of covariance estimated that the difference between latanoprost and timolol was -0.48. The 90% confidence interval for this difference constructed by the company is (-1.11, 0.14). The corresponding 95% confidence interval is (-1.22, 0.26). In both cases, the upper limit is well below 1.5 and hence latanoprost can be considered equivalent to timolol. Note that in this study, both intervals include 0, and thus provide no evidence that latanoprost is superior to timolol in terms of reduction in diurnal IOP.

The results of the PP analysis of the primary objective are very similar. Diurnal IOP was reduced by an average of 8.53 mmHg (34%) in the latanoprost group, and by an average of 8.37 mmHg (33%) in the timolol group (corresponding to an average difference of -0.16 for latanoprost minus timolol). The analysis of covariance estimated the difference between latanoprost and timolol was -0.32 mmHg. The 90% confidence interval for this difference constructed by the company is (-0.76, 0.13). The corresponding 95% confidence interval is (-0.85, 0.21). Again, in both cases the upper limit is well below 1.5, so latanoprost can be considered equivalent to timolol in terms of reduction in diurnal IOP.

No differences were found in average diurnal IOP reduction in patients treated with latanoprost for different sexes, age groups, ocular disease, or duration of ocular disease (p-values from the analyses of covariance of 0.30, 0.71, 0.13, and 0.10, respectively). The response to treatment with latanoprost did vary somewhat for patients with different eye color. Patients with hazel eyes responded better than patients with blue/green/grey eyes ($p = 0.006$).

Of the 20 patients who were treated unilaterally with latanoprost and completed the study and the 10 patients treated unilaterally with timolol who completed the study, the average diurnal IOP reduction in the untreated fellow eye was 1.2 and 3.0 mmHg, respectively.

Both reductions were significant ($p = 0.02$ and $p < 0.001$, respectively). The difference in reduction between the two groups was also significant ($p = 0.046$).

Reduction from baseline in IOP was monitored throughout the study, and is examined for each visit/time point (morning visits 2, 3, 4, and 5, and three exams during visit 6). IOP is reduced an average of 8.6 mmHg in the both treatment groups by visit 2 (2 weeks), and fluctuates only slightly throughout the rest of the study. The sponsor states that the difference in reduction for latanoprost is significantly better than timolol at visits 4 and 5 (3 and 4.5 months of treatment), $p = 0.04$ and $p < 0.001$, respectively. After adjusting for multiple comparisons, however, only the difference at visit 5 is significant (significance is reached if the p-value is less than 0.05 / 7 = 0.007).

Overall, the safety profile of latanoprost appears acceptable. In both treatment groups there was a statistically, but not clinically, significant reduction in systolic and diastolic blood pressure. In the latanoprost group, systolic blood pressure was reduced by 3.5 mmHg ($p = 0.02$) and diastolic blood pressure was reduced by 2.8 mmHg ($p < 0.001$). The differences between the treatment groups were not significant ($p = 0.97$ for systolic and $p = 0.82$ for diastolic). The sponsor suggests that these decreases more likely reflect an adaptation of the patients to the blood pressure measuring procedure than a drug-induced effect, which seems reasonable. The increase in maximum conjunctival hyperemia score was significant in the latanoprost group ($p < 0.001$), but not in the timolol group ($p = 0.65$). The difference between the two groups was significant ($p < 0.001$). The sponsor emphasizes that only in 3% of latanoprost patients was the increase in hyperemia 1.5 units, regarded as mild-moderate. The mean maximum hyperemia for latanoprost patients changed from 0.28 units at baseline to 0.46 units at the final visit (recall hyperemia was graded on a scale of 0-3). Slight aqueous flare was detected in 1 latanoprost patient, and a few cells were detected in the aqueous humor of two other latanoprost patients. A statistically, but not clinically, significant change in visual acuity was noticed in both treatment groups (latanoprost patients went from an average of 1.0 at baseline to an average of 1.03 at 6 months, $p = 0.01$; timolol patients went from an average of 0.93 to an average of 0.96, $p = 0.01$; and the difference in change from baseline was not statistically different for latanoprost vs. timolol, $p = 0.73$). No other changes were noted in the latanoprost group.

Of the 149 patients in the latanoprost group, increased pigmentation of the iris was diagnosed or suspected in 15 patients (10.1%). Two patients in the timolol group were also suspected of having a change in eye color, but it was later determined that these were likely both false positives. Of the latanoprost patients who exhibited an increase in iris pigmentation, according to the investigator classification of eye color, 2 had blue/green/grey eyes, 7 had hazel eyes, and 6 had brown eyes. According to the Pharmacia classification, all 15 patients had hazel eyes (3 blue/grey-brown and 12 green-brown).

Fifty-three patients (36%) treated with latanoprost reported adverse events. The number for timolol was 50 (34%). Of the adverse events in the latanoprost group, 14 cases of conjunctival hyperemia, 2 cases of increased iris pigmentation, 13 cases of punctate epithelial erosions (19 cases were reported overall, but only 13 were considered adverse events; 10 timolol cases were reported, 4 of which were considered adverse events), 1

case of a microcystic epithelial change, 1 case of couplet beats of the heart, 2 cases of shortness of breath, 2 cases of central nervous system symptoms such as lethargy and blackout, and 3 cases of mild-moderate increases in liver enzymes were reported. The adverse event profile of timolol was similar. Nine serious adverse events were reported in 8 patients (4 events in the latanoprost group and 5 events in the timolol group). Of the 4 events in the latanoprost group, one patient experienced chest pain and another had a myocardial infarction, one patient had a retinal detachment, and one had external carotid stenosis. None of the serious adverse events in either group were considered to be related to treatment. Fifty-two percent of latanoprost patients reported ocular symptoms not considered to be adverse events, as did 48% of the timolol group. As for non-ocular symptoms not considered to be adverse events, 28% of latanoprost patients and 32% of timolol patients experienced some.

Comments

Recall that in the ITT analysis of the primary objective, change from baseline in diurnal IOP for latanoprost minus timolol, patients with missing data were treated differently than specified in the protocol. The protocol specified that for patients with missing data at month 6, the last observed value would be carried forward to estimate IOP at month 6. Instead, the baseline value was carried forward, so that for patients with missing data at month 6, the change in diurnal IOP was always specified to be 0. There were 11 patients in the latanoprost group and 9 patients in the timolol group who had missing values at month 6. This reviewer reanalyzed the data using the method specified in the protocol (i.e., using the last observed value rather than the baseline value to estimate IOP at month 6), and found that the results are very similar. Diurnal IOP is reduced by an average of 8.34 mmHg in the latanoprost group (the value given in the sponsor's analysis is 7.84), and 7.93 mmHg in the timolol group (previously 7.48). Thus, the new difference in change from baseline of diurnal IOP between latanoprost and timolol (sample mean) is -0.41 (previously -0.36).

C. Protocol No. 9200PG006 (Scandinavian Study)

Methods

The study design was slightly different in Protocol 9200PG006. On baseline day, patients were randomly allocated to one of three treatment groups. One group received timolol, 0.5%, twice daily, and two groups received latanoprost, 0.005%, once daily. The main objective of this study was the same as in the other two: to determine whether latanoprost was equivalent to timolol in terms of diurnal IOP reduction at 6 months. An additional secondary objective, unique to this study, was to determine whether morning and evening administration of latanoprost were equivalent in terms of diurnal IOP reduction. In order to address this secondary objective, the sponsor utilized a cross-over design in the two latanoprost treatment arms (treatment on timolol remained as in the previous two studies). In latanoprost group 1, patients received active drug in the morning and placebo in the evening for the first three months, and then switched to active drug in the evening and placebo in the morning for the remaining three months. In latanoprost group 2, the order was reversed with patients receiving active drug in the evening and placebo in the morning for the first half of the study and then active drug in the morning

and placebo in the evening for the second half. Note that there was no wash-out period in between switching latanoprost patients from morning to evening administration, and vice-versa. The sponsor does not explain why this was left out of the design. One could argue that a wash-out period would unfairly bias results against latanoprost as there is no wash-out period, or time off drug, in the timolol group. Dr. Carreras, the reviewing medical officer, states that any drug left in the system after the first half of the study would be gone in several days. Since the first IOP measurements after switching from morning to evening administration, and vice-versa, are not taken until 1.5 months has elapsed, there should be no carry-over effect. In fact, the sponsor tests for such an effect and does not find one.

The question of whether the IOP-reducing effect of latanoprost administered in the morning is equivalent to that of latanoprost administered in the evening was assessed using a PP analysis. All patients with diurnal IOP measurements at both months 3 and 6 were included (in this study there were 3 exams conducted at the month 3 visit, one at 8:00am, one at 12:00pm, and one at 4:00pm). Analysis of variance was used to estimate the difference in diurnal IOP reduction from baseline for morning minus evening administration of latanoprost. The original model included treatment sequence (i.e., group 1 versus group 2), patient within sequence, period, and treatment (i.e., morning versus evening administration). Treatment sequence and period are not significant ($p = 0.27$ and $p = 0.19$, respectively), thus the final model included only patient and treatment (morning/evening). A two-sided 90% confidence interval was constructed for the difference in diurnal IOP reduction from baseline between the two groups at month 3. If the confidence interval was within the limits ± 1.5 mmHg, then the two groups were to be considered equivalent. In the Results section below, 95% confidence intervals are constructed and compared to the 90% confidence intervals provided by the sponsor. If the two groups were considered equivalent, then they were to be combined (treated as one group) in the analysis of the primary objective, the comparison of latanoprost with timolol. Otherwise, the two groups were to be compared separately to timolol.

The protocol specified that patients would be randomized in equal numbers to latanoprost and timolol. Inclusion of 260-300 patients was planned, with 130-150 in the timolol group and 65-75 in each latanoprost group. Allowing for withdrawals, if 111 patients completed the study on each treatment (latanoprost and timolol), the trial would have 80% power to detect equivalence between treatments, assuming that the true difference between treatments was no more than 0.5 mmHg (in favor of timolol), and that the standard deviation in IOP reduction was 3.0 mmHg. By mistake, patients were actually randomized in equal numbers to each of the three treatment groups (timolol, latanoprost group 1, and latanoprost group 2), increasing the power to test equivalence of morning and evening administration of latanoprost but decreasing the power to test equivalence of latanoprost and timolol. This was not detected until after the study when the blind was broken. However, since more patients completed the study than were expected, the power with the sample sizes actually obtained remained about the same (I checked and found it to be 79%).

In this study, patients previously treated with topical β-adrenergic antagonists such as timolol were excluded from participation. More specifically, patients were excluded if they had had "treatment of elevated IOP with any topical β-adrenergic antagonist regularly for a

period longer than 3 months and/or treatment at any time during 6 months prior to study start".

The analysis of diurnal IOP reduction in the untreated fellow eye in patients treated unilaterally was performed using an analysis of variance rather than an analysis of covariance as in the other studies. This was due to the fact that baseline IOP (the covariate used in the other studies) was only very weakly correlated with change in IOP.

Results

A total of 267 patients were enrolled in this study, and all were included in the ITT analysis. Of these, 248 patients (84, or 94%, in latanoprost group 1; 85, or 90%, in latanoprost group 2; and 79, or 94%, on timolol) completed the study according to protocol and were included in the PP analysis of the primary objective. Of the 19 patients excluded from the PP analysis, 14 were withdrawn from treatment (4 in latanoprost group 1, 6 in latanoprost group 2, and 4 on timolol) and 5 had protocol deviations (1 in latanoprost group 1, 3 in latanoprost group 2, and 1 in the timolol group). Of the 10 latanoprost treatment withdrawals, 1 was due to IOP not being controlled, 1 experienced increased iris pigmentation, 2 dropped out due to information about increased iris pigmentation in other patients, 1 had repeated corneal erosions, 1 experienced a burning sensation in the tongue, 1 had an embolus of the retinal artery, 1 had central retinal vein thrombosis, 1 had cancer, and 1 experienced decreased visual acuity probably due to diabetes. Of the 4 latanoprost protocol deviations, 1 used systemic β-adrenergic medication between weeks 18 and 26, 2 did not receive medication after the morning exam at the final visit, and 1 completed the study too early.

Of the 13 centers in this study, each contributed approximately 20-30 patients, with the exception of 3 centers that contributed 5, 10, and 15 patients, respectively. Demographic characteristics were similar across treatment groups (note: this was not tested statistically). Slightly more females than males were included (approximately 57%). The average age was 66.5 years. All patients, except for one of Indian origin, were Caucasian. About 35% of the patients reported a family history of glaucoma. Approximately half of the patients suffered from primary open angle glaucoma, and half from ocular hypertension. Of the POAG sufferers, 32% were diagnosed with exfoliation glaucoma, 67% with simplex glaucoma, and one patient with pigmentary glaucoma. Many of the patients with glaucoma were newly diagnosed, whereas most of the patients with ocular hypertension had experienced increased IOP for a long time (an average of 33 months). Of the 267 patients, 36% were treated unilaterally. Eye color was classified by the investigators as blue/green/grey for 85% of the patients, hazel for 7%, and brown fo 8%. After reclassification by Pharmacia staff, 71% were considered to have blue/green/grey eyes, 26% hazel eyes, and 3% brown eyes.

In the ITT analysis of the primary objective, reduction in diurnal IOP from baseline at month 6, the latanoprost groups were pooled (see below) and found to be superior to timolol. Diurnal IOP was reduced from an average baseline of 25.1 mmHg by an average of 7.72 mmHg (31%) in the pooled latanoprost group, and from an average baseline of 24.6 mmHg by an average of 6.36 mmHg (26%) in the timolol group (corresponding to an average difference of -1.37 for latanoprost minus timolol). The analysis of covariance estimated

that latanoprost was superior to timolol by 1.27 mmHg. The 90% confidence interval for this difference constructed by the company is (-1.93, -0.60). The corresponding 95% confidence interval is (-2.07, -0.47). In both cases, the upper limit is well below both 1.5 and 0, so latanoprost is statistically superior to timolol in terms of reduction in diurnal IOP. The results of the PP analysis of the primary objective are very similar. Diurnal IOP was reduced by an average of 8.03 mmHg (32%) in the latanoprost group, and by an average of 6.43 mmHg (26%) in the timolol group (a difference of -1.59). The analysis of covariance estimated that latanoprost was superior to timolol by 1.23 mmHg. The 90% confidence interval for this difference constructed by the company is (-1.78, -0.69), and the 95% confidence interval is (-1.88, -0.58). Again, in both cases the upper limit is well below both 1.5 and 0, so latanoprost is statistically superior to timolol in terms of reduction in diurnal IOP.

One of the secondary objectives in this study was to determine whether morning and evening administration of latanoprost are equivalent. If they were considered equivalent after 3 months, then the data was to be pooled in the analysis of the primary objective, diurnal IOP reduction at 6 months. Since IOP seems to drop fairly quickly after treatment is initiated and then stay level for the remainder of the trial (most of the reduction is accomplished by 2 weeks in the Phase III studies), this approach seems reasonable. After 3 months of morning administration of latanoprost, the mean diurnal IOP reduction from baseline was 7.6 mmHg. With evening administration it was 8.7 mmHg. The least squares estimate of the difference between morning and evening administration of latanoprost (morning minus evening) is 1.06 mmHg, with a corresponding 90% confidence interval of (0.80, 1.32). Since this confidence interval falls within the limits ± 1.5 mmHg, the two treatments are considered equivalent according to the sponsor's definition in the protocol and pooled in the analysis of the primary objective, discussed above. The 95% confidence interval for the difference is (0.74, 1.37), which still falls within the protocol-defined limits. Note, however, that both confidence intervals lie entirely above 0, suggesting that evening administration of latanoprost is actually statistically superior to morning administration. This is further supported by looking at the average IOP reduction (7.4 mmHg for morning administration and 9.0 mmHg for evening administration) of all latanoprost patients with IOP measurements at month 3 (recall that the previous analysis includes only patients with measurements at both months 3 and 6). In this case, the difference between morning and evening administration is 1.6 mmHg, which lies outside the specified limits of ± 1.5. Thus, it is important to look at how the individual latanoprost administrations compare to timolol. The reduction in diurnal IOP with evening administration of latanoprost is statistically superior to timolol at 3 and 6 months of treatment ($p = 0.001$, $p < 0.001$, respectively). However, there is no significant difference between morning administration of latanoprost and timolol at 3 and 6 months ($p = 0.54$, $p = 0.08$, respectively).

No statistically significant difference in response to treatment with latanoprost, as measured by IOP reduction, was found in different sexes, subgroups of disease, variable duration of ocular disease, or eye color (p-values for the pooled latanoprost group of 0.60, 0.99, 0.82, and 0.73, respectively). The difference in IOP reduction was significant in the latanoprost 2 group for different age groups, with IOP reduction in the 60-<70 year old group being significantly less than in the <60 year and ≥70 year age groups (a difference of 1.5 in both comparisons and p-values of 0.04 and 0.01, respectively). No such

difference was observed in the latanoprost 1 group ($p = 0.95$) or in the pooled latanoprost group ($p = 0.13$). If we account for multiple comparisons (in this case we are looking at 5 different subgroups, and often more than 1 comparison within each subgroup), then the difference in response according to age in latanoprost group 2 is no longer significant.

Response to treatment was similar across centers. In addition, at all centers, evening administration of latanoprost produced larger reductions in IOP than morning administration. Diurnal IOP was slightly, but significantly ($p = 0.01$), reduced from baseline after 6 months in the untreated fellow eyes of the timolol group. There was no significant reduction in the untreated latanoprost eyes (pooled group $p = 0.07$). IOP reduction in the untreated fellow eye was not significantly different between the latanoprost and timolol groups ($p = 0.29$).

Overall, the safety profile of latanoprost appears acceptable. There was a slight decrease in systolic blood pressure, diastolic blood pressure, and heart rate in all treatment groups (which, as suggested in the U.K. study, could be due to patients' adaptation to the measuring procedures). For systolic pressure, this decrease was statistically significant in the latanoprost 2 and pooled latanoprost groups ($p = 0.048$ and $p = 0.04$, respectively). The decrease was not significant in the latanoprost 1 group ($p = 0.34$) and was marginally significant in the timolol group ($p = 0.055$). For diastolic pressure, the reduction was significant in the latanoprost 1 group ($p = 0.02$), marginally significant in the pooled latanoprost group ($p = 0.051$), and not significant in the latanoprost 2 or timolol groups ($p = 0.68$, $p = 0.34$, respectively). For heart rate, the reduction was significant in the pooled latanoprost group ($p = 0.04$) and highly significant in the timolol group ($p < 0.001$; perhaps the only real clinical change observed in blood pressure and heart rate). In the latanoprost 1 and 2 groups it was not significant ($p = 0.12$ and $p = 0.17$, respectively). None of the differences between treatment groups were significant.

In all latanoprost treatment groups, the increase in maximum conjunctival hyperemia at 6 months was significant ($p = 0.02$ for group 1, $p = 0.01$ for group 2, and $p < 0.001$ for the pooled group). In the timolol group, it was not ($p = 1.0$). No aqueous flare was detected in any of the patients, and only 1 latanoprost patient presented with cells in the aqueous humor (1 cell was observed at the 4:00pm exam of the 3 month visit). There was no change in visual acuity, refractive error, visual field, or optic nerve head in latanoprost patients, and in a general examination of the eye no pathological changes were seen in any of the tissues examined. In addition, latanoprost had no apparent effect on hematology, clinical chemistry values, or urinary analysis.

Increased iris pigmentation occurred in 12 of the 183 patients who received latanoprost (6.6%). Of these 12 patients, 9 were considered to have green-brown eyes and 3 blue/grey-brown eyes, as classified by Pharmacia staff. According to the investigators' classification, however, 3 had blue/green/grey eyes, 5 had hazel eyes, and 4 had brown eyes. The increase in pigmentation was seen after 3-6 months of treatment, and there was no consistent pattern in where the iris pigmentation increased. *There was one odd development, which should be noted. Patient #116, in latanoprost group 1, was only treated in the left eye, but an increase in iris pigmentation was observed in both eyes (increase in iris pigmentation was classified as "suspected" in both eyes at month 3, and "definite" in both eyes at month 4.5). The patient was classified as having "hazel" eyes*

by the investigator, and as having "blue/grey and brown" eyes by Pharmacia staff. This event is not discussed anywhere in the reports by Pharmacia. However, I can imagine two possible explanations for the occurrence, the first being that the increase in iris pigmentation was a false-positive in the non-study eye and the second being that the patient actually administered drops in both eyes, even though only the left eye qualified as a study eye. If neither of these is true, then one must assume that enough drug entered the system to produce such a reaction in the untreated study eye.

Adverse events occurred in 24% of patients in latanoprost group 1, 26% of patients in latanoprost group 2, and 24% of timolol patients. In latanoprost group 1, 3 of the adverse events were rash or allergy, in which a causal relationship could not be determined. There were also 3 cases of increased iris pigmentation, 2 cases of conjunctival hyperamia, 1 vitreous detachment with retinal tear, 1 very mild epithelial haze with blurred vision and a sticky tear film in the right eye, and several cases of irritation of the eye. In the latanoprost 2 group, there was 1 case of skin allergy, 1 case of eczema in the hand of unknown etiology, 2 cases of increased iris pigmentation, 1 corneal erosion, and 4 cases of eye irritation. Non-ocular signs and symptoms, not regarded as adverse events, were reported in 19% of latanoprost and 21% of timolol patients. Ocular signs and symptoms, not regarded as adverse events, were reported in 30% of the latanoprost and 24% of the timolol group. Approximately twice the number of latanoprost, as compared to timolol, patients experienced conjunctival hyperemia, stinging, burning, itching, foreign body sensation, and tearing. In addition, 10 latanoprost patients had punctate epithelial erosions, compared to only 1 timolol patient. The sponsor claims that the high number of punctate epithelial erosions may be due to the fact that latanoprost patients are overdosed 100% with benzalkonium chloride, a component of both the latanoprost and vehicle drops, and that this problem would lessen with once daily administration of latanoprost (as is intended if the drug is approved). Sixteen serious adverse events were reported in 13 patients (14 events in 11 (6%) latanoprost patients and 2 events in 2 (2%) timolol patients). Of these events, 2 (cardiac arrhythmia and sudden visual field loss due to an arterial embolus) were considered possibly related to treatment with latanoprost by the investigator, as was 1 (retinal branch vein occlusion) in the timolol group.

<u>Comments</u>

Recall that in the ITT analysis of the primary objective, change from baseline in diurnal IOP for latanoprost timolol, patients with missing data were treated differently than specified in the ol. The protocol specified that for patients with missing data at month 6, the last observed value would be carried forward to estimate IOP at month 6. Instead, the baseline value was carried forward, so that for patients with missing data at month 6, the change in diurnal IOP was always specified to be 0. There were 8 patients in the combined latanoprost group (3 in latanoprost group 1 and 5 in latanoprost group 2) and 2 patients in the timolol group who had missing values at month 6. This reviewer reanalyzed the data using the method specified in the protocol (i.e., using the last observed value rather than the baseline value to estimate IOP at month 6), and found that the results are very similar. Diurnal IOP is reduced by an average of 8.08 mmHg in the combined latanoprost group (the value given in the sponsor's analysis is 7.72), and 6.55 mmHg in the timolol group (previously 6.36). Thus, the new difference in change from baseline of diurnal IOP between latanoprost and timolol (sample mean) is -1.53 (previously -1.37).

D. Interim Results (Protocols 9200PG008, 9200PG009, and 9200PG010)

At the end of Protocols 9200PG004, 9200PG005, and 9200PG006, patients who had been treated for 6 months with latanoprost were given the option to continue another 6 months on latanoprost in an open-label study (Protocol 9200PG008 in the U.K., Protocol 9200PG009 in Scandinavia, and Protocol 9200PG010 in the U.S.). The main purpose of the open-label continuation was to collect information on safety. Efficacy information is given, but it is important to remember when attempting to draw conclusions about efficacy that all patients in the open-label study completed 6 months of treatment with latanoprost successfully and thus are a select group.

The interim report summarized here presents data on all patients treated with latanoprost for 1 year. In the open-label phase, patients took latanoprost once daily (there was no placebo drop), and were allowed to administer the drug in the morning or evening, as they wished. Notes were kept in the CRF's of whether administration was in the morning or evening. Investigators were also allowed to add timolol, 0.25% or 0.5%, once or twice daily, as needed. This had to be clearly indicated in the CRF's.

Out of a total of 273 patients who were enrolled in the 3 Phase III controlled clinical trials by April 30, 1993 and could have been treated for 1 year with latanoprost, 198 (73%) successfully completed the 12 months of treatment. Of the 75 patients who failed to complete 1 year of treatment, 15 were withdrawn due to increased iris pigmentation and 13 dropped out due to information about increased iris pigmentation in other patients. Seventeen patients were simply unwilling to continue into the open-label phase of the study, and 6 were lost to follow-up (most moved). Three patients had IOP which was not controlled. The remainder either had ocular symptoms (8), non-ocular symptoms (9), their center withdrew from the study due to information about increased iris pigmentation in patients (2), or they were prescribed a systemic β-blocker (2).

Approximately half of the patients who continued into the open-label continuation phase were female. The average age was 65.7 years. Ninety-one percent of the patients were Caucasian, 7% were black, and 2% were hispanic. Approximately half of the patients suffered from glaucoma and half from ocular hypertension. About 1/4 of the patients had a family history of glaucoma and/or ocular hypertension. Eye color, as classified by the investigator, was blue/green/grey for 67% of patients, hazel for 11%, and brown for 22%. As classified by Pharmacia staff, it was hazel (blue/grey-brown, green-brown, or yellow-brown) for 35%, blue/grey/green for 52%, and brown for 13%.

Diurnal IOP was reduced from an average baseline of 25.3 mmHg by an average of 8.1 mmHg after 6 months of treatment, and by an average of 7.9 mmHg after 12 months of treatment (including 12 (6%) patients who needed additional treatment with timolol; if these patients are removed from the analysis, the average reduction after 12 months is approximately the same, 7.8 mmHg). IOP reduction at 6 and 12 months was not statistically significantly different ($p = 0.32$) when all 3 protocols are considered together. However, in the U.K. study, latanoprost reduced diurnal IOP by an average of 8.5 mmHg at 6 months and by an average of 7.7 mmHg at 12 months, and the difference is statistically significantly different ($p = 0.007$). No difference was seen in the U.S. or Scandinavian studies ($p = 0.45$ and $p = 0.18$, respectively). More patients instilled latanoprost in the

morning during the last 6 months of treatment, compared to the first 6 months of treatment, which could possibly account for the difference found in the U.K. study (those patients received latanoprost in the evening for the first 6 months, and evening administration appears superior to morning administration; note, however, that no such difference was found in the U.S. study). In the U.K. study, 0% of patients received morning administration during the first 6 months, as opposed to 65% during the last 6 months. In the U.S. study, 0% received morning administration during the first 6 months and 62% received morning administration during the last 6 months. In the Scandinavian study, 51% administered latanoprost in the morning during the first 6 months, and 68% did so during the last 6 months.

No major changes in the IOP of untreated fellow eyes were observed during the course of the study. There also appeared to be no difference in response to treatment with latanoprost, as measured by IOP reduction, in different genders, age groups, races, eye colors, subgroups of ocular disease, duration of ocular disease, or pre-study treatment with glaucoma medication (this was not formally tested, however).

There was a statistically, but not clinically, significant reduction in systolic blood pressure (averages of 147.9 mmHg at baseline, 143.5 mmHg at month 6, and 144.2 mmHg at month 12), diastolic blood pressure (averages of 85.4 mmHg at baseline, 83.5 mmHg at month 6, and 84.0 mmHg at month 12), and heart rate (averages of 74.5 beats/minute at baseline, 73.3 beats/minute at month 6, and 72.3 beats/minute at month 12).

The mean maximum conjunctival hyperemia score for all patients was 0.26 at baseline, 0.48 at 6 months, and 0.37 at 12 months. The difference between months 6 and 12 was statistically significant ($p=0.03$). This difference could be seen individually in the U.K. study ($p=0.005$), but not in the U.S. ($p=0.19$) or Scandinavian ($p=0.90$) study. Only 3 patients exhibited conjunctival hyperemia scores of 2 (on a scale of 0-3) at 6 or 12 months of treatment. Slight aqueous flare was detected in 3 patients, and cells were detected in the aqueous humor in 10 patients (in 2 of these patients, the cells were present at baseline). There were 7 patients with a significant drop in visual acuity, with 6 of these cases being probably due to other ocular disease. In one patient, a deterioration in the visual field was reported, probably due to an increasing retinal edema and proliferative diabetic retinopathy with vitreous hemorrhage. No changes were found in the optic nerve head or any eye tissues.

Increased iris pigmentation occurred in 33 (15.4%) patients out of 214 (198 who were treated for 12 months, plus 14 who were withdrawn due to increased iris pigmentation and 2 who dropped out and were later found to have increased pigmentation). Using the Pharmacia classification system, 18.4% of patients treated with latanoprost with blue/grey-brown eyes experienced increased iris pigmentation, 57.9% of patients treated with latanoprost with green-brown eyes experienced increased iris pigmentation, and 37.5% of patients treated with latanoprost with yellow-brown eyes experienced increased iris pigmentation.

Serious adverse events occurred in 11 patients, none of which were believed to be causally related to latanoprost use. The significant events were vitreous hemorrhage in 1 patient and chest pain/angina in 2 patients. As for non-serious adverse events, there were

very few in the U.S. (the one significant event was hematuria in one patient at the month 6 visit). In the U.K., 5 cases of increased iris pigmentation, 5 cases of corneal punctate epithelial erosions, and 6 cases of conjunctival hyperemia were reported as adverse events. Other events included 1 corneal limbal infiltrate, 1 posterior vitreous detachment, 1 case of thrombocytopenia, 1 hematuria, and 1 case of change in refraction. In the Scandinavian study, 1 case of increased iris pigmentation, 1 increase in liver enzymes, 1 increase in bilirubin, 2 cases of chest pain/angina, 1 case of keratoconjunctivitis, and 1 case of transient corneal epithelial haze were reported.

E. Integrated Summary of Safety

A total of 890 patients who suffer from either glaucoma or ocular hypertension have been exposed to latanoprost for periods ranging from 2 days to 1 year. Of these, 5.1% were withdrawn before the endpoint of interest. In the Phase III clinical trials the corresponding figure is 7.0%. For patients who continued into the open-label Phase III studies, 27.5% withdrew before the end of treatment. The major contributing factor for the high withdrawal rate in the 12 year treatment patient cohort was increased pigmentation of the iris, or information about such events.

The three most common ocular adverse events in the patients treated for 6 months with latanoprost in the Phase III studies were increased pigmentation of the iris (6.7%), conjunctival hyperemia (3.9%), and punctate epithelial erosions (2.8%). The most common ocular symptoms in the latanoprost group were stinging (8.9%), foreign body sensation (8.0%), punctate epithelial erosions (6.7%), burning (6.3%), itching (5.9%), blurred vision (5.7%), and conjunctival hyperemia/redness (4.1%). In some cases, there were fewer timolol patients with these ocular symptoms (foreign body sensation and conjunctival hyperemia), but in most cases the timolol patients actually had a slightly higher percentage of symptoms (stinging, burning, itching, and blurred vision).

The average maximum conjunctival hyperemia score was 0.37 at baseline, 0.51 at 6 months, and 0.45 at 12 months for all patients treated with latanoprost during Phase III trials. Of the 431 patients treated with latanoprost for 6 months, 65% experienced no increase in maximum conjunctival hyperemia score, 28% experienced an increase of 0.5 units, 6% experienced an increase of 1.0 unit, and 1% experienced an increase of ±1.5 units. For the timolol patients, the corresponding percentages were 78%, 19%, 3%, and 0.3%.

Of 429 patients who completed 6 months of treatment during Phase III trials, 7.2% experienced an increase in iris pigmentation, none of which either lessened or reversed with time. Of patients who were "pre-disposed" to this condition (i.e., had hazel eyes using Pharmacia's classification system), the incidence rate was 16.3%. There was no difference in outcome according to age. However, more males than females were affected (20.6% versus 11.4% of pre-disposed patients). In addition, a higher percentage of patients with green-brown eyes, versus blue/grey-brown or yellow-brown eyes, were affected (57.9% of patients with green-brown eyes, 18.4% of patients with blue/grey-brown eyes, and 37.5% of patients with yellow-brown eyes). *One concern is whether practicing ophthalmologists will be able to recognize "blue/grey-brown", "green-brown", and "yellow-brown" irides in order to determine which patients are at risk for increased iris*

pigmentation if treated over a longer period of time with latanoprost. Of the 45 patients who experienced an increase in iris pigmentation, only 21 were classified by the investigators as having "hazel" eyes (6 were thought to have blue/green/grey eyes and 18 to have brown eyes).

The percentages of latanoprost and timolol patients, respectively, reporting symptoms and events for various body systems is as follows: cardiovascular system (2.6% and 3.0%), respiratory system (3.3% and 5.7%), infections (13.5% and 11.1%), gastrointestinal system (2.6% and 3.8%), reproductive/urinary system (1.5% and 2.2%), central nervous system (8.5% and 12.5%), skin/allergy (5.0% and 2.7%), musculo-skeletal system (6.1% and 4.9%), and "other" symptoms (5.6% and 5.1%). None of these system differences were statistically significant (all p-values > 0.064). However, slightly more timolol patients experienced headache/migraine (7% compared to 3.5% for latanoprost; this is statistically significant, p = 0.027), which falls under the central nervous system. Also, slightly more latanoprost patients experienced dysfunction/pain in muscle/joint/back (6.1% compared to 4.3% for timolol; this is not statistically significant, p = 0.24), which is part of the musculo-skeletal system.

No deaths occurred during the clinical trials with latanoprost (Phase I through III, including the interim report). However, 5 deaths occurred during the extension of the Phase III clinical trials (that is, during either Protocol 9200PG008, 9200PG009, or 9200PG010, but after the interim report): 3 myocardial infarctions, 1 stroke, and 1 lung cancer. The sponsor states that these will be reported separately in the extended Phase III clinical trial reports which will be submitted to the FDA as a supplement to the NDA. The medical officer will have to determine if this is acceptable, however I note that the patient population being studied is fairly old (the average age in the latanoprost cohort that continued into the extension phase was 65.7 years old), and the safety profile probably reflects this.

IV. CONCLUSIONS (Which May be Conveyed to the Sponsor)

1. Latanoprost appears to be as effective as timolol in reducing diurnal IOP in patients with both primary open angle glaucoma and ocular hypertension. In fact, when administered in the evening, latanoprost appears statistically superior to timolol. Whether this difference is clinically relevant will have to be determined by the reviewing medical officer.

These conclusions are supported by data from the 3 Phase III trials, the U.S. study, the U.K. study, and the Scandinavian study. The U.S. study shows that evening administration of latanoprost is statistically superior to timolol, with a 95% confidence interval for the difference in average diurnal IOP reduction after 6 months of treatment for latanoprost minus timolol (using the per protocol group of patients) of (-2.23, -0.93). The corresponding confidence interval for the U.K. study is (-0.85, 0.21), suggesting that evening administration of latanoprost is equivalent to timolol in reducing diurnal IOP. However, if the two studies are combined they support the conclusion that evening administration of latanoprost is statistically superior to timolol with a 95% confidence interval of (-1.51, -0.41). The Scandinavian study is somewhat different from the first two as it used a cross-over design to compare morning and evening administration of latanoprost. Treatment on timolol remained the same. Evening administration of

latanoprost is statistically superior to morning administration of latanoprost in reducing diurnal IOP at both the 3 and 6 month visit ($p = 0.008$ and $p = 0.002$, respectively). Evening administration of latanoprost is also statistically superior to timolol in reducing diurnal IOP at the 3 and 6 month visit ($p = 0.001$ and $p < 0.001$, respectively). Morning administration of latanoprost is equivalent to timolol in reducing diurnal IOP at the 3 and 6 month visit ($p = 0.54$ and $p = 0.08$, respectively).

2. No difference in response to latanoprost, as measured by IOP reduction, was observed in any of the following subgroups in the U.S. study: gender, race, age, eye color, ocular disease (POAG versus ocular hypertension), or duration of ocular disease. In the U.K. study, patients with hazel eyes responded better than patients with blue/green/grey eyes ($p = 0.006$), but no other subgroup differences were observed. In the Scandinavian study, no significant subgroup differences were observed when all latanoprost patients are considered together. However, when considering patients in the latanoprost group that received evening administration for the first 3 months and morning administration for the second 3 months, patients aged 60-69 were observed to respond less well than patients either < 60 years or ≥ 70 years of age ($p = 0.04$ and $p = 0.01$, respectively). The significance of the difference in response according to age is probably just a result of multiple comparisons (i.e., if we look at enough subgroups, eventually we will see a difference due to chance variablility alone) since it is not replicated in the other latanoprost group, and hence is most likely not clinically relevant.

3. Safety on latanoprost appears acceptable, and similar to timolol with a few exceptions, the most marked being the increase in iris pigmentation observed in certain latanoprost patients. The three most common ocular adverse events in the patients treated for 6 months with latanoprost in the Phase III studies were increased pigmentation of the iris (6.7%), conjunctival hyperemia (3.9%), and punctate epithelial erosions (2.8%).

Increased iris pigmentation was observed in 7.2% of Phase III latanoprost patients, and in 16.3% of Phase III latanoprost patients with hazel eyes (as defined by Pharmacia staff -- there is some concern whether clinicians will be able to pick out such "hazel" eyes). More males than females with hazel eyes experienced this increased iris pigmentation (20.6% versus 11.4%). In addition, a higher percentage of patients with green-brown eyes, versus blue/grey-brown or yellow-brown eyes, were affected (57.9% versus 18.4% and 37.5%, respectively).

RECOMMENDED REGULATORY ACTION:

The data from 3 Phase III controlled, clinical trials (Protocol 9200PG004 in the U.S., Protocol 9200PG005 in the U.K., and Protocol 9200PG006 in Scandinavia) statistically support the conclusion that latanoprost is equivalent to timolol in reducing diurnal IOP in patients with primary open angle glaucoma and ocular hypertension. In fact, evening administration of latanoprost appears statistically superior to timolol, in terms of reducing diurnal IOP. Whether this difference is clinically relevant will have to be determined by the reviewing medical officer.

Safety of latanoprost is acceptable. However, patients should be cautioned about the possible increase in iris pigmentation with extended use of latanoprost.

Nancy Paul Silliman, Ph.D.
11/28/95

Nancy Paul Silliman, Ph.D.
Biomedical Statistician, Biometrics IV

Nov 28, '95

Concur: Rajagopalan Srinivasan, Ph.D.
Acting Team Leader, Biometrics IV

Ralph Harkins, Ph.D
11/28/95

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Acting Division Director, Biometrics IV

cc:
Archival: NDA #20-597
HFD-540
HFD-540/Dr. Wiley Chambers
HFD-540/Dr. Tony Carreras
HFD-540/Kennerly Chapman
HFD-701/Dr. Anello
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Dr. Silliman
HFD-344/Dr. Pierce
Chron.
This review contains 23 pages.

JAN 16 1996

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-597	**SUBMISSION DATE:** 6/16/95
PRODUCT: Latanoprost Sterile Ophthalmic Solution	
BRAND NAME: XALATAN™	**REVIEWER:** Dan Wang, Ph.D.
SPONSOR: Pharmacia Inc.	
7001 Post Road	**TYPE OF SUBMISSION:** Original
Dublin, OH 43017	**CATEGORY:** 1 P , NME

SYNOPSIS

This submission consists of 5 study reports (three human pharmacokinetics studies). The applicant has adequately studied the absorption, excretion and metabolism of latanoprost (PhXA41). It was found that (^{3}H)-PhXA41 and its metabolites were rapidly absorbed following ocular administration of 3 μg/volunteer. An estimated 77% of the dose entered the systemic circulation. Renal elimination represented the major route of elimination (87.88 ± 6.41%) with the remainder recovered in faeces (15.31 ± 3.56%). *In vivo*, (^{3}H)-PhXA41 was rapidly hydrolyzed to the biologically active acid PhXA85 which had a short half-life of 16.6 min in plasma. The mean Cmax value of PhXA85 is 57 pg/ml. Compared to IV dose, the systemic bioavailability for PhXA85 following ocular administration was 45%. PhXA85 was extensively metabolized mainly through β-oxidation. Plasma concentration of PhXA85 from patients who had been treated with latanoprost during at least one year showed that there was no signs of accumulation of the biologically active acid of latanoprost in plasma.

The bioavailability of the biologically active acid of latanoprost PhXA85 was also evaluated in human aqueous humor. Human aqueous humor latanoprost concentrations after one eye drop of latanoprost administration (1.5 μg/patient) at 0.5, 1, 2, 4 and 24 hours before surgery were studied in 20 patients who underwent cataract surgery. The mean concentration (±SD) at around 0.5, 1, 2, 4 and 24 hours after topical administration of latanoprost are 5.7 (2.8), 18.7 (5.6), 32.6 (20.6), 29.0 (8.2) and 0.2 (0) ng/ml, respectively.

RECOMMENDATION

The applicant's Human Pharmacokinetics and Biopharmaceutics Section of NDA 20-597 is acceptable for meeting the requirements of 21 CFR 320.21 and the applicable clinical pharmacology labeling requirement under 21 CFR 201.57. However, the comments (1) to (4) on pages 4-5 to the applicant should be adequately addressed.

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW
NDA 20-597

TABLE OF CONTENTS: Page No.

BACKGROUND

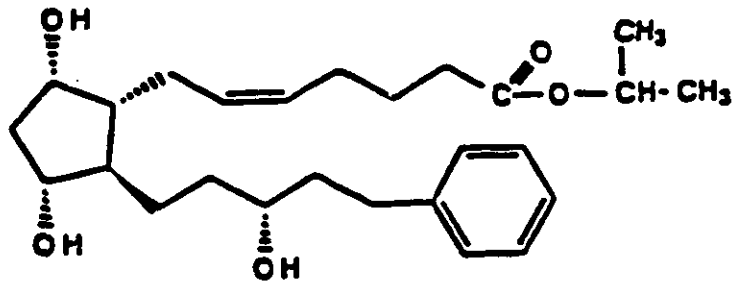
XALATAN™ (latanoprost), a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humor. Latanoprost is an isopropyl ester pro-drug designed to enhance the bioavailability in the eye. Latanoprost is rapidly and completely hydrolyzed to the biologically active acid during passage through the cornea by esterase presented in the cornea.

XALATAN™ is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension. It can also be used in combination with beta-adrenergic antagonists (timolol), adrenergic antagonists (dipivalyl epinephrine), cholinergic agonists (pilocarpine) and carbonic anhydrase inhibitors (acetazolamide) to achieve an additive effect.

The recommended dose for adults is one drop in the affected eye(s) once daily in the evening. The dosage of XALATAN should not exceed once daily since it has been shown that more frequent administration decreases the intraocular pressure lowering effect.

Chemistry

Physical form: A colorless to slightly yellow viscous oil.
Chemical name:
CA Index name: 5-Heptenoic acid, 7-[3,5-dihydroxy-2(3-hydroxy-5-phenylpentyl) cyclopentyl]-1-methylethyl ester,[IR-[1α(Z),2β(R*),3α,5α]]
Structural formula:



Molecular formula: $C_{26}H_{30}O_5$
Molecular weight: 432.58
Solubility: Practically insoluble in water (5mg/100ml), freely soluble in ethanol, octanol, and very soluble in acetonitrile.
Partition coefficient: The partition coefficient (Log p) of latanoprost was determined in octanol/water at pH 7.4. Log p =4.3.
pKa value of the acid of latanoprost: 4.88 (in 0.01 M KCl solution).

SUMMARY OF BIOAVAILABILITY/PK/PD

BIOAVAILABILITY (Single Dose)

The absorption, excretion and metabolism of latanoprost were studied in a two way cross-over study in four healthy male volunteers after single dose of IV and ocular administration of [13,14-^{3}H] labelled latanoprost ((^{3}H)-PhXA41) (Study reports # 9400460 and # 9400107). It was concluded that (^{3}H)-PhXA41 and its metabolites were rapidly absorbed following ocular administration. An estimated 77% of the dose entered the systemic circulation. Renal – elimination represented the major route of elimination with a small percentage being biliary excreted. *In vivo*, (^{3}H)-PhXA41 was rapidly hydrolyzed to the biologically active acid PhXA85 which had a short half-life of 16.6 min in plasma. Compared to IV dose, the systemic bioavailability for PhXA85 following ocular administration was 45%. PhXA85 was extensively metabolized mainly through β-oxidation.

PROTEIN BINDING

It was found that during the intravenous infusion (7.5 min), possibly equating to active

compound, binding to plasma proteins was approximately 90%. This decreased to about 62% by 2.25 h after the start of the infusion. After ocular administration a similar pattern was observed to that of intravenous dosing, with binding of about 90% at 3 min post-dose decreasing to about 72% at 2 h post-dose.

MULTIPLE DOSE STUDY

Plasma samples collected from ten patients who had been treated with latanoprost during at least one year were analyzed by radioimmunoassay (RIA) and showed that there was no sign of accumulation of the biologically active acid of latanoprost in plasma. The maximal plasma level obtained was around the quantification limit of the RIA method used (60 pg/ml) and similar to the concentration obtained in plasma after a single dose administration in healthy volunteers.

BIOAVAILABILITY IN HUMAN AQUEOUS HUMOR

Human aqueous humor latanoprost concentrations after one eye drop of latanoprost administration (1.5 μg/patient) at 0.5, 1, 2, 4 and 24 hours before surgery were studied in 20 patients who underwent cataract surgery. The mean concentration (±SD) at around 0.5, 1, 2, 4 and 24 hours after topical administration of latanoprost are 5.7 (2.8), 18.7 (5.6), 32.6 (20.6), 29.0 (8.2) and 0.2 (0) ng/ml, respectively.

SPECIAL POPULATIONS

The age of patients and healthy volunteers ranged from 47 to 86 years old in the study submitted. The patients studied included both males and females. No gender analysis was conducted.

FORMULATION

Five formulations were used in clinical trials. (See Appendix 1)

COMMENTS (need not to be sent to the applicant):

The applicant indicated that the mean maximum concentration of the acid of latanoprost in human aqueous humor was 33-34 ng/ml obtained 2.5 h after topical administration of 1.5 μg latanoprost to the eye. However, there is no explanation of how these values were obtained.

COMMENTS (need to be sent to the applicant):

1. In the proposed package insert, the applicant stated that there was practically no metabolism of the acid of latanoprost in the eye. However, the metabolism of the acid of latanoprost was not evaluated in the eye in studies submitted. The applicant should provide the information

to support this statement.

2. In the proposed package insert, the applicant listed the main metabolites of latanoprost obtained in animal studies. Since the metabolism of the acid of latanoprost has also been studied in humans, information about the metabolism in humans should be incorporated in the label.

3. In the proposed package insert, on page 6, 2nd paragraph, it is stated that "In man, the half-life of the biologically active acid in plasma is approximately 17 minutes". On page 29, 2nd paragraph, the applicant also states that "the half-life of the biologically active acid in plasma is approximately 10 minutes". The applicant should correct this inconsistency.

4. Assay validation was not conducted at the levels of concentrations studied and was not submitted for each individual study. The applicant should have provided the assay validation or quality control data for each individual study at the levels of drug concentrations studied.

Dan Wang, Ph.D.
Pharmacokinetics Evaluation Branch III

First Draft initialed by F. Pelsor, Pharm.D. (Nov.20,1995)
FT initialed by F. Pelsor, Pharm.D. F. Pelsor

Biopharm-Day Dec. 1, 1995 (Attendees: N. Fleischer, H. Malinowski, ML. Chen, Wang)

cc: NDA 20-597 original. HFD-540(Clinical, Chapman), HFD-880(N. Fleischer, Pelsor, D. Wang), Chron, Drug, Reviewer, HFD-19(FOI), HFD-340(Viswanathan)

APPENDIX 1

Pharmacia
Pharmaceuticals Uppsala

XALATAN ™ Eye Drops 50µg/ml
CLINICAL TRIAL FORMULA(E) USED

Phase I/II

FORMULA 1

1 ml contains:

Active ingredient

Latanoprost	35, 60, 115, 350 µg

The vehicle has been used as placebo

Late phase II trials, phase III trials, final formulation

FORMULA 2

1 ml contains:

Active ingredient

Latanoprost	12.5, 15, 25, 50*) µg

The vehicle has been used as placebo

*) The final formulation contains latanoprost 50 µg.
**) The final formulation contains equivalent amount of disodium phosphate anhydrous, i.e. 4.74 mg.

Pharmacia
Pharmaceuticals Uppsala

Modified formulations for pharmacokinetic studies in humans

FORMULA 3

1 ml contains:

Active ingredient

Latanoprost (13,14-^{3}H radio labelled) } Latanoprost }	10.5µg

FORMULA 4

1 ml contains:

Active ingredient

Latanoprost	40µg

FORMULA 5

1 ml contains:

Active ingredient

Latanoprost (13,14-^{3}H radio labelled) } Latanoprost }	50 µg

B

02-00065

APPENDIX 2

TITLE: Tritium Labelled Latanoprost, (^{3}H)-PhXA41: A Study of The Absorption and Excretion Following Ocular and Intravenous Administration to Healthy Human Volunteers

STUDY NO: 9400460 (369/51) VOLUME: 1.42

INVESTIGATORS

STUDY DATE: July, 6, 1993 - July, 29, 1994. DATE OF REPORT: July, 29, 1994

OBJECTIVES:

1. To define the plasma and whole blood concentrations versus time curves for total radioactivity following ocular and intravenous administration of (^{3}H)-PhXA41 to healthy male volunteers.

2. To describe the availability of (^{3}H)-PhXA41 related material after ocular administration.

3. To obtain a material balance by quantifying the urinary and faecal excretion of radioactivity.

4. To examine the pattern of metabolites in plasma, urine and faeces

5. To determine the extent of *in vivo* plasma protein binding of (^{3}H)-PhXA41 related material.

Ocular administration was selected as this is the proposed therapeutic route, while intravenous administration was selected to assess the systemic availability.

FORMULATION: Formulation 5, Lot B 039307

STUDY DESIGN: An open 2-way cross-over study design was used to investigate the absorption, metabolism and excretion of (^{3}H)-PhXA41 in four healthy male volunteers following intravenous infusion and ocular administrations. (^{3}H)-PhXA41 was administered by intravenous infusion, at a nominal dose level of 0.003 mg/kg body weight corresponding to a nominal radioactive dose of 100 µCi per volunteer at a dose rate of 1.6 ml/min over 15 min. (^{3}H)-PhXA41 was administered by the ocular route, at a nominal dose volume of 37 µl/eye (dose level 3 µg/volunteer) corresponding to a nominal radioactive dose of 100 µCi per volunteer (1.5 µg and 50 µCi per eye. The dose administered to each volunteer was determined from the radioactivity present in the dose equipment prior to dosing minus the residual radioactivity recovered from the dosing equipment after dosing. The dosing information was shown in Tables 7.1 and 7.2.

Blood (9 mL or 16 mL) was sampled by venepuncture or by indwelling cannula of the ante-cubital veins at the following times after dosing: 0 (predose), 1, 3 , 5, 10, 15, 20 and 40 min, 1, 2, 4, 6, 9, 12, 24, 48*, 72* and 96* h post-infusion (* 9 mL blood collected at these time points). Additional blood samples (16 mL) were collected at 7.5 and 15 min after the start of the intravenous infusion.

Additional blood samples (9 mL) were collected at 120, 144 and 168 h post intravenous infusion and at 120 and 144 h post ocular dose administration.

Blood samples were used for the measurement of total radioactivity and plasma protein binding determination.

Urine and faeces were collected at the following intervals after dosing:

Urine: 0 (predose, -12 to 0) , 0 to 2, 2 to 4, 4 to 6, 6 to 9, 9 to 12, 12 to 24, 24 to 36, 36 to 48, 46 to 72, 72 to 96, 96 to 120, 120 to 144 and 144 to 168 h post-dose

Faeces: 0 (predose, -12 to 0), 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168 h post-dose

Thirty minutes after the ocular dose, each volunteer had the surrounds of his eyes gently swabbed to remove any residual radioactivity which may have leaked from the eye. The radioactivity present in samples of urine, faeces and eye wash was determined.

DATA ANALYSIS: Non-model dependent pharmacokinetic evaluations of plasma and blood radioactivity data were performed to determine terminal half-life ($t_{1/2}$), AUC values (AUC_{0-t}, $AUC_{0-\infty}$), Cmax and tmax.

RESULTS:

1. Specific radioactivity

The mean specific radioactivity of each formulation was determined using the mass data supplied by the applicant and radioactivity content determined at HE. Values for the intravenous and ocular formulations were 18.18 MBq/mg (491.4 μCi/mg) and 1219.0 MBq/mg (32947.2 μCi/mg) respectively.

2. Blood and plasma radioactivity profiles

Dose information, blood and plasma radioactivity, concentration profiles and PK parameters are summarized in Table 7.3 to 7.10. Mean concentrations of radioactivity in the plasma following IV and ocular administration are shown in Figures 8.1 and 8.2. At the end of an intravenous infusion of (^{3}H)-PhXA41 for 15 minutes, at a nominal flow rate of 1.6 mL/min, a mean blood radioactivity level of 7.46 ± 1.01 ng equivalents of (^{3}H)-PhXA41/mL was determined. The corresponding concentration in plasma was 12.43 ± 2.01 ng equivalents of (^{3}H)-PhXA41/mL. Thereafter levels declined in a biexponential manner such that radioactivity was not detected in blood beyond 4 h (with the exception of volunteer 002M where radioactivity was still detected at 6 h post-dose) while levels were still detected in plasma up to 6 h after the infusion (except 002M where radioactivity was still detected at 9 h). The initial phase half-lives were 0.19 ± 0.22 h (blood) and 0.24 ± 0.17 h (plasma). The terminal elimination half-lives for radioactivity were 1.60 ± 0.55 h (blood) and 1.47 ± 0.32 h (plasma). Mean areas under the blood and plasma concentration time curve (AUC) were 11.55 ± 0.70 ng equiv.h/mL and 20.20 ± 2.93 ng equiv.h/ml respectively.

Following a single ocular administration of (^{3}H)-PhXA41, blood and plasma radioactivity concentrations reached maxima of 0.039 ± 0.010 and 0.064 ± 0.01 ng equivalents of (^{3}H)-PhXA41/mL respectively within 40 min post-dose. Thereafter levels declined rapidly such that radioactivity was not detected beyond 12 h post-dose (blood) or 6 h post-dose (plasma). Insufficient data points were present to enable the half-lives of the initial elimination phase to be calculated. The mean terminal elimination half-lives were 2.21± 0.71 h (blood) and 1.84 ± 0.13 h (plasma) and the corresponding area under the blood and plasma concentration time curves (AUC) were 0.11 ± 0.02 ng equiv.h/mL and 0.17 ± 0.03 ng equiv.h/ml respectively.

3. Excretion of radioactivity

Urinary and faecal excretion data are listed in Tables 7.11 to 7.20, and mean urinary and faecal excretion of radioactivity following IV and ocular administration is shown in Figures 8.21 and 8.26. The extent of tritium exchange was investigated in selected samples of plasma and urine, after freeze drying. Results indicated that the extent of tritium exchange was less than 10% and therefore no further work was necessary.

Within 168 h of a single intravenous infusion of (^{3}H)-PhXA41 for 15 minutes, a mean of 114.50 ± 0.51% of the radioactivity administered was recovered, principally in urine (98.31 ± 1.72%). Most radioactivity was eliminated in urine by 12 h post-dose, but continued at low levels thereafter. Faecal elimination of radioactivity accounted for 16.19 ± 1.99% of administered dose. Most radioactivity was excreted in faeces within 72 h of dosing, although small amounts were still being eliminated from volunteers 002M and 003M at 168 h post-dose.

After an single ocular administration of (^{3}H)-PhXA41, a mean recovery of 103.5 ± 8.95% was achieved. Radioactivity was predominantly renally eliminated (87.88 ± 6.41%) with the remainder recovered in faeces (15.31 ± 3.56%) and eye washes (0.32 ± 0.23%). Excretion of radioactivity in urine was essentially complete within 24 h, although low levels of radioactivity

were still detected in all subjects at 96 h (0.12 ± 0.03%). The majority of radioactivity eliminated in the faeces was recovered within 72 h of dosing, with radioactivity not detected beyond 96 h post-dose in 2 out of four volunteers (001M and 004M). Protracted faecal elimination was observed for volunteers 002M and 003M, where low levels of radioactivity (< 0.09%) were still detected at 144 h and 168 h respectively.

4. Protein Binding

Protein binding data in plasma following IV and ocular administration are shown in Tables 7.21 and 7.22. Binding of radioactivity was shown to decrease with time after both intravenous and ocular administration.

During the intravenous infusion (7.5 min), possibly equating to active compound, binding to plasma proteins was approximately 90%. This decreased to about 62% by 2.25 h after the start of the infusion.

After ocular administration a similar pattern was observed to that of intravenous dosing, with binding of about 90% at 3 min post-dose decreasing to about 72% at 2 h post-dose.

5. Adverse events

During the course of the study no adverse events were recorded.

DISCUSSION AND CONCLUSION:

The blood and plasma profiles and routes and rates of excretion of radioactivity have been investigated in healthy male human volunteers following single ocular and intravenous administrations of (^{3}H)-PhXA41 at nominal dose levels of about 3 µg/subject (ocular) and about 210 µg/subject (intravenous). In addition, the extent of plasma protein binding has been evaluated after intravenous and ocular administration.

(^{3}H)-PhXA41 and/or its radiolabelled metabolites was rapidly absorbed following ocular administration. Comparison of the ocular and intravenous AUC data indicated that the maximum systemic availability was about 77%, assuming no route dependent differences in metabolism while urinary data would suggest that the extent of absorption was about 88%.

Radioactivity was predominantly cleared by renal mechanisms, although the protracted faecal elimination of radioactivity in two of the four volunteers after ocular dosing suggests that PhXA41 and/or its radiolabelled metabolites may undergo biliary excretion to a small extent. This is evidenced by the appearance of radioactivity in the faeces after intravenous administration.

In conclusion, (^{3}H)-PhXA41 and/or its radiolabelled metabolites were rapidly absorbed following ocular administration to healthy male volunteers. Renal elimination represents the major route of excretion of radioactivity after both intravenous and ocular dosing. There was evidence to support

biliary excretion of (^{3}H)-PhXA41 and/or its radiolabelled metabolites.

TITLE: The metabolism of tritium Labelled Latanoprost in healthy male volunteers after a single intravenous or topical administration on the eyes

STUDY NO: 9400107 (369/51) VOLUME: 1.43

DATE OF REPORT: Dec., 29, 1994

OBJECTIVES: To examine the pattern of metabolites in plasma, urine and faeces

STUDY DESIGN: This is an analysis of urine, plasma, and feces samples from healthy volunteers in study 9400460.

DATA ANALYSIS:

The concentration of PhXA85 in plasma was calculated from the total radioactivity in the sample multiplied by the percentage of PhXA85 obtained from the run divided by the volume multiplied by the specific activity of the administered PhXA41. According to the following formula:

$$C = \frac{PxR}{VxSx60x100}$$

C = concentration of PhXA85 µg equivalent/ml
P = percentage of PhXA85 in the chromatogram
R = total radioactivity in the plasma sample (dpm)
V = sample volume (ml)
S= specific activity of PhXA41 (Bq/µg)

The plasma data obtained were analyzed by a non-compartmental model to obtain the AUC and elimination half-life. From the given dose and AUC the plasma clearance was estimated

(Cl=dose/AUC). The volume of distribution was estimated as V=Cl/elimination rate constant. The used model (model 200) uses the trapezoidal rule and linear regression to estimate the AUC and elimination rate constant.

RESULTS:

1. Metabolic profiles in plasma

Plasma samples collected within 35 minutes after the start of the intravenous infusion and within 40 minutes after topical administration contained measurable amounts of radioactivity for chromatography with on line radiochemical detection from individuals. The plasma samples collected between 40-120 minutes after intravenous administration were pooled to one sample from the four individuals at each time point. Latanoprost was completely hydrolyzed in plasma. The only significant radioactive component in plasma during the first hour after administration had a retention time in the chromatography system equivalent to PhXA85. It is evident that PhXA85 was measurable in pooled samples 40 and 60 minutes after intravenous administration but not after 120 minutes.

2. The pharmacokinetics of PhXA85

From the total radioactivity and the chromatograms the concentration of PhXA85 was calculated (Table I and II). In figure 13 the mean plasma elimination curve of PhXA85 after intravenous and topical administration on the eyes are presented. The pharmacokinetic parameters calculated for PhXA85 after intravenous administration are presented in Table III. The plasma elimination half life of PhXA85 was as a mean (n = 4) found to be 16.6 ± 0.9 minutes, the plasma clearance 0.40 ± 0.04 L/h*kg and the volume of distribution 0.16 ± 0.02 L/kg. After topical administration on the eyes, mean plasma concentration values of PhXA85 from 3 individuals were used to calculate the pharmacokinetic parameters due to sparse data, see table IV. The maximal plasma concentration 53 pg/ml was obtained 5 minutes after administration. The plasma elimination half-life was 17 minutes. The systemic bioavailability for PhXA85 was 0.45 (45%) calculated as

$$(AUC_{top}/dose_{top})/(AUC_{i.v.}/dose_{i.v.}) = (0.0337/2.27)/(7.15/216) = 0.45$$

3. Metabolites in urine and faeces

In the mass balance study (study 9400460) it was found that the major part of the radioactivity administered was recovered in urine both after intravenous as well as after topical administration. The excretion in urine was nearly completed during the first 24 hours after administration. The two urine samples from each person containing most radioactivity were analyzed. In figure 14 urine samples were run on in gradient 4 to investigate if any PhXA41 was present. This figure shows the absence of both PhXA41 and PhXA85 in all four volunteers in the first urine samples collected after intravenous administration. Further separation of the metabolites in urine using gradient 1 showed that the metabolites more polar than PhXA85 were present in every urine

sample. There was no obvious qualitative difference in the metabolic pattern after intravenous and topical administration. However, quantitatively the most polar metabolites constituted a greater share of the radioactivity profile after intravenous compared to after topical administration. The least polar metabolite had a retention time equivalent to 1,2-dinor PhXA85. The 1,2,3,4-tetranor-PhXA85 has a structure that easily forms a δ-lactone, that means an internal ester between the carboxylic group and the hydroxyl group on carbon 5 (=carbon 9 in PhXA85). There is an equilibrium between the acid and the lactone. In HPLC gradient 1 the acid had a retention time of around 21 min and the less polar lactone 28 min.

The major metabolites in human urine after topical administration chromatographed as 1,2-dinor-PhXA85 and 1,2,3,4-tetranor-PhXA85 in the form of acid in equilibration with its corresponding δ-lactone. The ß-oxidation metabolites, 1,2-dinor PhXA85 and 1,2,3,4-tetranor PhXA85, amounted together to about 42% of radioactivity in the metabolic profile after intravenous administration and to 66% (range 57-73%) after topical administration.

To investigate if the more polar metabolites were glucuronic acid or sulfate conjugates, urine samples collected 0-2 h after the end of the intravenous infusion of latanoprost, were incubated with glucuronidase and sulfatase. HPLC chromatograms of the same urine incubated with and without glucuronidase are presented in figure 24. The peaks with retention times 7.7 and 11.9 minutes decreased and those with retention times 26.1 and 28.9 minutes increased. These data indicate the presence of a glucuronide conjugate of 1,2-dinor-PhXA85 (retention time for 1,2-dinor-PhXA85, 28.9 min) and at least one unknown glucuronide conjugate. No further changes in the chromatographic profile were observed after incubation with arylsulfatase. The applicant indicated that possible polar metabolites could be formed through hydroxylation and conjugation in the ω-chain in combination with ß-oxidation in the α-chain of PhXA85. However, due to the small amounts of material present and lack of reference standards no further investigation were performed on these metabolites.

About 15% of the total radioactivity administered was found in faeces. One of the two metabolites was judged to correspond to 1,2-dinor PhXA85. The 1,2-dinor PhXA85 metabolite amounted to about 45-60% after intravenous administration and to 7-23% after topical administration. Another prominent very polar metabolite was present. This metabolite was not identified. The major metabolic pathways are presented in figure 28. The faeces samples from the volunteer 001M was not analyzed due to technical problems to process the sample.

DISCUSSION AND CONCLUSION

From studies in human plasma it has been shown that ester hydrolysis of latanoprost (PhXA41) occurs rapidly and completely and the biologically active acid of latanoprost (PhXA85) is thus formed. PhXA41 acts as a pro-drug to enhance the penetration through the cornea.

In plasma PhXA85 disappeared rapidly both after intravenous and topical administration. The systemic bioavailability of PhXA85 after topical administration was around 45%. The plasma clearance of PhXA85 was high, mainly due to liver metabolism, thus no PhXA85 was recovered in

urine. The volume of distribution for PhXA85 was small and the plasma elimination half life was short and similar after intravenous and topical administration. The only prominent radioactive peak in the human plasma samples was the one corresponding to PhXA85.

The in vivo plasma protein binding of PhXA85 in man varied between 62-90% studied by ultracentrifugation (study 9400460).

In man the majority of the radioactivity, following both ocular and intravenous administration, was recovered in urine. About 15% of the dose was recovered in faeces. The faeces excretion after intravenous administration indicates biliary excretion.

No latanoprost or PhXA85 were found in urine or faeces. The metabolic pattern of the urine samples contained several peaks. The most lipophilic compound was identified as 1,2- dinor PhXA85. Another ß-oxidation metabolite identified was 1,2,3,4-tetranor PhXA85 present both as free acid and as the δ-lactone. After topical application of latanoprost these metabolites in urine amounted to about 66% of the radioactivity. The remaining part of the radioactivity was divided into several more polar metabolites. One of these seemed to be a glucuronic acid conjugate of 1,2-dinor PhXA85. Two compounds predominated in the faeces samples. One chromatographed as 1,2-dinor PhXA85 and the other was a very polar metabolite not identified.

In conclusion, in man latanoprost (PhXA41) was rapidly and completely hydrolyzed to the acid of latanoprost (PhXA85). The topically applied drug was partly absorbed into the systemic circulation. The plasma elimination half life of PhXA85 was short, the clearance high and the volume of distribution was small. The metabolites were mainly excreted into urine. The major metabolic pathway was ß-oxidation of PhXA85.

10. TABLES

Table I Individual and mean values of the calculated concentrations of PhXA85 in plasma after intravenous administration of PhXA41 (3 µg/kg).

Time min	PhXA85 ng eq/ml Subject no. 001M	002M	003M	004M	Mean ± S.D. ng eq/ml
-7.5					
0					
1					
3					
5					
10					
15					
20					
40					
60					
120					

M = male
nd = not detected
* = pool of four individuals (001-004M)

Table II Individual and mean values of the calculated concentrations of PhXA85 in plasma after topical administration of PhXA41 on the eyes (1.5 µg/eye)

Time min	PhXA85 ng eq/ml Subject no. 001M	002M	003M *	004M	Mean ± S.D. pg eq/ml
1					
3					
5					
10					
15					
20					
40					
60					

* = Statistical outlier, not included in the calculations.
M = male
nd = not detected
na = not analysed

Table III Pharmacokinetic parameters of PhXA85 in plasma after intravenous administration of PhXA41 to four healthy male volunteers using PCnonlin, model 200 or by hand using the equations stated below.

Subject	001M	002M	003M	004M	Mean (n=4)

Tmax was reached at the end of the infusion
$t_{1/2}$ = elimination half-life (time : 0.4-3 h)
AUC = area under curve, is calculated by the trapezoidal method
Clp = plasma clearence, dose/AUC
V = volume of distribution, Clp/k
k = elimination rate constant

Table IV Pharmacokinetic parameters of PhXA85 in plasma after ocular administration of PhXA41 to healthy male volunteers.
Mean plasma concentrations were used. Calculated by PCnonlin, model 200 or by hand using the equations stated below.

Route	Topical (n=3)
Weight (kg)	76.3 ± 2.4
Dose (µg/individual)	2.27 ± 0.18
Cmax (pg eq/ml)	53
Tmax (min)	5
$t_{1/2}$ (min)	17
AUC (pg eq·h/ml)	33.7
Clp (L/h·kg)	0.88
V (L/kg)	0.36

$t_{1/2}$ = elimination half-life (time : 0.4-3 h)
AUC = area under curve, is calculated by the trapezoidal method
Clp = plasma clearence, dose/AUC
V = volume of distribution, Clp/k
k = elimination rate constant

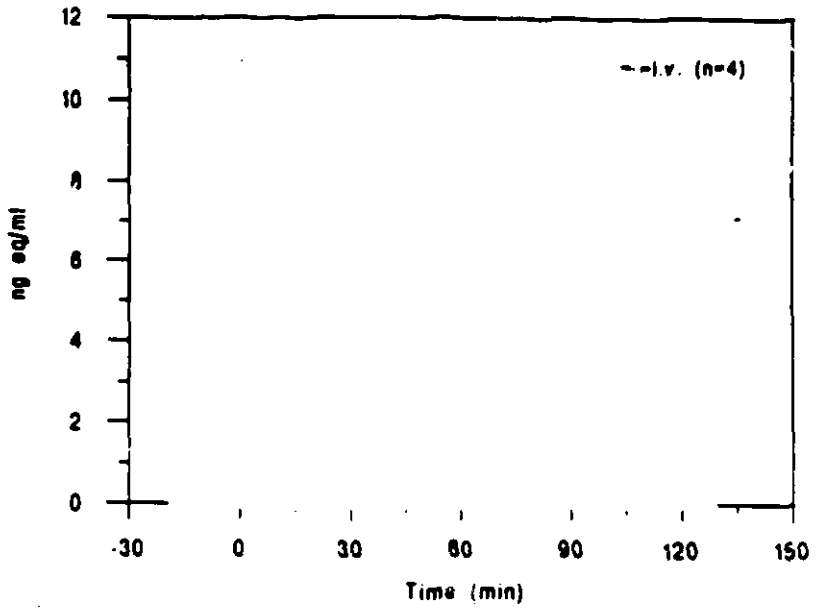


Figure 13A Mean plasma concentration of PhXA85 following an intravenous infusion of [^{3}H]-PhXA41 at a nominal dose level of 210 µg/subject.

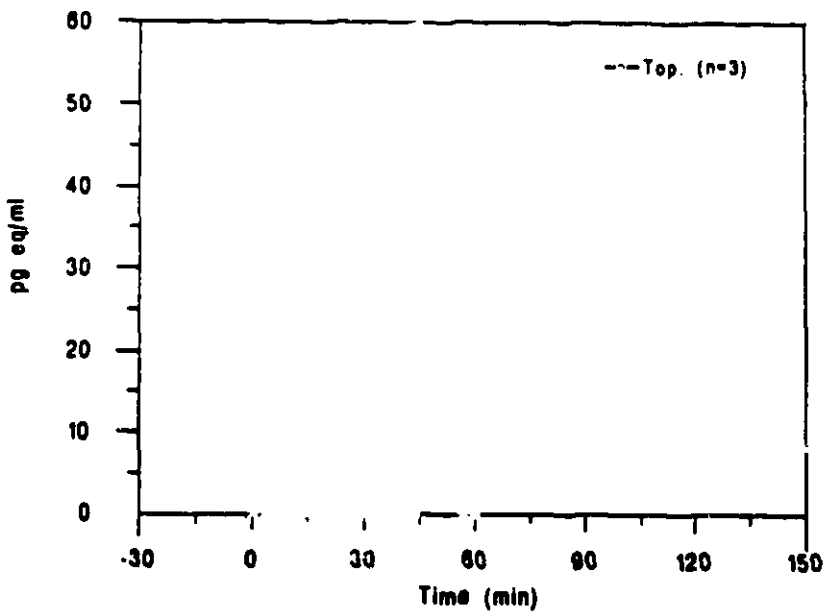


Figure 13B Mean plasma concentrations of PhXA85 following a single ocular administration of [^{3}H]-PhXA41 at a nominal dose level of 3 µg/subject

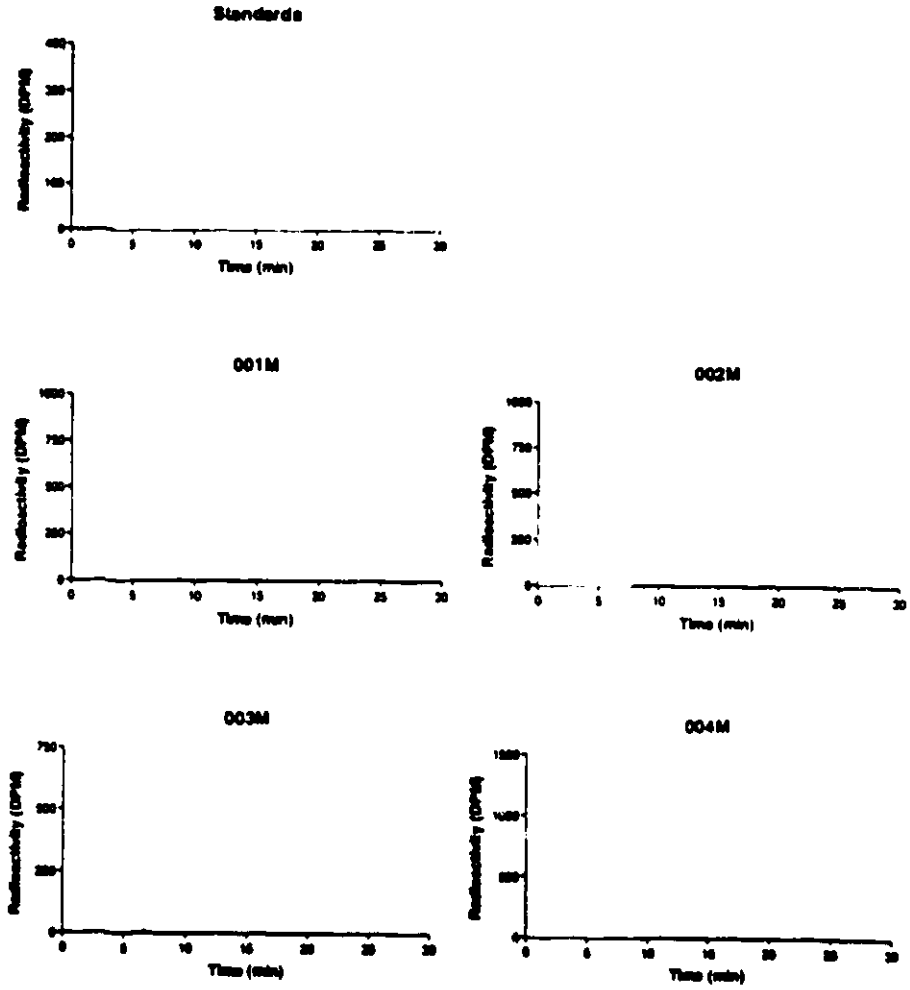
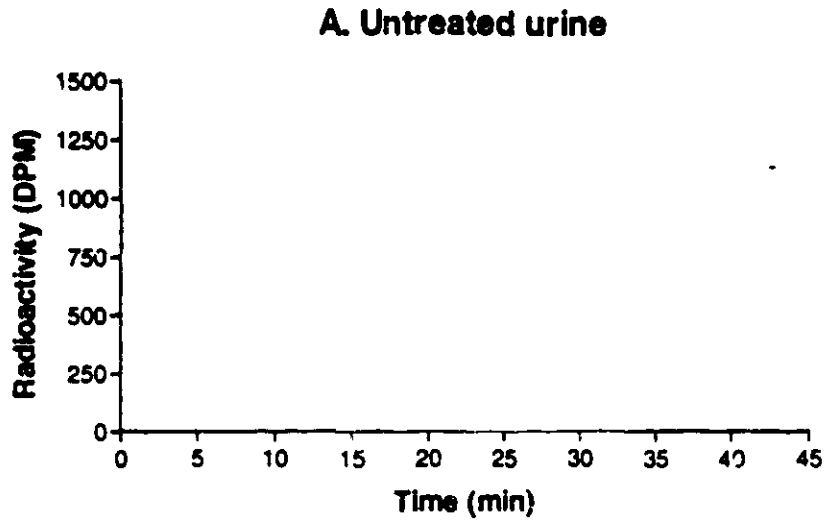


Figure 14 Metabolic profiles (in gradient 4) of urine samples collected 0-2 hours after intravenous administration to male volunteers (001M-004M). At the top is the reference standard PhXA41/PhXA85. The chromatograms show the absence of PhXA41 and PhXA85 in urine samples.



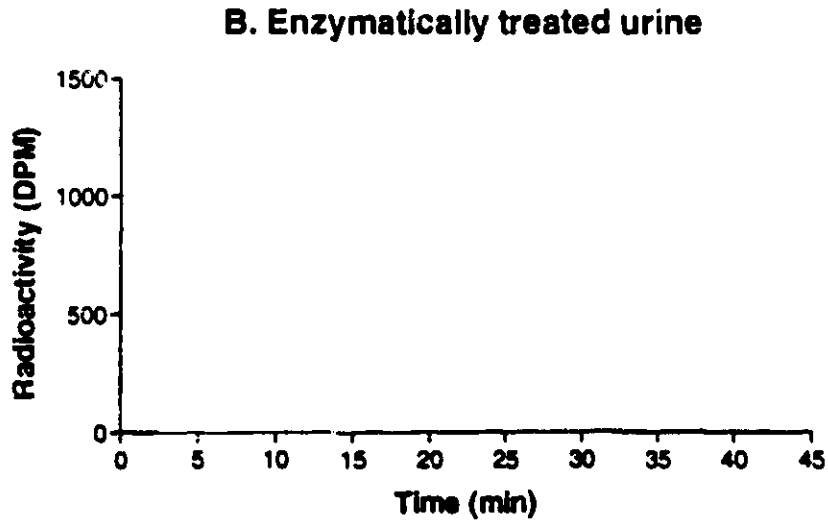


Figure 24 A chromatogram of a 0-2 h urine sample in gradient 1.
B. The same urine sample as above after enzymatic hydrolysis with ß-glucuronidase. The two polar compounds with retention time 7.7 min and 11.9 min decreased, while two less polar peaks with retention time 26.1 and 23.9 min (1,2-dinorPhXA85) increased.

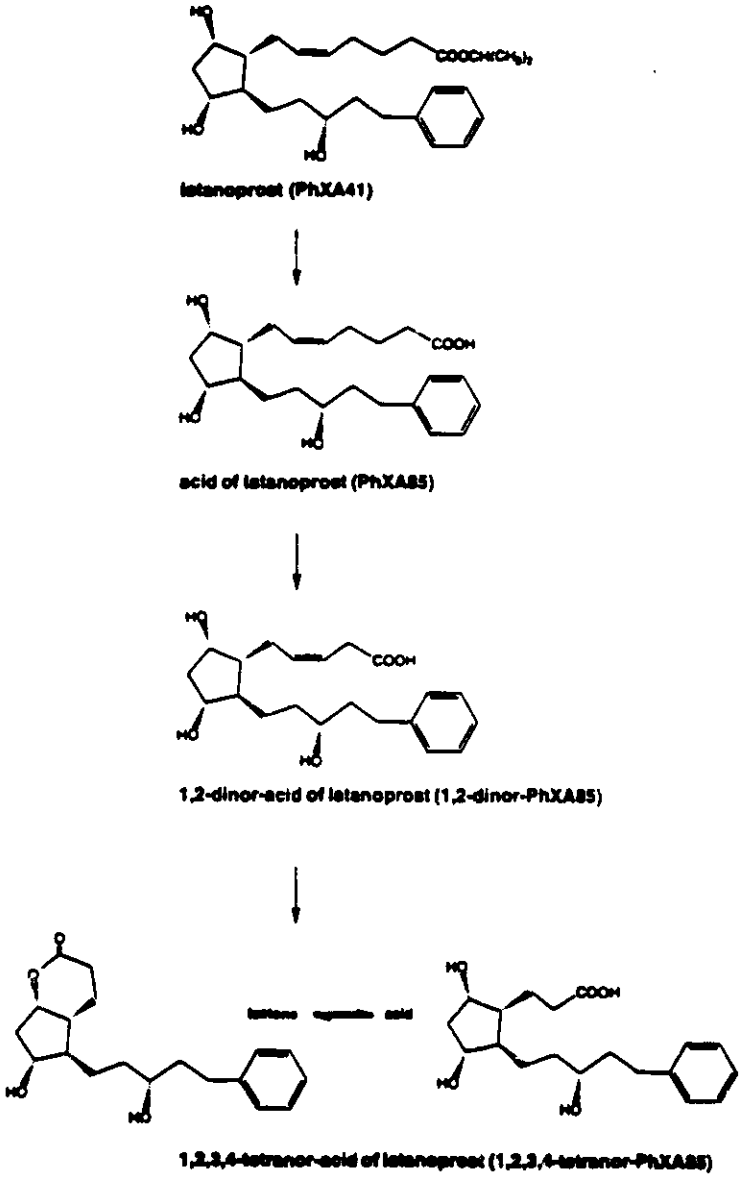


Figure 28 The metabolism of latanoprost in man.

TITLE: Bioanalysis of the acid of Latanoprost by radioimmunoassay in plasma from patients

STUDY NO: *9400109 (KPO/GLAU 9408)*

VOLUME: 1.43

DATE OF STUDY: Week 24 - week 26, 1994 DATE OF REPORT: Oct. 28, 1994

OBJECTIVES: To investigate if PhXA85 could be analyzed by in human plasma in the clinical situation.

FORMULATION: Formulation 2. Lot B 099308

STUDY DESIGN: Blood samples were collected from patients in "A six-month open-label study with PhXA41 in patients with open angle glaucoma or ocular hypertension. A multi-center study in Scandinavia, CTN 9200PG009". The patients in this study had previously been involved in "A six-month randomized, double-masked comparison of PhXA41 to timolol in patients with open angle glaucoma or ocular hypertension. A multi-center in Scandinavia, CTN 9200PG006".

Ten patients were included in this study: 601-H.B., 602-A.J., 603-E.S., 608-M.L., 611-G.J., 632-O.F. from Department of Ophthalmology, University of Umea and 703-K.B., 704-S.O., 709-N.K., 715-I.F. from Department of Ophthalmology, University of Uppsala. Two of the patients from Uppsala received Latanoprost Eye Drops on one eye, 1.5µg/day. The other patients obtained Latanoprost Eye Drops on both eyes 2 x 1.5 µg/day (one drop = 30 µl of 50 µg PhXA41/ml). For patient data see table 1. These patient had been treated daily with latanoprost for at least one year before blood was collected for this study.

A heparinized cannula was inserted into a vein in the bend of one arm. A zero sample was collected just before administration of 30 µl Latanoprost on each eye with a micropipette. Further blood samples were collected 5, 15, 30 and 60 minutes after administration of the eye drops.

RESULTS:

The results of the analysis of the acid of latanoprost, PhXA85 in the human plasma samples by are presented in table II. In 4 individuals a Cmax value of 32, 45, 54 and 67 pg/ml plasma (mean 55 pg/ml) was observed 5 - 15 minutes after administration. These peak values were above the detection limit but only one (67 pg/ml) was above the quantification limit. One patients had concentrations in single plasma sample close to the detection limit and the other 5 patients had plasma levels below the detection limit of the RIA method. It is interesting to notice that among the 4 patients who had plasma concentrations above the detection limit patient 703-KB was one of the two patients who had only half of the dose (1.5 μg) of the rest of patients.

DISCUSSION AND CONCLUSION:

In a study (Report # 9400460) in 4 healthy male volunteers a single administration on the eyes of a clinical dose (1.5 μg/eye = 3 μg) containing tritium labelled latanoprost as a tracer, gave a maximal plasma concentration of 53 ± 6 pg/ml (mean ± S.D.) of the acid of latanoprost 5 minutes after topical application. In this clinical study on patients the sensitivity of the was limiting for the possibility to obtain reliable plasma values of the acid of latanoprost. However, the mean value obtained from the 3 patients with the highest plasma concentrations was 55 pg/ml in good agreement with the study with radioactive latanoprost in the healthy volunteers (53 pg/ml). These sparse data, thus confirms that there is no systemic accumulation of the biologically active acid of latanoprost in plasma in the clinical situation after daily administration of latanoprost to patients during one year. Thus the Cmax value obtained in the healthy volunteers after a single administration is relevant in the clinical situation and could be used to evaluate the safety margin in relation to the toxicological studies.

Pharmacia

Document: 9400109

Table I Data on patient from whom blood samples were collected

Patient No	Sex	Age	Diagnosis	Treated eye µg/eye
601				
602				
603				
608				
611				
632				
703				
704				
709				
715				

Table II Plasma levels of the acid of latanoprost (PhXA85) measured after topical administration of latanoprost

Patient	Dose µg	Concentrations pg/ml 0 min	5 min	15 min	30 min	60 min
F 608-ML	3					
F 603-ES	3					
F 703-KB	1.5					
M 601-HB	3					
M 704-SÖ	3					
M 611-GF	3					
M 709-NK	3					
M 632-OJ	3					
F 715-IF	1.5					
M 602-AJ	3					

* NS = No sample

TITLE: Bioavailability of latanoprost; examination of the aqueous humor after topical application to patients undergoing cataract surgery

STUDY NO: Report # 9400503 (KPO/GLAU 9408) & Report # 9400108 (KPO/GLAU 9409)
VOLUME: 1.43

STUDY DATE: May 1994 - Feb. 1995 DATE OF REPORT: April 4, 1995

OBJECTIVES: *The primary objective was to measure the concentration of acid of latanoprost in* aqueous humor 30 min and 1, 2, 4 and 24 hours after topical administration of a single drop (30 µl) of latanoprost [50 µg/ml] to the eye. The secondary objective was to follow the safety variables.

FORMULATION: Eye drops latanoprost, [50 µg/ml], 30 µl administered once before cataract surgery. Formulation 2. Lot B 029301

STUDY DESIGN: The study was designed as an open study comprising 5 groups with four patients in each group. The age of patients ranged from 47 to 86 with mean of 69.3. Seven (7) males and 13 females were included. The patients were about to undergo cataract surgery during which aqueous humor could be sampled. Before surgery the patients were treated each with one drop of 30 µl latanoprost [50 µg/ml]. Each group was to have latanoprost administered at a specific time: 30 min, 1, 2, 4 or 24 hours before aqueous humor sampling. The 4 and 24 hours sampling were performed only if acid of latanoprost was detected in the samples taken 2 hours after topical administration. Due to a mistake, six 2 hours samples were collected while only two 24 hours samples were collected.

DATA ANALYSIS: The pharmacokinetic calculations were performed by graphic reading from a manual plot. Cmax, Tmax, and the rate constants for the absorption (ka) and elimination (ke) for the acid of latanoprost in aqueous humor was estimated and the corresponding $t_{1/2}$ calculated.

RESULTS: The concentrations of the acid of latanoprost obtained in human aqueous humor at different times after administration are presented in Table I, and Figure 1 and 2. The mean concentration (±SD) for groups 1 to 5 are 5.7 (2.8), 18.7 (5.6), 32.6 (20.6), 29.0 (8.2) and 0.2 (0) ng/ml, respectively. For group 5 (sampling at 24 hours), patient #19 had a concentration value of 0.2 ng/ml and reported concentration for patient #20 was <0.2 ng/ml. It was also reported that the loss of latanoprost at administration was 20 µl for patient #20. Thus the only value obtained at 24

hours was 0.2 ng/ml for patient #19. Based on these data, the applicant estimated the ka and ke values and the corresponding half-lives by manual graphic calculation. The ka value was estimated to be 0.87/hr and thus the absorption half-life was 0.6 hour. The elimination rate constant, ke, was 0.25/hr and thus the elimination half-life is 2.8 hour of the acid of latanoprost in aqueous humor. From Figure 2, it is observed that except for one point at 24 hours, no other points were collected during the elimination phase. Therefore the calculation of the PK parameters was heavily relied on the single point at 24 hours. This makes the PK parameter estimation not reliable. More data between 4 and 24 hours are need to obtained reliable estimates.

Safety of the treatment was evaluated. The applicant concluded that all patients experienced adverse events which were related to and expected from the cataract surgery, with conjunctival hyperaemia, subconjunctival bleeding and corneal oedema as the predominant findings. No event was regarded as related to latanoprost treatment. There was one report of an elevated IOP which was reported as serious. This patient later recovered completely from the event.

DISCUSSION AND CONCLUSIONS:

Based on this study, the applicant indicated that the mean maximum concentration of the acid of latanoprost in human aqueous humor was 33-34 ng/ml obtained 2.5 h after topical administration of 1.5 μg latanoprost to the eye of sampling. However, there is no explanation of how these values were obtained.

The applicant also indicated that in a similar study of the bioavailability of timolol into human aqueous humor the concentration of the timolol eye drop administered was 100 times higher than the latanoprost eye drop concentration is this study. The mean maximum concentration obtained of timolol in aqueous humor was 554.6 ng/ml and for the acid of latanoprost 33-34 ng/ml. After adjusting for the dose the bioavailability of latanoprost in the human aqueous humor was more than 10 times higher than that for timolol.

The applicant also stated that in receptor binding studies of the acid of latanoprost to cell membrane preparations from bovine corpora lutea, containing FP receptors, the concentration of unlabelled latanoprost acid needed to inhibit 50% of the binding of the tritiated ligand was found to be 2.01×10^{-8}M. During at least the first 4 hours after administration of a clinical dose of latanoprost to patients the concentration of the acid of latanoprost in aqueous humor was 10^{-8}-10^{-7}M that is in the range of the IC_{50} value obtained in corpora lutea or higher.

In conclusion, this study shows that the acid of latanoprost is available in human aqueous humor. The peak concentration was obtained about 2 hours after topical administration of 1.5 μg latanoprost to the eye of study. The aqueous humor concentration had dropped to less than 1% of the peak concentration 24 hours after the adrninistration. The concentration obtained in aqueous humor were similar between 1-4 hours after administration and in a concentration range that in vitro has been reported to interact with the prostaglandin FP receptors.

7. TABLES

Table I The concentration of the acid of latanoprost (PhXA85) in human aqueous humour at different times after topical administration of 30 µl eye drop with a concentration of 50 µg/ml latanoprost (dose 1.5 µg)

Patient	Protocol time	Actual time	Concentration ng/ml
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19		[illegible]	
20		24 hrs 42 min	

* Loss of latanoprost at administration, 20 µl in patient 20 and an unknown amount in patient 11.

8. FIGURES

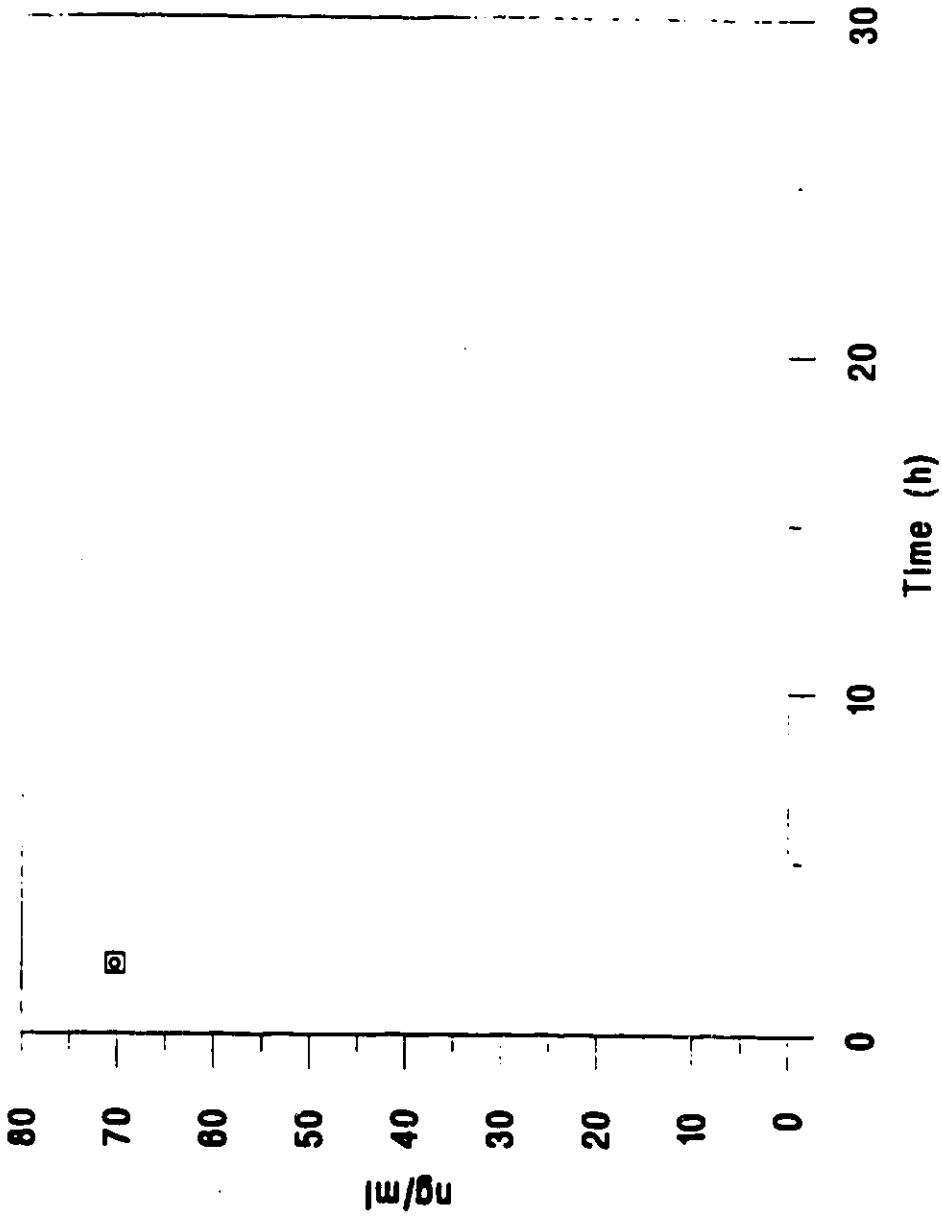


Figure 1 Concentrations of the acid of latanoprost are presented. Individual data at real sampling times ⊡ and mean concentrations at protocol sampling times —■— are shown (compare Table I)

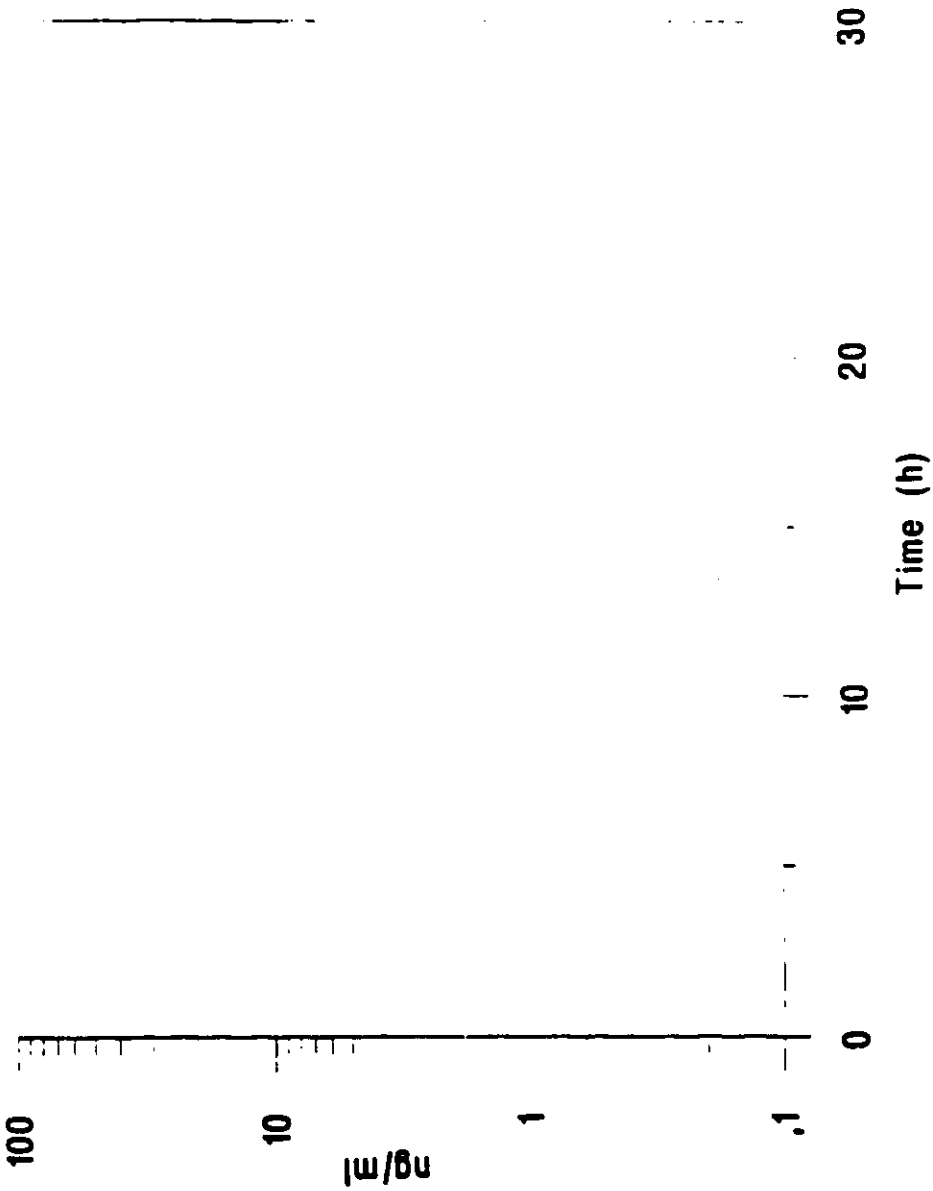


Figure 2 Lin-log plot of the time-concentration relationship of the acid of latanoprost in human aqueous homour is presented (individual data at real times ⊕ and mean concentrations at protocol times) —■—

TABLE 7.1

Doses of (^{3}H)-PhXA41 administered to male volunteers by intravenous infusion at a nominal dose level of 210 µg/subject

Subject number	Radioactivity administered (µCi)	Weight of test article administered (µg/subject)
001M		
002M		
003M		
004M		

TABLE 7.2

Doses of (^{3}H)-PhXA41 administered to male volunteers by the ocular route at a nominal dose level of 3 µg/subject

Subject number	Radioactivity administered (µCi)	Weight of test article administered (µg/subject)
001M		
002M		
003M		
004M		

NOT TO BE COPIED

TABLE 7.3

Plasma radioactivity pharmacokinetic parameters following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

Subject number	$C_{0,max}$ (ng eq/mL)	$t_{½}$ (h)	AUC_{0-t} ng h/mL	$AUC_{0-\infty}$ ng h/mL
001M				
002M				
003M				
004M				
Mean	12.43	1.471 (0.257)	19.37	20.20
SD	2.007	0.315 (0.174)	2.887	2.930

Values in brackets refer to $t_{½}$ estimated over the initial phase (up to 1 h)
* poor correlation coefficient for this half-life estimation

TABLE 7.4

Blood radioactivity pharmacokinetic parameters following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

Subject number	$C_{10\,min}$ (ng equiv/mL)	$t_{½}$ (h)	AUC_{0-1} ng h/mL	$AUC_{0-\infty}$ ng h/mL
001M				
002M				
003M				
004M				
Mean	7.463	1.600 (0.189)	10.17	11.55
SD	1.006	0.545 (0.217)	0.856	0.704

Values in brackets refer to $t_{½}$ estimated over the initial phase (up to 1 h)

TABLE 7.5

Plasma radioactivity pharmacokinetic parameters following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

Subject number	C_{max} (ng equiv/mL)	T_{max} (h)	$t_{½}$ (h)	Time range (h)	AUC_{0-t} ng h/mL	$AUC_{0-\infty}$ ng h/mL
001M						
002M						
003M						
004M						
Mean						
SD	0.0118	0.246	0.134	NA	0.023	0.025

NA = Not applicable

TABLE 7.6

Blood radioactivity pharmacokinetic parameters following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

Subject number	C_{max} (ng equiv/mL)	T_{max} (h)	$t_{½}$ (h)	Time range (h)	AUC_{0-t} ng h/mL	$AUC_{0-\infty}$ ng h/mL
001M						
002M						
003M						
004M						
Mean						
SD	0.0097	0.080	0.713	NA	0.022	0.022

NA = Not applicable

TABLE 7.7

Plasma concentrations of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

	ng equivalents of (^{3}H)-PhXA41 /mL					
Time	001M	002M	003M	004M	Mean	SD
Predose	ND	ND	ND	ND	ND	NA
-7.5 m						
0 h						
1 m						
3 m						
5 m						
10 m						
15 m						
20 m						
40 m						
1 h						
2 h						
4 h						
6 h						
9 h						
12 h						
24 h						
48 h						
72 h						
96 h						
120 h						
144 h						
168 h						

ND = Not detected
NA = Not applicable

TABLE 7.8

Blood concentrations of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

	ng equivalents of (^{3}H)-PhXA41 /mL					
Time	001M	002M	003M	004M	Mean	SD
Predose						
-7.5 m						
0 h						
1 m						
3 m						
5 m						
10 m						
15 m						
20 m						
40 m						
1 h						
2 h						
4 h						
6 h						
9 h						
12 h						
24 h						
48 h						
72 h						
96 h						
120 h						
144 h						
168 h						

ND = Not detected

NA = Not applicable

TABLE 7.9

Plasma concentrations of radioactivity following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 1 µg/subject

	ng equivalents of (^{3}H)-PhXA41 /mL					
Time	001M	002M	003M	004M	Mean	SD
Predose						
1 m						
3 m						
5 m						
10 m						
15 m						
20 m						
40 m						
1 h						
2 h						
4 h						
6 h						
9 h						
12 h						
24 h						
48 h						
72 h						
96 h						

ND = Not detected

NA = Not applicable

TABLE 7.10

Blood concentrations of radioactivity following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

	ng equivalents of (^{3}H)-PhXA41 /mL					
Time	001M	002M	003M	004M	Mean	SD
Predose						
1 m						
3 m						
5 m						
10 m						
15 m						
20 m						
40 m						
1 h						
2 h						
4 h						
6 h						
9 h						
12 h						
24 h						
48 h						
72 h						
96 h						
120 h						
144 h						

ND = Not detected

NA = Not applicable

TABLE 7.11

Recovery of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

Tissue	Percent of administered dose					
	001M	002M	003M	004M	Mean	SD
Urine	98.68	95.79	99.6'	99.14	98.31	1.719
Faeces	16 41	18.92	14.50	14.94	16.19	1.991
TOTAL	115.1	114.7	114 1	114.1	114.5	0.512

TABLE 7.12

Urinary excretion of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

	Percent of administered dose					
Time	001M	002M	003M	004M	Mean	SD
Predose						
2 h						
4 h						
6 h						
9 h						
12 h						
24 h						
36 h						
48 h						
72 h						
96 h						
120 h						
144 h						
168 h						
TOTAL	98.68	95.79	99.61	99.[illegible]	99.3[illegible]	[illegible].715

ND = Not detected

NA = Not applicable

06-00120

TABLE 7.13

Cumulative urinary excretion of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

	Percent of administered dose				
Time	001M	002M	003M	004M	Mean
Predose					
2 h					
4 h					
6 h					
9 h					
12 h					
24 h					
36 h					
48 h					
72 h					
96 h					
120 h					
144 h					
168 h					
TOTAL	98 68	95 79	99 61	99 15	98 31

TABLE 7.14

Faecal elimination of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

	Percent of administered dose					
Time	001M	002M	003M	004M	Mean	SD
Predose						
24 h						
48 h						
72 h						
96 h						
120 h						
144 h						
168 h						
TOTAL	16.41	18.92	14.50	14.94	15.19	1.991

ND = Not detected
NA = Not applicable
NS = No sample

TABLE 7.15

Cumulative faecal elimination of radioactivity following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

	Percent of administered dose				
Time	001M	002M	003M	004M	Mean
Predose					
24 h					
48 h					
72 h					
96 h					
120 h					
144 h					
168 h					
TOTAL	16.41	18.92	14.50	14.94	16.19

TABLE 7.16

Recovery of radioactivity following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

Tissue	Percent of administered dose					
	001M	002M	003M	004M	Mean	SD
Urine	83.22	91.36	81.84	95.14	87.88	6.404
Faeces	13.14	20.31	12.42	15.35	15.31	3.558
Eye wash	0.495	0.243	0.507	0.015	0.315	0.234
Total	96.86	111.9	94.77	110.5	103.5	8.942

TABLE 7.17

Urinary excretion of radioactivity following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

	Percent of administered dose					
Time	001M	002M	003M	004M	Mean	SD
Predose						
2 h						
4 h						
6 h						
9 h						
12 h						
24 h						
36 h						
48 h						
72 h						
96 h						
120 h						
144 h						
168 h						
TOTAL	83.22	91.36	81.84	95.14	87.89	6.404

ND = Not detected

NA = Not applicable

TABLE 7.18

Cumulative urinar xcretion of radioactivity following a single ocular administ. _cion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

	Percent of administered dose				
Time	001M	002M	003M	[illegible]	Mean
Predose					
2 h					
4 h					
6 h					
9 h					
12 h					
24 h					
36 h					
48 h					
72 h					
96 h					
120 h					
144 h					
168 h					
TOTAL	83.22	91.36	81.84	95.14	87.69

TABLE 7.19

Faecal elimination of radioactivity following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

Time	Percent of administered dose					
	001M	002M	003M	004M	Mean	SD
Predose						
24 h						
48 h						
72 h						
96 h						
120 h						
144 h						
168 h						
TOTAL	13.14	20.31	12.42	15.35	15.31	3.558

ND = Not detected

NA = Not applicable

TABLE 7.20

Cumulative faecal elimination of radioactivity following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

	Percent of administered dose				
Time	001M	002M	003M	004M	Mean
Predose					
24 h					
48 h					
72 h					
96 h					
120 h					
144 h					
168 h					
TOTAL	13.15	20.31	12.42	15.35	15.3[illegible]

TABLE 7.21

Protein binding in plasma following an intravenous infusion of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 210 µg/subject

Time from start of infusion	Percent protein binding					
	001M	002M	003M	004M	Mean	SD
7.5 min						
15 min						
25 min						
1.25 h						
2.25 h						

TABLE 7.22

Protein binding in plasma following a single ocular administration of (^{3}H)-PhXA41 to male volunteers at a nominal dose level of 3 µg/subject

	Percent protein binding					
Time	001M	002M	003M	004M	Mean	SD
3 min						
15 min						
20 min						
40 min						
2 h						

NOT TO BE COPIED

Figure 8.1

Mean concentrations of radioactivity in the plasma of male volunteers following an intravenous infusion of (^{3}H)-PhIA41 at a nominal dose level of 210 µg/subject

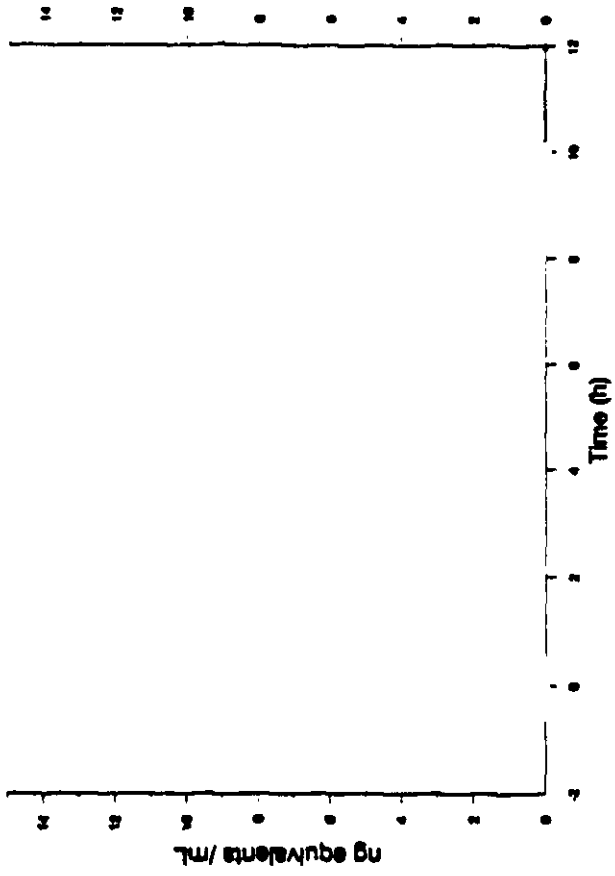
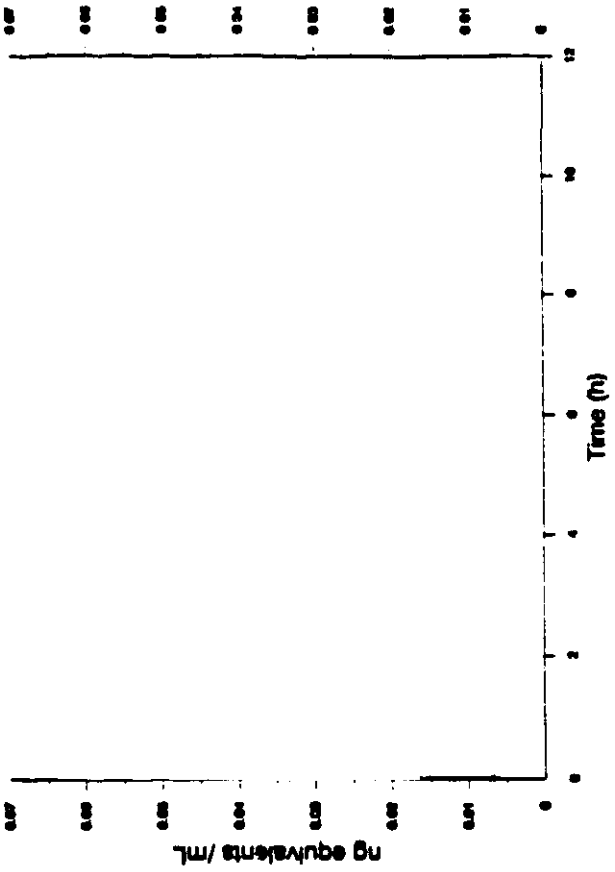


Figure 8.2

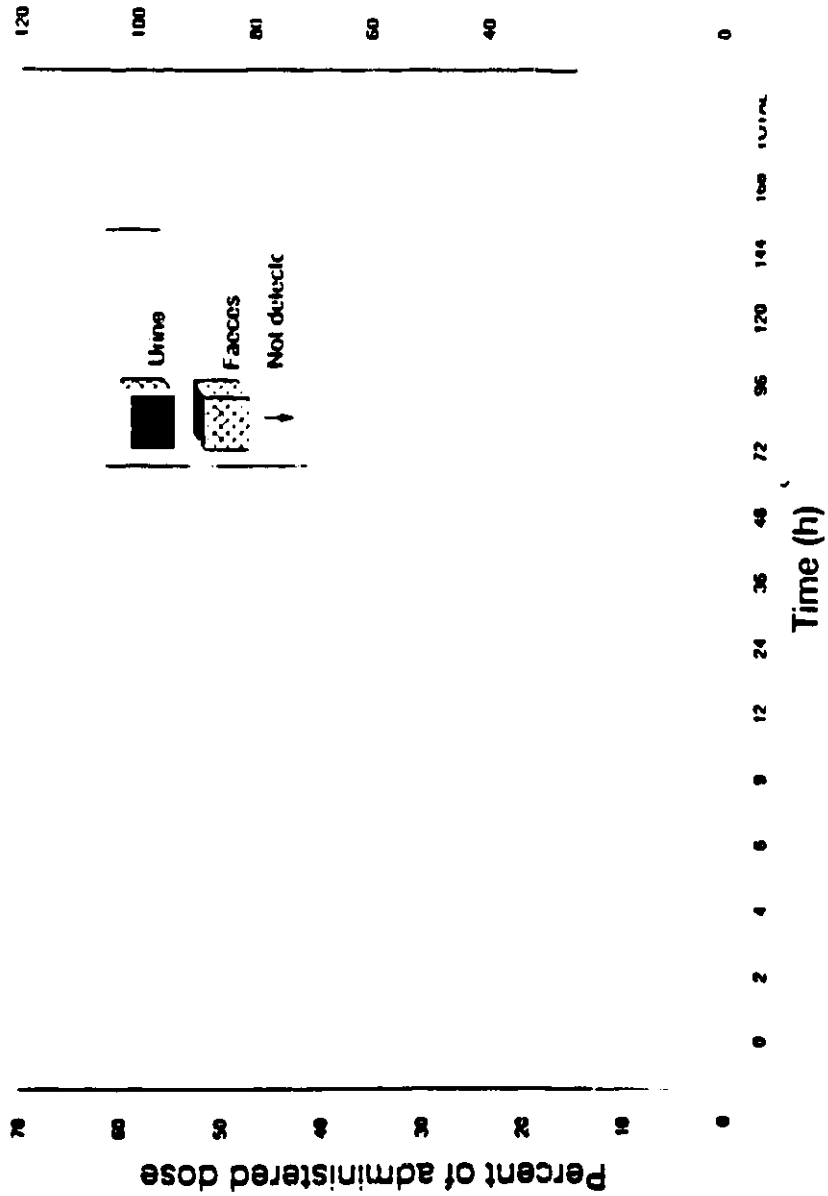
Mean concentrations of radioactivity in the plasma of male volunteers following a single ocular administration of (^{3}H)-PhXA41 at a nominal dose level of 3 µg/subject



NOT TO BE COPIED

Figure 8.21

Mean faecal and urinary excretion of radioactivity following a single intravenous infusion of (^{3}H)-PhXA01 to male volunteers at a nominal dose level of 210 µg/subject



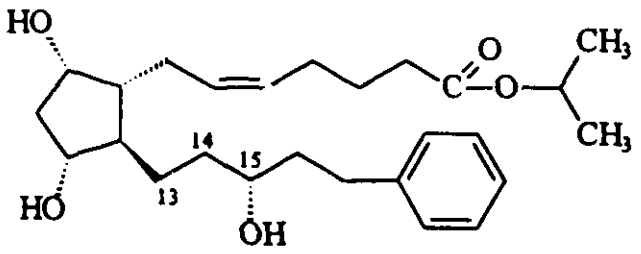
Holmes 1 7 1996

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Ophthalmologic Drug Products (HFD-540)

NDA#:	20-597 (original)
Date Submitted:	6/14/95
Date CDER Received:	6/16/95
Date Assigned:	6/19/95
Date First Draft:	12/1/95
Date Review Completed:	1/11/96
Date Accepted by Supervisor:	1/11/96
Sponsor:	Pharmacia Inc.
Authorized Representative:	Mr. Michael A. Trapani Senior Director Regulatory Affairs, Pharmacia Inc. P. O., Box 16529 Columbus, OH 43216-6529, Phone: 614-764-8100, Fax: 614-761-8102
Name of Drug:	isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate; PhXA41; 13,14-dihydro-17-phenyl-15(R)-18,19,10-trinor-$PGF_2\alpha$ isopropyl ester; latanoprost; XALATAN™; CAS Number: 130209-82-4
Formula Weight:	432.58
Empirical Formula:	$C_{26}H_{40}O_5$
Octanol:Water Partition Coefficient:	Log P = 4.35 (pH 7.4 @ 23.5°C)

Structure:

Pharmacological Category:



Prostanoid F receptor agonist, an isopropyl ester prostaglandin $F_2\alpha$ analog prodrug which is hydrolyzed in the cornea to the biologically active prodrug

A:\N20597 001

Related Submissions: IND

Review Objectives: Review the preclinical safety data.

Background: Prostaglandins (PGs) are 20 carbon cyclized unsaturated hydroxyl fatty acids. They are end products of the cyclooxygenase limb of the arachidonic acid cascade, and are synthesized at the site of action. Most tissues possess enzymes that rapidly inactivate the PGs through metabolic degradation. Any PGs that remain in the general circulation are taken up and metabolized by the lungs, livers and kidneys. Generally the initial metabolic step is to oxidize the 15-hydroxyl to 15-keto. This reaction is followed by enzymatic reduction of the Δ^{13} double bond. The 15-keto-13,14-dihydro prostaglandins thus formed are biologically inactive. Further metabolism of the 15-keto-13,14-dihydro prostaglandins involves one or two steps of β-oxidation. Hydroxylation in the 19 and 20 position with subsequent oxidation is also common. Pharmacia has undertaken a drug discovery /development program to design an antiglaucoma drug that has a mechanism of action different from currently prescribed therapies and has a prolonged local effect. They selected prostaglandin $F_{2\alpha}$ as a synthetic starting point and modified the structures to enhance the absorption of topically applied material and prolong the biological effect by inhibiting some of sites for enzymatic degradation. They achieved this by increasing the lipid solubility by synthesizing an isopropyl ester. This increased octanol:water partition coefficient (log) to 4.35 from 0.52 for the corresponding free acid. Thus esterification increased the lipophilicity about 7000 times. They enhanced the duration of action by protecting the compound from rapid enzymatic degradation by saturating the Δ^{13} double bond and protected B-chain from oxidation by substitution with a phenyl ring. This New Drug Application describes the studies that Kabi Pharmacia has provided to support the safety and efficacy for isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate; PhXA41; 13,14-dihydro-17-phenyl-15(R)-18,19,10-trinor-$PGF_{2\alpha}$ isopropyl ester; latanoprost; XALATAN™Expected toxicology of class: The major side effects associated with the use of prostaglandins are those identified with stimulation of smooth muscles and/or secretion. Therefore nausea, gi coli and diarrhea are often observed following treatment with prostaglandins. During the last two trimesters of pregnancy prostaglandin $F_{2\alpha}$ causes strong contractions of the uterus and can induce abortion. It has also possible for patients to experience transient pyrexia following PG administration, and large doses of $PGF_{2\alpha}$ can induce hypertension by constricting vascular smooth muscle.

Indication: Reduction of intraocular pressure

Route of Administration: Topically to the Eye

Ingredient	Complete Formula(1 ml contents)	Percentage(% w/w)
Active ingredient		
Latanoprost	50.0 μg	0.005

Overview :Preclinical Efficacy Studies: The preclinical animal efficacy data are not being reviewed for the NDA because they were previously reviewed (IND Original submission, dated 7/10/91 - see attachment 1) and also efficacy will be measured by the clinical studies.

Animal Safety Studies:

Table of Studies

Animal Safety Studies:

Test to evaluate the acute toxicity following a single intravenous administration of 2.0 mg/kg in the mouse

Report Number: L411 S015; Study site:
Report Date: 1/17/91; Date started: 10/22/90; Species: mouse; Strain: OF1 (IOPS Caw); N: 6; Gender: M/F; Doses evaluated: 2 mg/kg; Route: i.v.; Dose Volume: 50 ml/kg; Rate of Dosing: 0.55 ml/min; Vehicle: unspecified; Lot: B 119009; GLP: yes; Reference: 1.13:428

No precautions were taken to ensure that all the test material was delivered, no effects observed at 2 mg/kg. (Also see Seethaler's review of IND in appendix)

Test to evaluate the acute toxicity following a single intravenous administration of 2.0 mg/kg in the rat

Report Number: L411 S016; Study site:
Report Date: January 1991; Date started: 10/22/90; Species: rat; Strain: OFA.SD (IOPS Caw); N: 6; Gender: M/F; Doses evaluated: 2 mg/kg; Route: i.v.; Dose Volume: 50 ml/kg; Rate of Dosing: 0.55 ml/min; Vehicle: saline; Lot: B 119009; GLP: yes; Reference: 1.13:496

Neither the stability nor the absorption of the test material was determined.

No clinical signs, differences in weight gain or deaths were observed following intravenous administration of a single dose of 2 mg/kg. (Also see Seethaler's review of IND in appendix)

Single dose oral (gavage) toxicity study in the mouse

Report Number: L411 S025R; Study site:
; Report Date: April 1992; Date started: 4/24/91; Species: mouse; Strain: Crl:CD-1(ICR)BR; N: 3; Gender: M/F; Doses evaluated: 0.1, 1.0, 10.0 and 50.0 mg/kg; Route: p.o.; Vehicle: Neutralolja TG8/10; Lot: B029103/2; GLP: yes; Reference: 1.13:379

Single oral administrations of latanoprost to mice at doses from 0.1 to 50 mg/kg caused some wetness around the anogenital areas at the intermediate dose and soft or loose stools at the intermediate (10 mg/kg) and high dose (50 mg/kg), but no deaths were observed. No precautions were taken to ensure that all the test material was delivered. (Also see

Seethaler's review of IND in appendix)

Single dose oral (gavage) toxicity study in the rat

Report Number: L411 S026 R001; Study site:
Report Date: April 1992; Date started: 4/16/91; Species: rat; Strain: Crl:CD(SD)BR; N: 3; Gender: M/F; Doses evaluated: 0.1, 1.0, 10.0 and 50.0 mg/kg; Route: p.o.; Vehicle: Neutralolja TG/8/10; Lot: B029103/2; GLP: yes; Reference: 1.13:447

No effects were observed following oral administration of doses from 0.1 to 50 mg/kg.

No precaution were taken to ensure that the dose reported was delivered. (Also see Seethaler's review of IND in appendix)

14 day oral (gavage administration) tolerance study in mouse

Report Number: L411 S047 R001; Study site:
Report Date: July 1992; Date started: 9/6/91; Species: mouse; Strain: Crl:CD-1(ICR)BR; N: 9; Gender: M/F; Doses evaluated: 200 μg/kg; Route: p.o.; Vehicle: Saline; Lot: 1321112; GLP: yes; Reference: 1.17:2220

No treatment related effects were observed. This study was conducted according to UK GLPs and the dose was the intended for the high dose for carcinogenicity study. (Also see Seethaler's review of IND . in appendix)

28 day oral (gavage) sub-acute toxicity in the mouse

Report Number: L411 S030; Study site:
Report Date: June 1992; Date started: 5/30/91; Species: mouse; Strain: CrlCD-1(ISR)BR; N: 6; Gender: M/F; Doses evaluated: 0, 2, 20 and 200 μg/kg; Route: p.o.; Vehicle: Saline; Lot: B259102, B269102; GLP: yes; Reference: 1.18:2252

No analytical evaluation was performed because microbial contamination of diluent used to dilute lower concentrations. No procedures to ensure that dosing apparatus was saturated with test material was performed.

There were no dose dependent moralities, clinical signs, decreases in body weight, food consumption, pathology observations or macroscopic findings. (Also see Seethaler's review of IND in appendix)

28 day oral (gavage) sub-chronic toxicity study in the mouse (oil vehicle)

Report Number: L411 S038; Study site:
Report Date: July 1992; Date started: 5/1/91; Species: mouse; Strain: CrlCD-1(ISR)BR; N: 6; Gender: M/F; Doses evaluated: 0, 0.01, 0.1, 1 and 10 mg/kg; Route: p.o.; Vehicle: Neutralolja TG8/10; Lot: B029103/1; GLP: yes; Reference: 1.18:2366

Samples of test material shipped to the sponsor for chemical analysis were spilled and no analysis is available. No procedures to ensure that dosing apparatus was saturated with test material was performed.

There was an usually high number of animals dying from dosing. The sponsor attributes this to the viscosity of the vehicle. A dose dependent occurrence of anogential staining was observed. (Also see Seethaler's review of IND n appendix)

29 day oral (gavage) sub-chronic toxicity study in the rat

Report Number: L411 S031; Study site:
Report Date: June 1992; Date started: 5/29/91; Species: rat; Strain: Crl:CD(SD)BR; N: 5; Gender: M/F; Doses evaluated: 0, 2, 20 and 200 μg/kg; Route: p.o.; Vehicle: Saline; Lot: B259102, B269102; GLP: yes; Reference: 1.19:2722

Samples were not analyzed because of microbial growth. No proof of absorption was determined.

No effect of test material treatment was observed following treatment with oral doses as high as 200 μg/kg.

29 day oral (gavage) sub-chronic toxicity study in the rat (oil vehicle)

Report Number: L411 S039; Study site:
Report Date: July 1992; Date started: 4/16/91; Species: rat; Strain: Crl:CD(SD)BR; N: 5; Gender: M/F; Doses evaluated: 0, 0.01, 0.1, 1 and 10 mg/kg; Route: p.o.; Vehicle: Neutralolja TG8/10 ; Lot: B029103/1; GLP: yes; Reference: 1.19:2822

The maximum dose employed in this study (10 mg/kg) approximates to 1 x 10^5 the assumed systemic exposure. The vehicle is viscous and there were deaths related to dosing and not drug.

4 week intravenous dose range-finding study in the rat

Report Number: L411 S032; Study site:

Report Date: June 1992; Date started: 5/14/91; Species: rat; Strain: OFA.SD (IOPS Caw); N: 5; Gender: M/F; Doses evaluated: 0, 1, 10, 100 and 340 μg/kg; Route: i.v.; Dose Volume: 1 to 7.1 ml/kg; Rate of Dosing: 0.5 ml/min; Vehicle: Saline; Lot: 069104; GLP: yes; Reference: 1.20:3203

There were no procedures designed to ensure that the intended dose was delivered.

This were a GLP study designed to select the dose for a 13 week rat i.v. study. At the doses selected no animals died during the study and there were no treatment related clinical signs, differences in weight gain, or food consumption. No biologically meaningful treatment related effects were observed in hematologic, blood chemistry, microscopic or macroscopic findings or organ weights.

13 week intravenous study in the rat

Report Number: 9300692; Study site:
Report Date: November 1993; Date started: 2/7/92; Species: rat; Strain: ; N: 10; Gender: M/F; Doses evaluated: 0, 5, 35 and 250 μg/kg; Route: i.v.; Dose Volume: 6.25 ml/kg; Rate of Dosing: 1 ml/min; Vehicle: saline; Lot: B17910%; GLP: yes; Reference: 1.20:3419

Four of 20 rats treated with 250 μg/kg died shortly after intravenous administration. Two males (1 week 6, 1 week 12) and two females (both during week 8) were found dead approximately 15 min. after dosing; no clinical signs were observed immediately prior to death for these animals. Macroscopic and microscopic examination revealed no remarkable effects that were consistent with drug-induced toxicity. One additional high dose male died during terminal blood collection before necropsy, the cause of death was attributed to esophageal perforation.

The failure to provide an explanation for the observance of esophageal perforation in an intravenous study is perplexing, since this is an event that is often seen following oral intubation.

In the remaining rats there were no test article related toxic effect.

Conclusion: 250 μg/kg, i.v. when administered in a concentration of 40 μg/ml at 1 ml/min is a minimal lethal dose.

13 week oral (gavage administration) sub-chronic toxicity study in the mouse

Report Number: 9400368; Study site:
Report Date: June 1994; Date started: 11/24/92; Species: mouse; Strain:

Crl:CD-1(ICR)BR; N: 12; Gender: M/F; Doses evaluated: 0, 2, 20 and 200 μg/kg; Route: p.o.; Vehicle: saline; Lot: 1022712; GLP: yes; Reference: 1.18:2502

The doses of test material were between 50 and 85% of the nominal doses to be delivered. The lower the concentration of test material the greater the deviation from nominal.

There were no clinical signs attributable to test article treatment and there were no test article related deaths.

13 week oral (gavage administration) sub-chronic toxicity study in the rat

Report Number: 9400367; Study site: .
Report Date: June 1994; Date started: 11/19/92; Species: rat; Strain: Crl:CD(SD)BR; N: 10; Gender: M/F; Male weight: 189-240 g; Female weight: 136-185 g; Doses evaluated: 0, 2, 20 and 200 μg/kg; Route: p.o.; Vehicle: saline; Lot: 1022712; GLP: yes; Reference: 1.19:2942

Procedures designed to saturate the dosing apparatus were used in this study.

The concentrations of test material varies from 35 to 87.5% of the expected concentrations.

There were no remarkable effects of oral treatment of rat with doses of approximately 170 μg/kg for 13 weeks.

4 week intravenous dose range-finding study in the beagle dog

Report Number: L411 S033; Study site:
Report Date: June 1992; Date started: 5/14/91; Species: dog; Strain: Beagle; N: 1; Gender: M/F; Male weight: 6.4 - 8.3 kg; Female weight: 6.8 - 7.9 kg; Study duration: 28 day; Doses evaluated: 0, 1, 10, 100 and 340μg/kg; Route: i.v.; Dose volume: 1 (control, 1 and 10 μg/kg), 2.1 (100 μg/kg) and (340 μg/kg) ml/kg Rate of Dosing: 10 ml/min; Vehicle: saline; Lot: B25910 B069104; GLP: yes; Reference: 1.21:3814

This is a GLP dose range finding study in beagle dogs. The average concentration of the test material was 95 % with a range of 90 to 100%.

Following intravenous administration of 100 and 340 μg/kg salivation and miosis were observed during administration, followed by vomiting and sometimes liquid stool immediately following treatment. In addition, a moderate to marked subdued behavior and

sporadic peripheral vasodilation were observed in the 340 μg/kg treated group starting during the injection .

Daily intravenous administration of latanoprost in doses up to 340 μg/kg for 28 days had no effect on body weight gain, food consumption, hematology, blood chemistry, or macro or micro pathology in male or female dogs.

13 Week intravenous toxicity study in the beagle dog

Report Number: 9300282; Study site: Report Date: June 1993; Date started: 10/2/91; Species: dog; Strain: beagle; N: 4; Gender: M/F; Male weight: 6.9 - 10.1 kg; Female weight: 6.8 - 9.8 kg; Study duration: 91 day; Doses evaluated: 0, 1, 10 and 100μg/kg; Route: i.v.; Dose volume: 2.5 or 2.75 ml/kg; Rate of Dosing: approximately 2 min; Vehicle: saline; Lot: B069109 B079109; GLP: yes; Reference: 1.21:3952

The average concentrations of the test material was 88% with a range of 75 to 100%. After the first analysis 10% was added to the low dose to account for amount adsorbed.

One male in the 1 μg/kg treated group was killed on day 20, and was found to have an abscessed parotid salivary gland which was attributed to a traumatic injury.

No treatment related clinical signs were observed the in the low dose treated dogs, however, salivation and miosis were observed following intravenous administration of 10 μg/kg. In addition to salivation and miosis the 100 μg/kg treated animals presented with vomiting .

There were no meaningful treatment related differences in weight gain, food consumption, ophthalmologic observations, hematology, blood chemistry, urine analysis, organ weights or macro or microscopic pathology. Thirty minutes after intravenous administration of 100 μg/kg there was a statistically significant increase in the heart rate. This was not observed following 1 or 10 μg/kg, i.v.

Ocular Studies:

4 week ocular toxicity in the rabbit

Report Number: L411 S019; Study site: France; Report Date: 5/23/91; Date started: 11/9/90; Species: rabbit; Strain: pigmented; N: 5; Gender: M/F; Male weight: 2.2 - 2.5 kg; Female weight: 2.05 - 5.5 kg; Study duration: 28 day; Doses evaluated: 1, 5 and 25μg; Route: ocular; Dose volume: 30 μl; Vehicle: Lot: ; GLP: yes; Reference:

1.14:515

The average concentration of the test material was 97 % with a range of 96 to 98%.

No treatment related effects were observed following twice daily ocular administration of 0.0037, 0.0185 and 0.0925 % solutions to pigmented rabbits.

PhXA41 in different vehicles - 4 week ocular tolerance study in the rabbit

Report Number: 9400064; Study site:

Report Date: February 1994; Date started: 2/18/93; Species: rabbit; Strain: fauve de Bourgogne (pigmented rabbit); N: 5; Gender: M/F; Male weight: 2.2 - 2.7 kg; Female weight: 2.1 - 2.8 kg; Study duration: 28 day; Doses evaluated: Vehicle B, 50 μg/ml in vehicle B, Vehicle D and 50 μg/ml in vehicle D μg/ml; Route: ocular; Dose volume: 1 drop; Vehicle:

Lot: B199301, B179208; GLP: yes; Reference: 1.29:7636

Five rabbits per sex per group were treated twice daily for 28 days with one drop to the eye as follows:

Group Number	Right eye	Left eye
1	Vehicle B	Latanoprost in vehicle B
2	Vehicle B	Nothing
3	Vehicle D	Latanoprost in vehicle D
4	Vehicle D	Nothing

Ref 1.29:7636

There were no deaths during the study; no treatment-related clinical related signs; no differences in body weight gain; no treatment-related changes in ocular irritation, corneal thickness or intraocular pressure and no treatment-related macroscopic or microscopic changes to the eye.

No precautions were taken to ensure that the expected dose was delivered to each animal.

52 Week ocular toxicity study in the rabbit

Report Number: 9400427; Study site:

Report Date: July 1994; Date started: 12/16/91; Species: rabbit; Strain: Dutch Belted; N: 10; Gender: M/F; Male weight: 1.8 - 2.69 kg; Female weight: 1.87 - 2.44 kg; Study duration: 365 day; Doses evaluated: 0, 10, 30 and 100μg; Route: ocular; Dose volume: 0.03 ml; Vehicle:

The average concentration of the test material was 95 % with a range of 91 to 98%.

0.0017, 0.0025 and 0.008 % solutions of latanoprost were administered to male and female Dutch Belted rabbits in one or two drops twice daily for 52 weeks. The test material was well tolerated and there were no treatment related deaths, differences in body weight gain, or food consumption. In the 51st week both male and female rabbits had elevated intraocular pressure in the treated eye of 3 or 2 mmHg greater than the untreated eye for males and females, respectively. No gross abnormalities were found at necropsy and no histopathology finding suggestive of ocular or systemic toxicity were seen.

There were, however, 4/10 females in the control group were observed to have minimal ovarian mineralization and in the 100 µg/kg 5/10 were observed to have minimal mineralization and 1/10 had slight mineralization of the ovaries.

PhXA41 an immunohistological research investigation of the numbers of iridial-stromal melanocytes in rabbits after 52 weeks of ocular treatment

Report Number: 9400483; Study site:

Report Date: September 1994; Date started: 12/16/91; Species: rabbit; Supports Study: Tissues taken from The 52 Week Ocular Toxicity Study in the Rabbit (Study No. 9400427 ref. 1.14:704); GLP: no; Reference: 1.38:11632

There were no differences in the numbers of pigmented or non-pigmented stromal iridal melanocytes.

52 Week ocular toxicity study in the cynomologus monkeys

Report Number: 9400425; Study site:

Report Date: June 1994; Date started: 2/14/91; Species: monkey; Strain: cynomolgus; N: 5; Gender: M/F; Male weight: 2.6 - 4.65 kg; Female weight: 2.05 - 3.3 kg; Study duration: 365 day; Doses evaluated: 0, 10, 25 and 50μg; Route: ocular;

Dose volume: 0.03 ml; Vehicle: Vehicle A;

Lot: B049102, B049103, B089106, B029102 & B069106; GLP: yes; Reference: 1.15:1157

The average concentration of the test material was 102% % with a range of 100 to 105%.

This is a GLP study in which 10, 25 or 50 μg of latanoprost was administered twice daily (total daily exposures were 20, 50 and 100 μg), 6 hours apart. The dose concentration was 0.035 % for the low dose treatment and 0.08% for the intermediate and high (twc drops were administered over 5 min.). Vehicle A was used for the treatment of the vehicle control group and the 25 and 50 μg treated groups and vehicle B was used only for the 10 μg treated group. These concentrations represent a 7 to 16 fold multiple of the concentration used in humans and a doubling to quadrupling of the frequency of the daily exposure.

These treatments were well tolerated and no signs of systemic toxicity or macro- or microscopic histopathology were observed, however, 18 out 30 animals treated with latanoprost developed visible increase in iris pigmentation. No histopathological (see report number 9400611) changes in the surrounding tissues or eyelids were associated with drug treatment. The increase in pigmentation of the iris did not seem to be due to an increase in the number of pigmented cells of the iris stroma, but instead to increased content of the pigment in the dendritic melanocyctes and possibly other pigment containing cells. No effect was seen on the iridial or ciliary pigment epithelium. The morphological appearance and shape of the melanocytes and other pigment containing cells were normal and no difference could be detected when comparing to the contralateral control (vehicle treated) eye. These results were not reversible following 26 or 30 weeks following cessation of treatment.

Topical application of latanoprost also induced a widening of the palpebal fissure in 27 out of 30 monkeys. No histopathological alterations could be detected and Müller's muscle as well as the other muscles of the eyelids appeared normal. These changes in the palpebral fissure were reversible within 3 to 6 months after termination of treatment.

52 Week ocular toxicity study in the cynomologus monkey

Report Number: 9400426; Study site:

Report Date: August 1004; Date started: 11/18/91; Species: monkey; Strain: cynomolgus ; N: ; Gender: M/F; Male weight: 1.96 - 3.15 kg; Female weight: 1.95 - 2.82 kg; Study duration: 365 day; Doses evaluated: 0, 1 and 3μg; Route: ocular; Dose

volume: 0.03 ml administered twice daily; Vehicle: Benzalkonium chloride 0.2-mg,

B049110, B049201, B059110 & B059201; GLP: yes; Reference: 1.16:1774

This is a GLP study in which 1 and 3 μg of latanoprost was administered twice daily (total daily exposures were 2 and 6 μg) , 6 hours apart. The dose concentration was 0.0035 % for the low dose treatment and 0.01% for the high dose. The average concentrations of the test material was 96 % with a range of 94 to 98%. These concentrations represent a 0.7 to 2 fold multiple of the human concentration and a doubling of the frequency of the daily exposure.

These doses were well tolerated and no signs of systemic toxicity or macro- or microscopic histopathology were observed. However, 12 out 19 animals treated with latanoprost developed visible increases in iris pigmentation. The change occurred from 8 to 12 weeks after initiation of treatment.

There was one high dose male that showed a slight increase of the palpebal fissure.

Evaluation of the increased pigmentation in the primate iris observed in a 52 week ocular toxicity study

Report Number: 9400611; Study site:

Report Date: October 1994; Date started: 3/28/94; Species: monkey; Strain: cynomolgus ; Supports Study: Tissues taken from The 52 Week Ocular Toxicity Study in the Rabbit (Study No. 940042 ref. 1.15:1157); GLP: yes; Reference: 1.38:11426

This study is the histologic support study for evaluation of the increased pigmentation seen in the eyes of cynomolgus monkeys (study number 9400425) and shows that there are no differences in the numbers of dendritic cells, any pigmented cell with dendritic processes; small pigmented cells, other pigmented cells with smaller nuclei than the dendritic cells; small unpigmented cell, round cells with small nuclei and no pigment; total cell count, the sum of all three cell types; total pigmented (melanin containing) cells, the sum of the small pigmented cell and dendritic cell; total small cells, the sum of small pigmented and small unpigmented cells and the ratio of dendritic to total small cells.

Evaluation of the increased pigmentation in the primate iris observed in a 52 week ocular toxicity study

Report Number: 9400612; Study site:

Report Date: October 1994; Date started: 2/22/94; Species: monkey; Strain: cynomolgus ; Supports Study: Tissues taken from The 52 Week Ocular Toxicity Study in the Rabbit (Study No. 940042 ref. 1.16:1774); GLP: yes; Reference: 1.38:11507

This study is the light microscopic support study for evaluation of the increased pigmentation seen in the eyes of cynomolgus monkeys (study number 9400426). There were no differences in the numbers of dendritic cells, any pigmented cell with dendritic processes; small pigmented cells, other pigmented dells with smaller nuclei than the dendritic cells; small unpigmented cell, round cells with small nuclei and no pigment; total cell count, the sum of all three cell types; total pigmented (melanin containing) cells, the sum of the small pigmented cell and dendritic cell; total small cells, the sum of small pigmented and small unpigmented cells and the ratio of dendritic to total small cells.

To characterize the cell components of the different regions of the iris of the cynomolgus monkey by electron microscopic examination

Report Number: 9400613; Study site: .

Report Date: October 1994; Date started: 3/28/94; Species: monkey; Strain: cynomolgus ; N: 1; Gender: unspecified; GLP: no; Reference: 1.38:11572

A preliminary study which concludes that cynomolgus monkey eye appears to be similar to rhesus monkey and man.

Reproductive Studies:

PhXA41 - Dose range-finding fertility and reproduction study by intravenous route in the female rat

Report Number: L411 S037 R 001; Study site:

Report Date: June 1994; Date started: 5/27/91; Species: rat; Strain: Ico, SD (IOPS Caw); N: 6; Gender: F; Male weight: 396-448 g; Female weight: 248-289 g; Study duration: 21 day; Doses evaluated: 0 5, 50 and 300μg/kg; Route: i.v., Dose volume: 6.25 ml/kg; Rate of Dosing: 2 ml/min; Vehicle: saline; Lot: B259102; GLP: yes; Reference: 1.30:7981

This study is uninterpretable because the methods say that the rats were dosed from day 6 to 15 of gestation inclusively, and the results report the effects of treatment on estrus and mating behavior.

The concentration of the test material delivered was 81, 67 and 80 % of expected dose for the low, intermediate and high dose , respectively, and was attributed to adsorption losses in the analysis.

Two females in the 300 μg/kg treatment group died after dosing on the first and seventh days of treatment, respectively. All other animals survived to necropsy.

PhXA41- Dose range-finding fertility and reproduction study by intravenous route in the male rat

Report Number: L411 S036 R 001; Study site: [illegible]; Report Date: June 1992; Date started: 5/13/91; Species: rat; Strain: OFA SD (IOPS Caw); N: 6; Gender: M/F; Male weight: 166 - 188 g; Female weight: 214 - 284 g; Study duration: 71 day; Doses evaluated: 5, 50 and 300μg/kg; Route: i.v.; Dose volume: 6.52 ml/kg; Rate of Dosing: 2 ml/min; Vehicle: saline; Lot: B259102; GLP: yes; Reference: 1.30:7855

All males were treated daily for 71 days with test material before mating and up to the day before necropsy. Each male was paired with two untreated females for a maximum of 14 days. The mating partners for a female which failed to mate within 7 days were exchanged for another male from the same group.

The concentration of the test material delivered was 80, 73, and 85 % of the expected concentration for the low, intermediate and high dose, respectively, which was attributed to absorption losses during analysis.

All treated males survived to terminal necropsy with no remarkable observances of differences in clinical sign, weight gain or food consumption. All males from all treatment groups copulated with at least one female and, with the exception of one 50 μg/kg male, induced pregnancy in at least one female. At necropsy there were no macroscopic lesions found and no adverse effects on testis and epididymides weights.

There were no test material induced effects associated with the pre- or post-implantation caesarean data or the fetal data.

Intravenous administration of latanoprost up to 300 μg/kg daily for 71 days had no adverse effects on reproductive performance or F1 generation as measured by live fetus weights or external abnormalities.

Fertility study by intravenous route in the rat (segment I)

Report Number: 9200027; Study site:

Report Date: April 1993; Date started: 10/14/91; Species: rat; Strain: Ico:OFA. SD. (IOPS Caw); N: 20; Gender: M/F; Male weight: 246-289 g; Female weight: 271-319 g; Study duration: 71 day; Doses evaluated: 0, 5, 35 and 250μg/kg; Route: i.v.; Dose volume: 6.25 ml/kg; Rate of Dosing: 2 ml/min; Vehicle: saline; Lot: B069109; GLP: yes; Reference: 1.30:0

The average concentrations of test material for this study was 89 % of expected for the low dose, 73 % of expected for the intermediate dose and 84% of expected for the high dose. The sponsor claims that the samples values are 80% of expected because of adsorption losses in analysis.

Males were dosed for 9 weeks before pairing and , through mating and up to the day before necropsy, and females were dosed daily from 2 weeks before pairing and until 7 days of gestation inclusive. Males were killed after confirmation of successful mating and females were killed on day 20 after mating.

Each fetus was examined for external defects and approximately one half from each litter was examined for visceral abnormalities and the carcasses were fixed and processed for skeletal examination.

By the end of week 12 of treatment 15/20 of the 250 μg/kg treated males died. They died during or shortly after dosing with one dying at 1 hr 20 min after dosing. These deaths were accompanied by respiratory difficulties and/or convulsion. Necropsy examination failed to reveal a cause of death. Some time after fertilization 1/20 females from the high dose group also died.

Surviving high dose males were mated with high dose females, however, the sponsor claims that only 6/20 males were mated, while the data show that 11/20 survived to mating, and that they fertilized from 1 to 4 females.

There were no differences in clinical condition, body weight gain or food consumption between treatment groups.

The fertility data are reported in the following table:

Parameter	Control	5 μg/kg	35 μg/kg	250 μg/kg
Males paired	20	20	20	11*
Females paired	20	20	20	20

Number inseminated	19	20	20	19
Number pregnant	18	17	20	18
Dams with viable fetuses	17**	17	20	16**
Number dams dead	0	0	0	1

* Number of males that were mated. Some males were paired with up to 4 females.
** One female mistimed pregnancy, i.e. corpora lutea and implantion sites present.

There were no aborted fetuses or early deliveries in any of the treated groups. The mean number of corpus lutea, implantation sites, preimplantation losses, postimplantation losses were similar for all treatment groups. Likewise the number of total, early and late resorptions were similar for all treatment groups and there were no fetal deaths. The number of live fetuses and the sex ratio was similar regardless of treatment.

The mean number of live fetuses, sex ratio, fetal weight compared either as a total or as genders were similar for all treatment groups. One fetus in the control group had an umbilical hernia. There were no other remarkable findings seen in any of the remaining litters.

Conclusion:

Latanoprost at an intravenous dose (250 μg/kg, i.v.) that killed both male and female rats had no effect on fertility, reproductive performance or fetuses.

PhXA41 - Dose range-finding study by intravenous route in the pregnant rat

Report Number: L411 S034 R 001; Study site. ?.
Report Date: June 1992; Date started: 6/10/91; Species: rat; Strain: Ico:OFA. SD. (IOPS Caw); N: 6; Gender: F;; Female weight: 222 - 260 g; Study duration: 9 day; Doses evaluated: 0, 0.1, 1.0, 5.0, 50 and 300μg/kg; Route: i.v.; Dose volume: 6.25 ml/kg; Rate of Dosing 2 ml/min; Vehicle: saline; Lot: B259102; GLP: yes; Reference: 1.31:8349

The average concentration of test material for this study was 79% of expected and ranged from 67 to 90% of expected.

The animals were doses daily by infusion in the tail vein from day 6 to day 15 of gestation, and they were killed on day 20 of gestation.

All females survived treatment, had no differences in weight gain, food consumption, clinical condition or macroscopic lesions at necropsy.

The number of rat pregnant and dams with viable or no viable fetuses are shown in the following table:

Parameter	Control	0.1 μg/kg	1 μg/kg	5 μg/kg	50 μg/kg	300 μg/kg
Number/group	6	6	6	6	6	6
Number pregnant	5	6	5	6	6	6
Dams with viable fetuses	5	6	5	5	6	6
Dams with no viable fetuses	0	0	0	1	0	0

There were no aborted fetuses, early delivered fetuses or fetal deaths in any of the treatment groups. The mean number of corpora lutea; implantation sites; preimplantation loss; total, early or late resorptions; post implantation losses or fetal sex ratios were similar for all groups.

There was one incidence of fetal abnormality, cleft palate, found in a 1.0 μg/kg treated dam. No other fetal abnormalities were observed.

Conclusion:

No signs of maternal or fetal toxicity were found with any of the doses evaluated.

Teratology study by intravenous route in the rat (Segment II)

Report Number: 9300279; Study site

Report Date: November 1993; Date started: 3/9/92; Species: rat; Strain: Ico:OFA. SD. (IOPS Caw); N: 25; Weight: 218 - 267 g; Study duration: Day 6 to day 15 of gestation ; Doses evaluated: 0. 5, 50 and 250μg/kg; Route: i.v.; Dose volume: 6.25 ml/kg; Rate of Dosing: 1 ml/min; Vehicle: saline; Lot: B179109; GLP: yes; Reference:

1.31:8451

The average concentration of test material in the formulations was 81, 81 and 86% for the 5, 50 and 250 μg/kg doses, respectively.

The rats were dosed from days 6 to 15 of gestation by intravenous administration through the tail vein. On day 20 of gestation the dams were killed, dissected and examined macroscopically. The fetuses were examined for external defects and approximately one half from each litter was examined for visceral abnormalities and the carcasses were fixed and process for skeletal examination.

The number of rat pregnant and dams with viable or no viable fetuses are shown in the following table:

Parameter	Control	5 μg/kg	50 μg/kg	250 μg/kg
Number/group	25	25	25	25
Number pregnant	23	22	25	22
Dams with viable fetuses	23	22	25	22
Dams with no viable fetuses	0	0	0	0

There were no aborted fetuses, early delivered fetuses or fetal deaths in any of the treatment groups. The mean number of corpora lutea; implantation sites; preimplantation loss; total, early or late resorptions; post implantation losses or fetal sex ratios were similar for all groups.

No treatment related abnormalities were observed in any of the fetuses.

Conclusion:

Latanoprost administered by the intravenous route to rats from day 6 to 15 inclusively had no maternal toxic or fetotoxic effects at doses up to 250 μg/kg.

PhXA41 - Dose range-finding study by intravenous route in the pregnant rabbit

Report Number: L411 S035 R001; Study site:

Report Date: 6/22/94; Date started: 6/8/91; Species:

rabbit; **Strain**: New Zealand; N: 6; **Weight**: 3.2 - 4.0 kg; **Study duration**: Rabbits were dosed from day 6 to 18 of gestation; **Doses evaluated**: 0, 0.1, 1.0, 5.0, 50 and 300μg/kg; **Route**: i.v.; **Dose volume**: 5.63 ml/kg; **Rate of Dosing**: 1 ml/min; **Vehicle**: ; **Lot**: B269102; **GLP**: yes; **Reference**: 1.32:8635

The average concentration of test material was 91% of expected, however, the two highest doses were 73 and 77% of expected, respectively. Also the sponsor asserts that "In higher concentration samples about 80% of expected due to adsorption in the analysis." If the decrease in potency of the formulation were due to adsorption one would expect to see the greatest deviations from the expected values at the lowest concentrations. This was not the case in this study because the lowest concentrations were 105 and 107 % of expected concentrations, respectively.

There were no deaths and immediately following treatment the 300 μg/kg treated rabbits displayed increased "in breathing" (presumably this means the rate of respiration), tremors and slight motor incoordination during the first 5 min after treatment on all days of treatment. These observations were not observed for other treatment groups. There no treatment related effects on body weight gain or food consumption. At necropsy 2 females treated with 50 μg/kg and 4 treated with 300 μg/kg had multiple ovarian cysts. Another female in the 50 μg/kg group had a movable pelvic mass.

The effect of treatment with latanoprost on pregnancy are shown in the following table (ref.: 1.32:8664):

Parameter	Measurement	Dose (μg/kg)					
		Control	0.1	1	5	50	300
Number/group	N	6	6	6	6	6	6
Number pregnant	N	5	5	6	6	6	4
Aborted/litter	N	0	0	0	1	0	0
Dams with viable fetuses	N	5	5	6	5	0	0
Dams with no viable fetuses	N	0	0	0	1	6	4
Corpora Lutea	Mean S.D.	12.4 2.1	11.0 1.9	10.3 1.8	12.0 1.9	0	0

Implantation sites	Mean S.D.	9.8 3.1	10.4 2.5	9.8 1.5	11.4 1.8	8.0 3.3	9.3 1.0
Preimplantation loss (fetuses)	Mean S.D.	22.2 16.0	6.3 9.8	4.3 7.1	4.8 7.3		
Early resorptions (fetuses)	Mean S.D.	0.2 0.4	0.6 1.3	0.3 0.5	0.8 1.8	8.0 3.3	9.3 1.0
Late resorptions (fetuses)	Mean S.D.	0.6 0.5	1.0 0.7	0.7 1.0	2.0 1.9	0	0
Dead fetuses	Total	0	0	0	0		
Postimplantation loss	Mean S.D.	10.2 13.7	15.5 8.4	10.3 8.8	22.9 20.1		
Live fetuses	Mean S.D.	9.0 3.5	8.8 2.4	8.8 1.6	8.6 1.8	0	0
Fetal weight (g) (All viable fetuses)	Mean S.D.	40.37 8.22	41.28 5.26	37.77 4.83	39.16 2.35		

As can be seen, all females receiving intravenous doses of 50 and 300 μg/kg administered between days 6 to 18 of gestation underwent early total resorption their litters. No abnormalities were found in the fetuses at necropsy of dams that received 5 μg/kg, i.v. or less of latanoprost, and there was no effect of treatment on fetal weight.

The occurrence of an abortion of one litter at 5 μg/kg, i.v., may represent the beginning of a treatment-induced effect since doses that were 10 and 60 times higher induced total resorptions of embryos and no abortions could have been observed. The sponsor should have explored doses between 5 and 50 μg/kg.

Conclusion:

Intravenous doses of 50 and 300 μg/kg, i.v. of latanoprost administered to gravid female rabbits from day 6 to 19 induced a dose dependent development of ovarian cysts and in dams treated between days 6 to 18 of gestation. These doses were also embryo toxic, since they induced complete early resorptions. A dose of 1 μg/kg, i.v., is a no effect dose.

Teratology study by intravenous route in the rabbit (Segment II)

Report Number: 9300280; Study site:

Report Date: November 1993; Date started: 4/6/92; Species: rabbit; Strain: New Zealand; N: 18; Gender: F; Female weight: 2.9 - 4.4 kg; Doses evaluated: 0, 0.2, 1, 5μg/kg; Route: i.v.; Dose volume: individual; Rate of Dosing: 5 ml/min (control and high dose), 30 sec (low dose) and 1 min (intermediate dose); Vehicle: saline; Lot: B179109; GLP: yes; Reference: 1.32:8738

All rabbits were dosed intravenously via the marginal ear vein from day 6 to 18 of gestation inclusively, and killed on day 29 of gestation.

The sponsor measured the concentration of the test material twice and found it be 90 and 80% of label concentration. They did not evaluate the test material as it was formulated for administration to the animals.

There were no treatment related deaths or clinical observations in gravid female rabbits treated with varying doses of from 0.2 to 5 μg/kg of latanoprost. The following table shows that the 5 μg/kg dose induced a 25% incidence of abortions and a concomitant decrease in average litter weights, suggesting that this dose is fetotoxic:

Parameter	Measurement	Dose (μg/kg)			
		Control	0.2	1	5
Number/group	N	18	18	18	18
Number pregnant	N	16	15	15*	16
Aborted/litter	N	1	0	0	4
Dams with viable fetuses	N	15	15	14	12
Dams with no viable fetuses	N	0	0	1	0
Corpora Lutea	Mean S.D.	11.1 1.9	12.9 4.4	12.2 2.1	12.2 2.6
Implantation sites	Mean S.D.	10.3 1.8	11.0 4.0	9.8 2.4	11.8 2.8
Preimplantation loss	Mean S.D.	6.8 8.0	11.1 21.4	13.4 9.4	3.1 8.7
Early resorptions/litter	Mean S.D.	0.3 0.6	0.5 0.9	0.3 0.6	0.2 0.6

Late resorptions/litter	Mean S.D.	0.1 0.3	0.7 1.0	0.1 0.4	1.1 1.2
Dead fetuses/litter	Total	1	1	1	0
Postimplantation loss/litter	Mean S.D.	3.9 6.6	9.0 11.5	12.8 28.4	9.6 8.2
Live fetuses/litter	Mean S.D.	9.9 1.8	9.8 3.3	8.2 3.2	10.6 2.2
Fetal weight (g) (All viable fetuses)	Mean S.D.	39.38 4.31	40.38 5.12	41.7 3.43	35.41** 3.97

* One gravid female found dead with lumbar hematoma

** significantly different from control $p \leq 0.05$ by analysis of covariance

Evaluation of body weight gain (fig. 1) and food consumption suggest that the high dose group may be slightly different from control, however, the interpretation is confounded by the induction of abortions during the observation period. Therefore, it is not possible to assess maternal toxicity using these parameters.

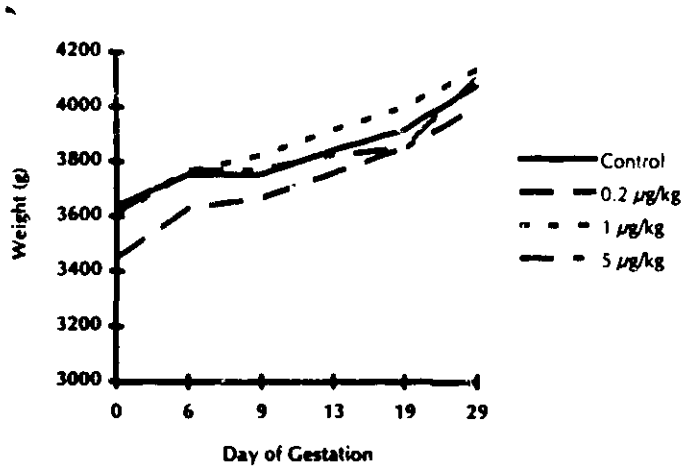


Figure 1 Body weight gain in gravid rabbits from day 0 to 29 of pregnancy following daily treatment with latanoprost.

No treatment related differences were found in the dams upon necropsy examination.

The sex ratios of the fetuses in all treatment groups appears to be similar. Gross

examination of the fetuses found one incidence of gastroschisis and acaudis in the control group and one incidence of spina bifida in the high dose treated group (5 μg/kg). There were no drug related incidences of abnormalities of the soft tissue or skeleton.

Conclusion:

Latanoprost was not teratogenic at intravenous doses up to 5 μg/kg, but was fetotoxic at this dose. The no effect dose in this study was 1 μg/kg.

Dose range-finding peri- and post-natal study (Segment III) by intravenous route in the rat

Report Number: 9200137; Study site:
Report Date: April 1993; Date started: 11/12/91; Species: rat; Strain: OFA, SD, (IOPS Caw); N: 8; Weight: 200 - 270 g; Study duration: Day 15 of gestation to day 21 of lactation; Doses evaluated: 0, 1, 3, 10 and 100μg/kg; Route: i.v.; Dose volume: variable; Rate of Dosing: 2 ml/min; Vehicle: saline; Lot: B079109; GLP: yes; Reference: 1.32:8957

The average concentration of test material was 74% of expected and the range of expected values was 67 -100%.

Rats were dosed daily from day 15 of gestation to day 21 of lactation. Dams were killed on day 21 of lactation or the death of pups. The litter sizes were adjusted to 10 pup on day 4 post partum. Pups were killed after weaning or when culled.

Two females from the 100 μg/kg died 5 days after parturition; necropsy was not able to determine the cause of death, and 2 from the same treatment group were killed on day 9 of lactation following complete loss of litters. No other deaths were observed, nor were there any treatment related changes in clinical condition. Body weight appears not to be affected by increasing doses of latanoprost, however, the variability appears to be greater than control variability at 10 and 100 μg/kg at the later observation periods and this may be indicative . Failure of the sponsor to perform statistical evaluation does not allow for discussion of the parameters of weight gain or food consumption as early indicators of maternal toxicity.

Necropsy of the dams revealed no remarkable findings.

Table 1 shows the data observed for females treated with latanoprost during late pregnancy, lactation and their F1 pups. One of 7 pregnant females in the high dose

group did not deliver any live pups. Deaths of fetuses were observed after parturition following treatment with 3, 10 and 100 μg/kg, and sex ratios for males was lower following treatment with the two highest doses.

Table 1 Effects of Latanoprost on Females Treated During Pregnancy and Lactation and Their F1 Pups

Parameter	Measurement	Dose (μg/kg)				
		0	1	3	10	100
Number/group	N	8	8	8	8	8
Number pregnant	N	8	8	8	6	7
Dams with live pups	N	8	8	8	6	6
Dams with no live pups	N	0	0	0	0	1
Duration of gestation	Mean S.D.	22 0	22 0	22.1 0.4	22.2 1.0	21.4 0.8
Litter size	Mean S.D.	11.6 2.8	11.6 3.5	11.2 5.3	10.3 5.5	12.6 5.8
Sex ratio at birth	%males	49	52	49	39	35
Sex ratio at 21 days	% males	50	54	39	45	33
Total litter death - day 1	litters with deaths/litters	0/8	0/8	1/8	2/6	1/7
Total litter death - day 7	litters with deaths/litters	0/8	0/8	0/7	0/4	2/5*

* One litter was dead by the day 4 observation.

Examination of the pups for physical development and reflexes in time to eye opening, incisor eruption, pinna unfolding, grip reflex, auditory reflex, pupil reflex or righting reflex and no differences were noted by inspection of the results (statistics were not performed).

Conclusion:

Daily intravenous dosing with 1 μg/kg to dams during the peri- and post- natal (day 15 of gestation to day 21 of lactation) was the no effect dose. Doses of 3 μg/kg and greater caused deaths within the litters and doses of 10 μg/kg or greater caused a decrease in the number of males pups delivered.

Developmental toxicity study by intravenous route in the rat (Segment III)

Report Number: 9300281; Study site:

Report Date: November 1993; Date started: 2/17/92; Species: rat; Strain: OFA, SD, (IOPS Caw); N: 25; Weight: 211-267 g; Doses evaluated: 0, 1, 3, and 10μg/kg; Route: i.v.; Dose volume: variable, calculated individually using most recent body weight; Rate of Dosing: 1 ml/min (low dose) and 2 ml/min for remaining groups; Vehicle: saline; Lot: B069109; GLP: yes; Reference: 1.33:9149

The average concentration of test material was 79% of expected and the range of expected values was 67 to 83%.

Females from the F0 generation were dosed daily from day 6 of pregnancy until weaning and the F1 generation was not treated.

Necropsy schedule:

F0 females:

- Killed after weaning of F1 pups (females that failed to produce a viable litter by day 26 post-coitum were killed and necropsied)

F1 pups:

- Unselected F1 pups were killed and necropsied after weaning.
- Dead and culled (day 4 post partum) F1 pups were necropsied.
- The F1 males were killed and necropsied after necropsy of the majority of F1 females.
- The F1 females were killed on day 20 post-coitum for examination of their uterine contents.
- The F1 females without evidence of mating were killed and necropsied after completion of the mating period.

Evaluation of F0 to F1 generation:

No F0 treated females died nor were differences in clinical condition, weight gain or food consumption observed. No treatment related abnormalities were noted at the necropsy of the F0 females.

The effects of treatment gravid females with intravenous latanoprost from day 6 of gestation through the period of lactation on delivery of pups and pup sex ratio, pup birth weight and

weight gain are presented in the following table:

Parameter	Measurement	Dose (μg/kg)			
		0	1	3	10
Number/mated	N	25	25	25	25
Number pregnant	N	22	24	24	24
Dams with stillborns	N	2	4	3	2
Dams with no live pups	N	0	0	0	0
Duration of gestation	Mean S.D.	21.8 0.4	22.0 0.3	22.0 0.2	22.0 0.4
Litter size	Mean S.D.	12.6 2.6	12.4 3.3	13.5 2.5	12.9 3.0
Sex ratio at birth	.%males	49	43	51	51
Sex ratio at 21 days	% males	48	47	50	51
Total litter death - Day 1	litter with deaths/litters	0/22	0/24	0/24	0/24
Pup weight/litter (G):					
Males: Day 1	Mean S.D. N	7.64 0.53 21	7.78 0.67 23	7.67 0.40 24	7.83 0.67 24
Females: Day 1	Mean S.D. N	7.27 0.49 21	7.40 0.61 24	7.27 0.38 24	7.58 0.80 24
Males: Day 21	Mean S.D. N	51.29 4.76 21	53.98 6.16 23	51.53 4.44 24	54.69 5.35 24
Females: Day 21	Mean S.D. N	49.74 4.36 21	51.94 5.82 24	50.37 4.10 24	54.34* 4.46 24

ref : 1.33:9204

* $p \leq 0.01$

There were no treatment related differences in pina unfolding, incisor eruption, eye opening, righting reflexes, grip reflex, auditory startle reflex, or pupil reflex. The results of the water maze test and open field activity test could not be properly evaluated because the sponsor failed to include a description of the methods, however, they claim that there were no treatment-related effects.

There no remarkable differences observed in gravid females or their progeny following intravenous doses up to 10 μg/kg.

Evaluation of F1 to F2 generation

In the F1 generation there were no treatment-related deaths, biologically meaningful differences in body weight gain or clinical condition.

Cesarean data for the F1 generation females and F2 generation pups are presented in the following table:

		Dose (μg/kg)			
Parameter	Measurement	0	1	3	10
Number/group	N*	24	24	25	25
Number pregnant	N	22	22	23	24
Pregnant at C-section	N	20	22	23	23
Dams with live pups	N	19	21	23	23
Dams with no live pups	N	1	1	0	0
Early resorptions	Mean S.D.	0.9 1.3	1.1 0.7	0.7 0.9	1.1 1.1
Litter size (live fetuses)	Mean S.D.	14.9 4.3	15.4 4.5	15.9 2.7	14.9 2.6
Sex ratio at birth	%males	53	49	56	55

ref : 1.33:9462

* N = number of animals

It can be seen that there were no biologically meaningful effects on mating, delivery of live or stillborn pups, early resorptions, litter size or sex ratios. In addition to there were no differences in the mean numbers of corpora lutea, implantation sites, preimplantation losses, dead fetuses, postimplantation losses or fetal weights for either males or females.

One litter of 23 at the 3 μg/kg had one incidence of spina bifida and 1/23 litters in the 10 μg/kg group had one incidence of gastroschisis.

Conclusion:

There were no treatment-related effects to dams of the F0 generation or F1 and F2 pups at intravenous doses of 1, 3 or 10 μg/kg.

Pharmacokinetic/toxicokinetic Studies

Tritium labeled latanoprost. (^{3}H)-PhXA41: Absorption, distribution and excretion following oral and intravenous administration to the rat

Report Number: 9400458; Study site: Report Date: December 1994; Date started: unspecified; Species: rat; Strain: Crl:CD(SD)BR and Lister Hooded for pregnancy study; N: 4; Gender: M/F; Male weight: 155-344; Female weight: 197-334; Study duration: 1 dose; Doses evaluated: 200μg/kg; Route: p.o., i.v.; Dose volume: 5 ml/kg; Rate of Dosing: *ca.* 1 ml/min for intravenous administration; Vehicle: saline; Lot: B179203, B049211 and B179109(used to pre-soak dosing apparatus and TRQ6506 (free acid); GLP: n; Reference: 1.35:10175

Tritium labeled latanoprost (labeled in the C-13 and C-14 positions) was used to evaluate pharmacokinetics, and the parameters presented by the sponsor assume that the majority of radioactivity in the systemic circulation is associated with the active acid metabolite.

Two lots of test material were used in these experiments and their concentration was 82 and 95 % of expected values. The sponsor did flush the dosing apparatus in order to reduce the adsorption of latanoprost to the dosing apparatus.

Following intravenous or oral administration of 200 μg/kg dissolved in saline in a dose volume of 5 ml/kg to Charles River rats, Crl:CD(SD)BR and administered either orally or by the lateral caudal vein at a rate of about 1 ml/min. Blood samples were of unspecified volume were withdrawn for the lateral tail vein at the following intervals:

Oral: Pre-dosing, 15, 30 min, 1, 2, 4, 6, 9, 12, 48, 72 and 96 hours after dosing.

Intravenous: Pre-dosing, 5, 10, 20, 30 min, 1, 2, 6, 24, 48, 72 and 96 hours after dosing.

The times selected for sampling biological fluids are not chosen well for a class of

compounds that are rapidly metabolized. Typically prostaglandins have short half lives, so a study should be designed to sample frequently in the beginning of study and would not be expected to sample at times that exceeded 4 to 5 half lives.

The experimental design of the present studies does not take these factors into consideration and consequently, the results have to viewed with caution and should be considered as preliminary. Therefore, the results will be discussed in qualitative rather in quantitative terms.

The studies show that the plasma levels rose and then declined in an apparent biexponential manner. The data collected show that following intravenous administration the half-life in males and females was less that 30 minutes and that the variability associated with these measurements is large (the mean ± 2 x SD include 0). The AUC measurements for oral administration when expressed as a percentage of the intravenous value, are 281 and 214% greater than iv values for males and females, respectively.

After intravenous administration of 200 μg/kg there was rapid and widespread distribution of radiolabel into tissues. At all time-points, up to 120 hr. after dosing, the distribution of label was generally similar for males and for females. The highest concentration of radiolabel was found in the organs of elimination, i.e. liver, kidney and intestinal tract.

Tissue distribution following administration of the same dose of latanoprost orally was again similar for both genders and the highest concentrations were observed in organs of elimination or secretion and in the contents of the gastrointestinal (GI) tract.

Recovery of radio activity from rats administered 200 μg/kg of tritium labeled latanoprost is presented in table 2. Radio activity is excreted primarily in the feces and urine of rats, and males appear to excrete more label in feces than do females and females seem to excrete more radio label in urine than do males.

Table 2 Recovery of radio label following administration of 200 μg/kg of ^{3}H-labeled latanoprost to Crl:CD(SD)BR, Charles River rats (percentage of administered dose) (N=4/sex)(mean ± SD)

	Intravenous		Oral	
Parameter	Male	Female	Male	Female
Total	90.7 ± 0.2	93.6 ± 7.6	111.6 ± 3.0	104.9 ± 10.2
Feces	49.1 ± 4.6	21.4 ± 2.4	63.7 ± 6.5	39.3 ± 5.0

Renal	36.8 ± 5.7	64.8 ± 7.7	42.8 ± 7.4	54.9 ± 9.8

Results after intravenous administration of 200 μg/kg of latanoprost to rats with their bile ducts cannulated are shown in table 3. In these experiments where bile secretion is diverted from the gastrointestinal tract, relatively little radio activity appears in feces and the percentage found in renal and bile secretion are similar.

Table 3 Bile excretion study following intravenous administration of 2[illegible] μg/kg of latanoprost (percentage of administered dose) (N=4/sex)(mean ± SD)

	male	female
Amount recovered within 24 hr	33.5 ± 8.8	35.3 ± 15.0
Feces	[illegible].9 ± 1.7	0.8 ± 0.6
Renal	10.4 ± 2.9	16.6 ± 6.4
Bile	20.0 ± 11.8	14.5 ± 13.9

Following addition of labeled latanoprost radiolabel is moderately bound to plasma protein of rats, rabbits, monkeys, dogs, and humans (table 4). However, as the concentration of compound increases from 0.01 to 0.100 μg/ml the binding in humans decreases from 87% to 52% and rises again to 80% at the highest concentration, 1.00 μg/ml. This trend holds for all species evaluated.

Table 4 In vitro plasma protein binding of latanoprost free acid in various species.

Concentration μg/ml	Percentage Latanoprost Free Acid Bound				
	Rat	Rabbit	Monkey	Dog	Human
0.001	74	86	71	63	82
0.01	76	84	72	64	87
0.1	56	46	56	58	53
0.25	63	53	52	59	59
1	76	59	62	61	80
Average	69	65.6	62.6	61	72.2

In an experiment where blood samples were pooled from rats treated with 200 μg/kg, iv, the percentage of bound radiolabel to free was approximately 50% at 1 hr after

Renal	36.8 ± 5.7	64.8 ± 7.7	42.8 ± 7.4	54.9 ± 9.8

Results after intravenous administration of 200 μg/kg of latanoprost to rats with their bile ducts cannulated are shown in table 3. In these experiments where bile secretion is diverted from the gastrointestinal tract, relatively little radio activity appears in feces and the percentage found in renal and bile secretion are similar.

Table 3 Bile excretion study following intravenous administration of 200 μg/kg of latanoprost (percentage of administered dose) (N=4/sex)(mean ± SD)

	male	female
Amount recovered within 24 hr	33.5 ± 8.8	35.3 ± 15.0
Feces	1.9 ± 1.7	0.8 ± 0.6
Renal	10.4 ± 2.9	16.6 ± 6.4
Bile	20.0 ± 11.8	14.5 ± 13.9

Following addition of labeled latanoprost radiolabel is moderately bound to plasma protein of rats, rabbits, monkeys, dogs, and humans (table 4). However, as the concentration of compound increases from 0.01 to 0.100 μg/ml the binding in humans decreases from 87% to 52% and rises again to 80% at the highest concentration, 1.00 μg/ml. This trend holds for all species evaluated.

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1	76	59	62	61	80
Average	69	65.6	62.6	61	72.2

In an experiment where blood samples were pooled from rats treated with 200 μg/kg, iv, the percentage of bound radiolabel to free was approximately 50% at 1 hr after

dosing and declined thereafter (fig 2).

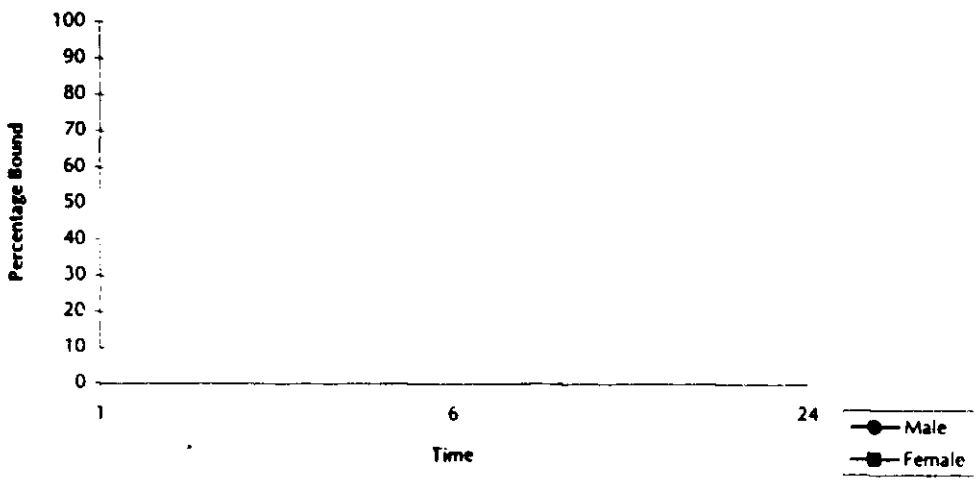

Figure 2 Protein binding of radiolabel in blood taken from rats treated with 200 $\mu g/kg$ of latanoprost.

Whole body autoradiography studies were performed in two day-18 pregnant Lister rats. They were treated intravenously with 200 $\mu g/kg$ of latanoprost. One rat was killed after 1 hr and the highest levels of radioactivity were associated with the contents of the intestinal tract, with moderate levels in the stomach contents, uterus, tongue, kidney cortex (inner renal cortex), kidney pyramid (urine), blood, lymph, nodes, bile ducts, liver, lungs and uveal tract. Low levels or radioactivity were observed in bone marrow, periosteum, brain and spinal cord, adrenal, pituitary, thyroid, thymus, Harderian gland, intra-orbital lachrymal gland, salivary glands, mucosa of the gastrointestinal tract, ovaries, muscle, pancreas, skin (both pigmented and non-pigmented), spleen and tooth pulp. In addition to these tissues, low levels of radioactivity were also found in the mammary tissue, placentae and evenly distributed throughout the fetuses.

By 24 hr high levels of radioactivity were detected and moderate levels were observed in the contents of the intestinal tract and kidney cortex. Low levels of activity were observed in the placentae and no detectable levels were observed in the fetuses or mammary tissue.

Conclusion:

Qualitatively, these studies confirm that like other prostaglandins, latanoprost and/or its free acid have half-lives of between 10 and 50 min, that radio activity is extensively excreted in bile and that radio activity is associated with organs of excretion. Bioavailability of latanoprost could not be estimated because in these preliminary experiments the values of AUC for the oral route of administration was greater than the iv route.

Metabolism of [13,14-^{3}H]-13,14-dihydro-17-phenyl-18,19,20-trinor-PGF$_2\alpha$-isoprpyl ester in the rat after a single intravenous or oral administration

Report Number: 9400105; Study site: Report Date: November 1994; Date started: 6/93; Species: rat; Strain: ; N: 3 for oral and 4 for intravenous; Gender: M/F; Male weight: unspecified; Female weight: unspecified; Study duration: 1 dose; Doses evaluated: 200μg/kg; Route: p.o., i.v.; Dose volume: unspecified; Rate of Dosing: unspecified; Vehicle: saline; Lot: B 179109; label: JS 431303; GLP: yes; Reference: 1.36:10748

Latanoprost was converted to the free acid which is extensively metabolized through β-oxidation before being excreted in the urine of females or the feces of males.

Tritium labeled latanoprost, Plasma levels and excretion of radioactivity following ocular and intravenous administration to the rabbit

Report Number: 9400424; Study site

Report Date: August 1994; Date started: ; Species: rabbit; Strain: Dutch Belted; N: 6; Gender: M/F; Study duration: 1 dose; Doses evaluated: 10 μg/animal and 200 μg /kg ; Route: ocular, i.v.; Dose volume: 30 μl for ocular & unspecified for i.v.; Rate of Dosing: 5 ml/min; Vehicle

Lot: labeled B189203 & B019205; GLP: n; Reference: 1.37:10819

Latanoprost was labeled in [13,14-^{3}H] position and the dosing apparatus was flushed with latanoprost prior to administration into the ear vein.

The collection times were as follows:

Urine: Pre-dose, 0 to 6 , 6 to 12 12 to 24 24 to 48, 48 to 96, 120 to 144 hr after dosing.

Feces: 0 to 12, 12, to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120 and 120 to 144

hr after dosing.

Blood: 5, 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 24, 48, 72, 96, 120 and 144 hr after dosing.

Again the sponsor has not designed the study to optimize the detection of a half-life that is relatively short, however, from the i.v. and ocular initial data they have calculated the following parameters (table 4):

Table 43 Pharmacokinetic parameters in plasma following ocular or intravenous administration to the rabbit.

Parameter	Ocular (10 μg)	Intravenous (200 μg/kg)
$C_{5\ min}$ (ng equiv/ml)	18.36±4.238	704.0±107.0
Initial phase $t_{½}$ (hr)	0.373±0.174	0.259±0.026
Terminal elimination $t_{½}$ (hr)	2.371±1.224	117.4±24.6
AUC estimate over 1st phase (ng equiv. hr/ml)	5.808±1.359	298.3±21.11
AUC over the total time (ng equiv. hr/ml)	7.149±1.612	752.3±76.06
Cl_p (using AUC up to 1.5 hr) (ml/min/kg)	Not Determined	12.80±0.88
Cl_p (total AUC utilized) ml/min/kg	Not Determined	5.098±0.526
Vd (using AUC up to 1.5 hr) (l/kg)	Not Determined	0.286±0.023
Vd (total AUC utilized)) (l/kg)	Not Determined	50.97±6.067
Overall recovery of radioactivity (%)	103.7	102.4

The majority of radioactivity following intravenous administration was eliminated within the first 24 hr by the kidney for both sexes, 49.15% (males) and 67.90% (females). Following ocular administration no apparent gender differences were observed for renal or fecal elimination. The mean urinary elimination was 74.10% and the majority was eliminated within the first 24 hr.

Conclusion: These studies show that radioactivity following administration of tritium labeled latanoprost could be detected in the plasma and excreta, primarily in urine of rabbits whether administered topically to the eye or intravenously. The clearance and volume of distribution could not be compared for the two routes of administration because these parameters were not obtained for the ocular route of administration.

Metabolism of [13,14-^{3}H]-latanoprost in the rabbit after intravenous or topical administration on the eye

Report Number: 9400531; Study site:
Report Date: October 199413,14; Date started: ; Species: rabbit; Strain: Dutch Belted; N: 3; Gender: M/F; Study duration: 1 dose; Doses evaluated: i.v. 0.2 mg/kg; Route: ocular, i.v.; Dose volume: unspecified; Rate of Dosing: unspecified; Vehicle: .
GLP: yes; Reference: 1.37:10926

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

The biological samples were taken from "Tritium labeled latanoprost, Plasma levels and excretion of radioactivity following ocular and intravenous administration to the rabbit," Report Number 9400424. In that study there were 3 male and 3 female rabbits per route of administration, however, the sponsor reports that after intravenous or topical administration to the eye 82.8±9.2% (n=11) and 96.8±15.2% (n=10) of the total administered dose, respectively, was recovered within 15 min.

The times of blood collection after administration were 5, 15, 30, 45, 60, 90 and 120 minutes and the calculated pharmacokinetic parameters are presented in table 5.

Table 5 Pharmacokinetic parameters for latanoprost free acid following ocular or intravenous administration of latanoprost to rabbits.

Parameter	Ocular[a] (10 μg)	Intravenous[b] (200 μg/kg)
Weight (kg)	2.96±0.21	2.46±0.1
Dose (μg/animal)	560±33	9.4±0.5
C_o (ng equiv./ml)	Not determined	627±178
$C_{5\,min}$ (ng equiv./ml) Maximum value measured	12.6±2.3	Not determined
Initial phase $t_{½}$ (min)	4.6±5.1	9.24±3.21
Terminal elimination $t_{½}$ (hr)	1.42±0.27	Not determined
$AUC_{120\,min}$ (ng equiv. hr/ml)	3.01±0.46	147±25
Cl_p (ml/min/kg)	8.0±2.8	30.0±4.6
V (l/kg)	0.39±0.28	0.39±0.11

Ref.: 1.37:10941

a. n=3 males and 2 females

b. n=3 males and 3 females

In the rabbit latanoprost is rapidly converted to the free acid and it's two major metabolites found in urine were the 1,2,3,4-tetranor of the free acid of latanoprost in the form of the δ-lactone and the acid (fig 3) according to retention times or and after derivatisation, according to retention times and mass spectra on GC-MS analysis. There were no obvious differences in the metabolic patterns following intravenous and topical administration and no differences between genders.

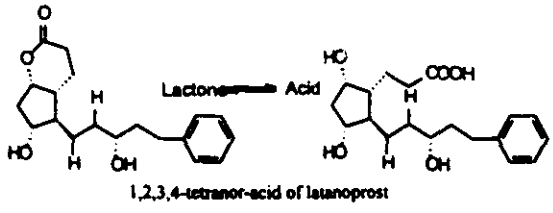

Figure 3 The structures of latanoprost free acid metabolism.

(^{3}H)-PhXA41: Absorption, distribution and excretion following oral, intravenous and

ocular administration to the cynomolgus monkey

Report Number: 9300006; Study site

Report Date: January 1993; Date started: 8/8/91; Species: monkey; Strain: cynomolgus ; N: 3; Gender: M/F; Male weight: 2.00-2.60 kg; Female weight: 2.15-2.40 kg; Study duration: 1 dose; Doses evaluated: 500μg/kg for p.o. and i.v. and 6 μg/eye topically; Route: i.v., p.o., ocular; Dose Volume:

This is a GLP absorption, distribution and excretion study following oral, intravenous and ocular administration of [9-^{3}H]-13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF-$_2$-1-isopropyl ester to the cynomolgus monkey. The tritium label is on the 9 position. 42 ml of blood was taken from each monkey for pharmacokinetic studies. No overt signs of pharmacology or toxicology were observed

The times of sampling for these studies were:

Urine: Pre-dose, 0 to 0.5 , 0.5 to 1, 1 to 1.5, 1.5 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 24, 24 to 48, 40 to 72, 72 to 96 and 96 to 120 hr after dosing

Feces: 0 to 8, 8, to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120 and 120 to 144 hr after dosing

- and blood from the femoral vein -

Blood: 1, 3, 5, 10, 15, 20 and 30 min, 1, 1.5, 2, 4, 8, and 24 hr after dosing

The experimental design of this study is adequate to characterize a compound that has short $t_{1/2}$, however, when the 24 hr samples were lyophilizated no radioactivity was associated with the residue, therefore, volatile radioactivity is probably associated with water.

Most of the activity excreted was recovered within the first 24 hr and the majority of that was recovered between 1.5 and 4 hr after dosing. Using these data one can

estimate the fate of the radio activity.

Results of studies of excretion of radiolabel are presented in table 6. The total values represent unexpectedly low recovery , when compared to rabbits (Report Number: 9400424). There were no substantial gender differences observed.

Table 6 The percent of administered dose of radioactivity excreted following a single dose of ^{3}H-latanoprost.

Route	Dose (μg/kg)	Urine	Feces	Cage Wash	Total
Intravenous	500	29	20	12	61
Oral	500	33	30	9	72
Ocular	12*	31	20	11	62

Ref. table 7.15 1.34:09845

* The actual dose delivered was 9.7 ± 1.7 μg.

Estimates of pharmacokinetic parameters (table 7) Show that clearance and volume of distribution are similar regardless of route of administration and the half-life is between 0.5 and 1 hour.

Table 7 Estimated Pharmacokinetic Parameters in Cynomologus Monkeys Administered Latanoprost by Various Routes (mean±SD (presumable))

Parameter	Intravenous (500 μg/kg)	Oral (500 μg/kg)	Ocular (12 μg)
C_{max} (ng equiv/ml)	774@ 1 min	353±125 @ 0.6 hr	7.5±0.9 @0.11 hr
Initial phase $t_{½}$ (hr)	0.493[a]	1.14±0.52[b]	0.506±0.052[a]
AUC estimate over 1st phase (ng equiv. hr/ml)	635±135	647±308	6.0±1.5
Cl_p (ml/min)	30±5	31±11	27±4
Vd (L)	1.28±0.21	1.45±1.28	1.17±0.17

A. Time range 0.083-2.00 hr
b. Time range 0.33-8.00 hr

At 5 min after intravenous administration detectable amounts of radioactivity were found in all tissues except the iris and lens of the eye. Most of the activity was found in the kidney (10.67 μg equiv./g), prostate (9.56 μg equiv./g) and liver (3.62 μg equiv./g). At

this time the urinary bladder also contained significant amounts of radioactivity (2.28 μg equiv./g). Apart from the above tissues and the GI contents, seminal vesicles, lungs small intestine and stomach, all other tissues sampled contained less than those in blood.

Of particular note, the retina/choroid, conjunctiva, cornea and eyelid) contained moderate levels of radioactivity.

Apart for the dosing site, ocular administration conferred tissue distribution similar to intravenous administration.

Using autoradiographic techniques the highest levels of radioactivity were associated the cornea (including the conjunctiva) 30 min after ocular administration of latanoprost. Moderate radioactivity was present in the ciliary body and humor of the anterior chamber and the anterior part of the sclera. Low levels of radioactivity were present in the iris.

The sponsor also preformed both Ex Vivo and In Vitro plasma and erythrocyte binding studies. Ex Vivo binding at 5 min was 28% to erythrocytes and 73% to plasma proteins. In Vitro binding studies in rat, monkey and man showed erythrocytes binding in rat ca 22%, in monkeys ca 17% and in man ca 12%, and plasma protein binding was ca 79% in rat, ca 87% in monkeys and ca 97% in man.

Conclusion: While the sponsor used adequate sampling times to characterize a short half-life compound the radiolabel selected exchanges with water. Therefore, the results can not be quantitatively evaluated. Qualitatively, the data show that latanoprost has a $t_{½}$ in monkeys of between 0.5 and 1 hour regardless of the route of administration, with a clearance of about 30 ml/min and a volume of distribution of about 1.3 L. They have also shown that Ex Vivo radiolabel binding to erythrocytes was 28% and to plasma protein was 73%, 5 min after exposure. In Vitro binding in man these values were ca 12% for erythrocytes binding and ca 97% for plasma protein binding.

Tissue distribution of [9b-^{3}H]-PhXA41 In the cynomologus monkey after topical administration on the eye, studied by whole body autoradiography

Report Number: L411 C054 R 001; Study site : ... Report Date: December 1994; Date started: unspecified; Species: monkey; Strain: cynomolgus ; N: 2; Gender: M; Weight: 3.86 & 4.42 kg; Study duration: 2 doses; Doses evaluated: 6μg; Route: ocular; Dose volume: 10 μl; Vehicle:

Lot: unspecified but 408783 for labeled material; GLP: no; Reference: 1.35:10061

The formulation differs from the clinical formulation by the presence of a surfactant

and less disodium phosphate.

One monkey was administered test material in one eye 2 hr before sacrifice and in the contralateral eye 30 min. before sacrifice. The other monkey was treated in one eye 24 hr and in the other eye 6 hr before sacrifice.

This study shows that when radio labeled latanoprost is administered to the eye radiolabel is associated with the corneas, anterior chamber, the iris and the ciliary muscle. Radiolabel was also observed in the esophagus.

Metabolism of latanoprost in the cynomolgus monkey after single intravenous, oral or topical administration or the eye

All data on the performance of the animal experiments were reported in the study entitled "**(^{3}H)-PhXA41: Absorption, distribution and excretion following oral, intravenous and ocular administration to the cynomolgus monkey**" Report No. 930006.

Report Number: L 411 C056 R001; Study site :
: Report Date: December 1994; Species: monkey; Strain: cynomolgus ; N: 3; Gender: M/F; Male weight: ; Female weight: ; Study duration: 1 dose; Doses evaluated: 0.5 mg/kg for p.o. and i.v. and 6 μg/eye; Route: ocular, i.v., p.o.; Dose Volume

en
3 ,

Latanoprost was labeled at the 9 position with tritium.

Regardless of the route of administration latanoprost is rapidly hydrolyzes to the free acid (fig 4) and is further metabolized by β-oxidation to the 1,2-dinor and then to the 1,2,3,4-tetranor metabolite of the free acid.

The animals were doses daily by infusion in the tail vein from day 6 to day 15 of gestation, and they were killed on day 20 of gestation.

All females survived treatment, had no differences in weight gain, food consumption, clinical condition or macroscopic lesions at necropsy.

The number of rat pregnant and dams with viable or no viable fetuses are shown in the following table:

Parameter	Control	0.1 μg/kg	1 μg/kg	5 μg/kg	50 μg/kg	300 μg/kg
Number/group	6	6	6	6	6	6
Number pregnant	5	6	5	6	6	6
Dams with viable fetuses	5	6	5	5	6	6
Dams with no viable fetuses	0	0	0	1	0	0

There were no aborted fetuses, early delivered fetuses or fetal deaths in any of the treatment groups. The mean number of corpora lutea; implantation sites; preimplantation loss; total, early or late resorptions; post implantation losses or fetal sex ratios were similar for all groups.

There was one incidence of fetal abnormality, cleft palate, found in a 1.0 μg/kg treated dam. No other fetal abnormalities were observed.

Conclusion:

No signs of maternal or fetal toxicity were found with any of the doses evaluated.

Teratology study by intravenous route in the rat (Segment II)

Report Number: 9300279; Study site

Report Date: November 1993; Date started: 3/9/92; Species: rat; Strain: Ico:OFA. SD. (IOPS Caw); N: 25; Weight: 218 - 267 g; Study duration: Day 6 to day 15 of gestation ; Doses evaluated: 0, 5, 50 and 250μg/kg; Route: i.v.; Dose volume: 6.25 ml/kg; Rate of Dosing: 1 ml/min; Vehicle: saline; Lot: B179109; GLP: yes; Reference:

1.31:8451

The average concentration of test material in the formulations was 81, 81 and 86% for the 5, 50 and 250 μg/kg doses, respectively.

The rats were dosed from days 6 to 15 of gestation by intravenous administration through the tail vein. On day 20 of gestation the dams were killed, dissected and examined macroscopically. The fetuses were examined for external defects and approximately one half from each litter was examined for visceral abnormalities and the carcasses were fixed and process for skeletal examination.

The number of rat pregnant and dams with viable or no viable fetuses are shown in the following table:

Parameter	Control	5 μg/kg	50 μg/kg	250 μg/kg
Number/group	25	25	25	25
Number pregnant	23	22	25	22
Dams with viable fetuses	23	22	25	22
Dams with no viable fetuses	0	0	0	0

There were no aborted fetuses, early delivered fetuses or fetal deaths in any of the treatment groups. The mean number of corpora lutea; implantation sites; preimplantation loss; total, early or late resorptions; post implantation losses or fetal sex ratios were similar for all groups.

No treatment related abnormalities were observed in any of the fetuses.

Conclusion:

Latanoprost administered by the intravenous route to rats from day 6 to 15 inclusively had no maternal toxic or fetotoxic effects at doses up to 250 μg/kg.

PhXA41 - Dose range-finding study by intravenous route in the pregnant rabbit

Report Number: L411 S035 R001; Study site

Report Date: 6/22/94; Date started: 6/8/91; Species:

rabbit; **Strain**: New Zealand; N: 6; **Weight**: 3.2 - 4.0 kg; **Study duration**: Rabbits were dosed from day 6 to 18 of gestation; **Doses evaluated**: 0, 0.1, 1.0, 5.0, 50 and 300μg/kg; **Route**: i.v.; **Dose volume**: 5.63 ml/kg; **Rate of Dosing**: 1 ml/min; **Vehicle**: ; **Lot**: B269[illegible]2; **GLP**: yes; **Reference**: 1.32:8635

The average concentration of test material was 91% of expected, however, the two highest doses were 73 and 77% of expected, respectively. Also the sponsor asserts that "In higher concentration samples about 80% of expected due to adsorption in the analysis." If the decrease in potency of the formulation were due to adsorption one would expect to see the greatest deviations from the expected values at the lowest concentrations. This was not the case in this study because the lowest concentrations were 105 and 107 % of expected concentrations, respectively.

There were no deaths and immediately following treatment the 300 μg/kg treated rabbits displayed increased "in breathing" (presumably this means the rate of respiration), tremors and slight motor incoordination during the first 5 min after treatment on all days of treatment. These observations were not observed for other treatment groups. There no treatment related effects on body weight gain or food consumption. At necropsy 2 females treated with 50 μg/kg and 4 treated with 300 μg/kg had multiple ovarian cysts. Another female in the 50 μg/kg group had a movable pelvic mass.

The effect of treatment with latanoprost on pregnancy are shown in the following table (ref.: 1.32:8664):

Parameter	Measurement	Dose (μg/kg)					
		Control	0.1	1	5	50	300
Number/group	N	6	6	6	6	6	6
Number pregnant	N	5	5	6	6	6	4
Aborted/litter	N	0	0	0	1	0	0
Dams with viable fetuses	N	5	5	6	5	0	0
Dams with no viable fetuses	N	0	0	0	1	6	4
Corpora Lutea	Mean S.D.	12.4 2.1	11.0 1.9	10.3 1.8	12.0 1.9	0	0

Implantation sites	Mean S.D.	9.8 3.1	10.4 2.5	9.8 1.5	11.4 1.8	8.0 3.3	9.3 1.0
Preimplantation loss (fetuses)	Mean S.D.	22.2 16.0	6.3 9.8	4.3 7.1	4.8 7.3		
Early resorptions (fetuses)	Mean S.D.	0.2 0.4	0.6 1.3	0.3 0.5	0.8 1.8	8.0 3.3	9.3 1.0
Late resorptions (fetuses)	Mean S.D.	0.6 0.5	1.0 0.7	0.7 1.0	2.0 1.9	0	0
Dead fetuses	Total	0	0	0	0		
Postimplantation loss	Mean S.D.	10.2 13.7	15.5 8.4	10.3 8.8	22.9 20.1		
Live fetuses	Mean S.D.	9.0 3.5	8.8 2.4	8.8 1.6	8.6 1.8	0	0
Fetal weight (g) (All viable fetuses)	Mean S.D.	40.37 8.22	41.28 5.26	37.77 4.83	39.16 2.35		

As can be seen, all females receiving intravenous doses of 50 and 300 μg/kg administered between days 6 to 18 of gestation underwent early total resorption their litters. No abnormalities were found in the fetuses at necropsy of dams that received 5 μg/kg, i.v. or less of latanoprost, and there was no effect of treatment on fetal weight.

The occurrence of an abortion of one litter at 5 μg/kg, i.v., may represent the beginning of a treatment-induced effect since doses that were 10 and 60 times higher induced total resorptions of embryos and no abortions could have been observed. The sponsor should have explored doses between 5 and 50 μg/kg.

Conclusion:

Intravenous doses of 50 and 300 μg/kg, i.v. of latanoprost administered to gravid female rabbits from day 6 to 19 induced a dose dependent development of ovarian cysts and in dams treated between days 6 to 18 of gestation. These doses were also embryo toxic, since they induced complete early resorptions. A dose of 1 μg/kg, i.v., is a no effect dose.

Teratology study by intravenous route in the rabbit (Segment II)

Report Number: 9300280; Study site:

Report Date: November 1993; Date started: 4/6/92; Species: rabbit; Strain: New Zealand; N: 18; Gender: F; Female weight: 2.9 - 4.4 kg; Doses evaluated: 0, 0.2, 1, 5μg/kg; Route: i.v.; Dose volume: individual; Rate of Dosing: 5 ml/min (control and high dose), 30 sec (low dose) and 1 min (intermediate dose); Vehicle: saline; Lot: B179109; GLP: yes; Reference: 1.32:8738

All rabbits were dosed intravenously via the marginal ear vein from day 6 to 18 of gestation inclusively, and killed on day 29 of gestation.

The sponsor measured the concentration of the test material twice and found it be 90 and 80% of label concentration. They did not evaluate the test material as it was formulated for administration to the animals.

There were no treatment related deaths or clinical observations in gravid female rabbits treated with varying doses of from 0.2 to 5 μg/kg of latanoprost. The following table shows that the 5 μg/kg dose induced a 25% incidence of abortions and a concomitant decrease in average litter weights, suggesting that this dose is fetotoxic:

Parameter	Measurement	Dose (μg/kg)			
		Control	0.2	1	5
Number/group	N	18	18	18	18
Number pregnant	N	16	15	15*	16
Aborted/litter	N	1	0	0	4
Dams with viable fetuses	N	15	15	14	12
Dams with no viable fetuses	N	0	0	1	0
Corpora Lutea	Mean S.D.	11.1 1.9	12.9 4.4	12.2 2.1	12.2 2.6
Implantation sites	Mean S.D.	10.3 1.8	11.0 4.0	9.8 2.4	11.8 2.8
Preimplantation loss	Mean S.D.	6.8 8.0	11.1 21.4	13.4 9.4	3.1 8.7
Early resorptions/litter	Mean S.D.	0.3 0.6	0.5 0.9	0.3 0.6	0.2 0.6

Late resorptions/litter	Mean S.D.	0.1 0.3	0.7 1.0	0.1 0.4	1.1 1.2
Dead fetuses/litter	Total	1	1	1	0
Postimplantation loss/litter	Mean S.D.	3.9 6.6	9.0 11.5	12.8 28.4	9.6 8.2
Live fetuses/litter	Mean S.D.	9.9 1.8	9.8 3.3	8.2 3.2	10.6 2.2
Fetal weight (g) (All viable fetuses)	Mean S.D.	39.38 4.31	40.38 5.12	41.7 3.43	35.41** 3.97

* One gravid female found dead with lumbar hematoma
** significantly different from control $p \leq 0.05$ by analysis of covariance

Evaluation of body weight gain (fig. 1) and food consumption suggest that the high dose group may be slightly different from control, however, the interpretation is confounded by the induction of abortions during the observation period. Therefore, it is not possible to assess maternal toxicity using these parameters.

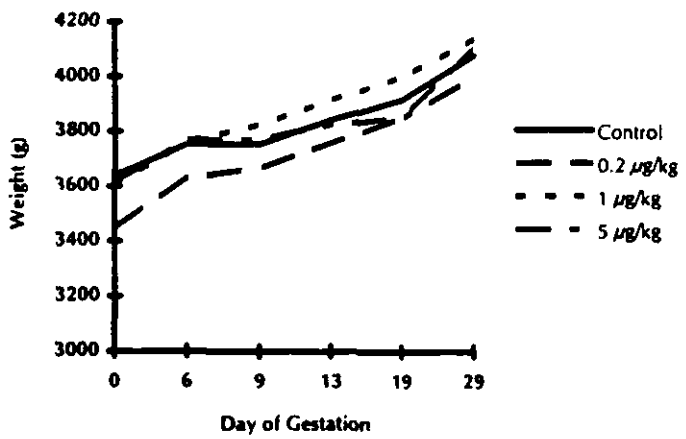

Figure 1 Body weight gain in gravid rabbits from day 0 to 29 of pregnancy following daily treatment with latanoprost.

No treatment related differences were found in the dams upon necropsy examination.

The sex ratios of the fetuses in all treatment groups appears to be similar. Gross

examination of the fetuses found one incidence of gastroschisis and acaudis in the control group and one incidence of spina bifida in the high dose treated group (5 μg/kg). There were no drug related incidences of abnormalities of the soft tissue or skeleton.

Conclusion:

Latanoprost was not teratogenic at intravenous doses up to 5 μg/kg, but was fetotoxic at this dose. The no effect dose in this study was 1 μg/kg.

Dose range-finding peri- and post-natal study (Segment III) by intravenous route in the rat

Report Number: 9200137; Study site:
Report Date: April 1993; Date started: 11/12/91; Species: rat; Strain: OFA, SD, (IOPS Caw); N: 8; Weight: 200 - 270 g; Study duration: Day 15 of gestation to day 21 of lactation; Doses evaluated: 0, 1, 3, 10 and 100μg/kg; Route: i.v.; Dose volume: variable; Rate of Dosing: 2 ml/min; Vehicle: saline; Lot: B079109; GLP: yes; Reference: 1.32:8957

The average concentration of test material was 74% of expected and the range of expected values was 67 -100%.

Rats were dosed daily from day 15 of gestation to day 21 of lactation. Dams were killed on day 21 of lactation or the death of pups. The litter sizes were adjusted to 10 pup on day 4 post partum. Pups were killed after weaning or when culled.

Two females from the 100 μg/kg died 5 days after parturition; necropsy was not able to determine the cause of death, and 2 from the same treatment group were killed on day 9 of lactation following complete loss of litters. No other deaths were observed, nor were there any treatment related changes in clinical condition. Body weight appears not to be affected by increasing doses of latanoprost, however, the variability appears to be greater than control variability at 10 and 100 μg/kg at the later observation periods and this may be indicative . Failure of the sponsor to perform statistical evaluation does not allow for discussion of the parameters of weight gain or food consumption as early indicators of maternal toxicity.

Necropsy of the dams revealed no remarkable findings.

Table 1 shows the data observed for females treated with latanoprost during late pregnancy, lactation and their F1 pups. One of 7 pregnant females in the high dose

group did not deliver any live pups. Deaths of fetuses were observed after parturition following treatment with 3, 10 and 100 μg/kg, and sex ratios for males was lower following treatment with the two highest doses.

Table 1 Effects of Latanoprost on Females Treated During Pregnancy and Lactation and Their F1 Pups

Parameter	Measurement	Dose (μg/kg)				
		0	1	3	10	100
Number/group	N	8	8	8	8	8
Number pregnant	N	8	8	8	6	7
Dams with live pups	N	8	8	8	6	6
Dams with no live pups	N	0	0	0	0	1
Duration of gestation	Mean S.D.	22 0	22 0	22.1 0.4	22.2 1.0	21.4 0.8
Litter size	Mean S.D.	11.6 2.8	11.6 3.5	11.2 5.3	10.3 5.5	12.6 5.8
Sex ratio at birth	%males	49	52	49	39	35
Sex ratio at 21 days	% males	50	54	39	45	33
Total litter death - day 1	litters with deaths/litters	0/8	0/8	1/8	2/6	1/7
Total litter death - day 7	litters with deaths/litters	0/8	0/8	0/7	0/4	2/5*

* One litter was dead by the day 4 observation.

Examination of the pups for physical development and reflexes in time to eye opening, incisor eruption, pinna unfolding, grip reflex, auditory reflex, pupil reflex or righting reflex and no differences were noted by inspection of the results (statistics were not performed).

Conclusion:

Daily intravenous dosing with 1 μg/kg to dams during the peri- and post- natal (day 15 of gestation to day 21 of lactation) was the no effect dose. Doses of 3 μg/kg and greater caused deaths within the litters and doses of 10 μg/kg or greater caused a decrease in the number of males pups delivered.

Developmental toxicity study by intravenous route in the rat (Segment III)

Report Number: 9300281; Study site

Report Date: November 1993; Date started: 2/17/92; Species: rat; Strain: OFA, SD, (IOPS Caw); N: 25; Weight: 211-267 g; Doses evaluated: 0, 1, 3, and 10μg/kg; Route: i.v.; Dose volume: variable, calculated individually using most recent body weight; Rate of Dosing: 1 ml/min (low dose) and 2 ml/min for remaining groups; Vehicle: saline; Lot: B069109; GLP: yes; Reference: 1.33:9149

The average concentration of test material was 79% of expected and the range of expected values was 67 to 83%.

Females from the F0 generation were dosed daily from day 6 of pregnancy until weaning and the F1 generation was not treated.

Necropsy schedule:

F0 females:

- Killed after weaning of F1 pups (females that failed to produce a viable litter by day 26 post-coitum were killed and necropsied)

F1 pups:

- Unselected F1 pups were killed and necropsied after weaning.
- Dead and culled (day 4 post partum) F1 pups were necropsied.
- The F1 males were killed and necropsied after necropsy of the majority of F1 females.
- The F1 females were killed on day 20 post-coitum for examination of their uterine contents.
- The F1 females without evidence of mating were killed and necropsied after completion of the mating period.

Evaluation of F0 to F1 generation:

No F0 treated females died nor were differences in clinical condition, weight gain or food consumption observed. No treatment related abnormalities were noted at the necropsy of the F0 females.

The effects of treatment gravid females with intravenous latanoprost from day 6 of gestation through the period of lactation on delivery of pups and pup sex ratio, pup birth weight and

weight gain are presented in the following table:

Parameter	Measurement	Dose (μg/kg)			
		0	1	3	10
Number/mated	N	25	25	25	25
Number pregnant	N	22	24	24	24
Dams with stillborns	N	2	4	3	2
Dams with no live pups	N	0	0	0	0
Duration of gestation	Mean S.D.	21.8 0.4	22.0 0.3	22.0 0 2	22.0 0.4
Litter size	Mean S.D.	12.6 2.6	12.4 3.3	13.5 2.5	12.9 3.0
Sex ratio at birth	.%males	49	43	51	51
Sex ratio at 21 days	% males	48	47	50	51
Total litter death - Day 1	litter with deaths/litters	0/22	0/24	0/24	0/24
Pup weight/litter (G):					
Males: Day 1	Mean S.D. N	7.64 0.53 21	7.78 0.67 23	7.67 0.40 24	7.83 0.67 24
Females: Day 1	Mean S.D. N	7.27 0.49 21	7.40 0.61 24	7.27 0.38 24	7.58 0.80 24
Males: Day 21	Mean S.D. N	51.29 4.76 21	53.98 6.16 23	51.53 4.44 24	54.69 5.35 24
Females: Day 21	Mean S.D. N	49.74 4.36 21	51.94 5.82 24	50.37 4.10 24	54.34* 4.46 24

ref : 1.33:9204

* $p \leq 0.01$

There were no treatment related differences in pina unfolding, incisor eruption, eye opening, righting reflexes, grip reflex, auditory startle reflex, or pupil reflex. The results of the water maze test and open field activity test could not be properly evaluated because the sponsor failed to include a description of the methods, however, they claim that there were no treatment-related effects.

There no remarkable differences observed in gravid females or their progeny following intravenous doses up to 10 μg/kg.

Evaluation of F1 to F2 generation

In the F1 generation there were no treatment-related deaths, biologically meaningful differences in body weight gain or clinical condition.

Cesarean data for the F1 generation females and F2 generation pups are presented in the following table:

		Dose (μg/kg)			
Parameter	Measurement	0	1	3	10
Number/group	N*	24	24	25	25
Number pregnant	N	22	22	23	24
Pregnant at C-section	N	20	22	23	23
Dams with live pups	N	19	21	23	23
Dams with no live pups	N	1	1	0	0
Early resorptions	Mean S.D.	0.9 1.3	1.1 0.7	0.7 0.9	1.1 1.1
Litter size (live fetuses)	Mean S.D.	14.9 4.3	15.4 4.5	15.9 2.7	14.9 2.6
Sex ratio at birth	%males	53	49	56	55

ref : 1.33:9462

* N = number of animals

It can be seen that there were no biologically meaningful effects on mating, delivery of live or stillborn pups, early resorptions, litter size or sex ratios. In addition to there were no differences in the mean numbers of corpora lutea, implantation sites, preimplantation losses, dead fetuses, postimplantation losses or fetal weights for either males or females.

One litter of 23 at the 3 μg/kg had one incidence of spina bifida and 1/23 litters in the 10 μg/kg group had one incidence of gastroschisis.

Conclusion:

There were no treatment-related effects to dams of the F0 generation or F1 and F2 pups at intravenous doses of 1, 3 or 10 μg/kg.

Pharmacokinetic/toxicokinetic Studies

Tritium labeled latanoprost. (^{3}H)-PhXA41: Absorption, distribution and excretion following oral and intravenous administration to the rat

Report Number: 9400458; Study site:
Report Date: December 1994; Date started: unspecified; Species: rat; Strain: Crl:CD(SD)BR and Lister Hooded for pregnancy study; N: 4; Gender: M/F; Male weight: 155-344; Female weight: 197-334; Study duration: 1 dose; Doses evaluated: 200μg/kg; Route: p.o., i.v.; Dose volume: 5 ml/kg; Rate of Dosing: *ca.* 1 ml/min for intravenous administration; Vehicle: saline; Lot: B179203, B049211 and B179109(used to pre-soak dosing apparatus and TRQ6506 (free acid); GLP: n; Reference: 1.35:10175

Tritium labeled latanoprost (labeled in the C-13 and C-14 positions) was used to evaluate pharmacokinetics, and the parameters presented by the sponsor assume that the majority of radioactivity in the systemic circulation is associated with the active acid metabolite.

Two lots of test material were used in these experiments and their concentration was 82 and 95 % of expected values. The sponsor did flush the dosing apparatus in order to reduce the adsorption of latanoprost to the dosing apparatus.

Following single intravenous or oral administration of 200 μg/kg dissolved in saline in a dose volume of 5 ml/kg to Charles River rats, Crl:CD(SD)BR and administered either orally or by the lateral caudal vein at a rate of about 1 ml/min. Blood samples were of unspecified volume were withdrawn for the lateral tail vein at the following intervals:

Oral: Pre-dosing, 15, 30 min, 1, 2, 4, 6, 9, 12, 48, 72 and 96 hours after dosing.

Intravenous: Pre-dosing, 5, 10, 20, 30 min, 1, 2, 6, 24, 48, 72 and 96 hours after dosing.

The times selected for sampling biological fluids are not chosen well for a class of

compounds that are rapidly metabolized. Typically prostaglandins have short half lives, so a study should be designed to sample frequently in the beginning of study and would not be expected to sample at times that exceeded 4 to 5 half lives.

The experimental design of the present studies does not take these factors into consideration and consequently, the results have to viewed with caution and should be considered as preliminary. Therefore, the results will be discussed in qualitative rather in quantitative terms.

The studies show that the plasma levels rose and then declined in an apparent biexponential manner. The data collected show that following intravenous administration the half-life in males and females was less that 30 minutes and that the variability associated with these measurements is large (the mean ± 2 x SD include 0). The AUC measurements for oral administration when expressed as a percentage of the intravenous value, are 281 and 214% greater than iv values for males and females, respectively.

After intravenous administration of 200 μg/kg there was rapid and widespread distribution of radiolabel into tissues. At all time-points, up to 120 hr. after dosing, the distribution of label was generally similar for males and for females. The highest concentration of radiolabel was found in the organs of elimination, i.e. liver, kidney and intestinal tract.

Tissue distribution following administration of the same dose of latanoprost orally was again similar for both genders and the highest concentrations were observed in organs of elimination or secretion and in the contents of the gastrointestinal (GI) tract.

Recovery of radio activity from rats administered 200 μg/kg of tritium labeled latanoprost is presented in table 2. Radio activity is excreted primarily in the feces and urine of rats, and males appear to excrete more label in feces than do females and females seem to excrete more radio label in urine than do males.

Table 2 Recovery of radio label following administration of 200 μg/kg of ^{3}H-labeled latanoprost to Crl:CD(SD)BR, Charles River rats (percentage of administered dose) (N=4/sex)(mean ± SD)

	Intravenous		Oral	
Parameter	Male	Female	Male	Female
Total	90.7 ± 0.2	93.6 ± 7.6	111.6 ± 3.0	104.9 ± 10.2
Feces	49.1 ± 4.6	21.4 ± 2.4	63.7 ± 6.5	39.3 ± 5.0

Renal	36.8 ± 5.7	64.8 ± 7.7	42.8 ± 7.4	54.9 ± 9.8

Results after intravenous administration of 200 μg/kg of latanoprost to rats with their bile ducts cannulated are shown in table 3. In these experiments where bile secretion is diverted from the gastrointestinal tract, relatively little radio activity appears in feces and the percentage found in renal and bile secretion are similar.

Table 3 Bile excretion study following intravenous administration of 200 μg/kg of latanoprost (percentage of administered dose) (N=4/sex)(mean ± SD)

	male	female
Amount recovered within 24 hr	33.5 ± 8.8	35.3 ± 15.0
Feces	1.9 ± 1.7	0.8 ± 0.6
Renal	10.[illegible] ± 2.9	16.6 ± 6.4
Bile	20.0 ± 11.8	14.5 ± 13.9

Following addition of labeled latanoprost radiolabel is moderately bound to plasma protein of rats, rabbits, monkeys, dogs, and humans (table 4). However, as the concentration of compound increases from 0.01 to 0.100 μg/ml the binding in humans decreases from 87% to 52% and rises again to 80% at the highest concentration, 1.00 μg/ml. This trend holds for all species evaluated.

Table 4 In vitro plasma protein binding of latanoprost free acid in various species.

Concentration μg/ml	Percentage Latanoprost Free Acid Bound				
	Rat	Rabbit	Monkey	Dog	Human
0.001	74	86	71	63	82
0.01	76	84	72	64	87
0.1	56	46	56	58	53
0.25	63	53	52	59	59
1	76	59	62	61	80
Average	69	65.6	62.6	61	72.2

In an experiment where blood samples were pooled from rats treated with 200 μg/kg, iv, the percentage of bound radiolabel to free was approximately 50% at 1 hr after

Renal	36.8 ± 5.7	64.8 ± 7.7	42.8 ± 7.4	54.9 ± 9.8

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	male	female
Amount recovered within 24 hr	33.5 ± 8.8	35.3 ± 15.0
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0.001	74	86	71	63	82
0.01	76	84	72	64	87
0.1	56	46	56	58	53
0.25	63	53	52	59	59
1	76	59	62	61	80
Average	69	65.6	62.6	61	72.2

In an experiment where blood samples were pooled from rats treated with 200 μg/kg, iv, the percentage of bound radiolabel to free was approximately 50% at 1 hr after

dosing and declined thereafter (fig 2).

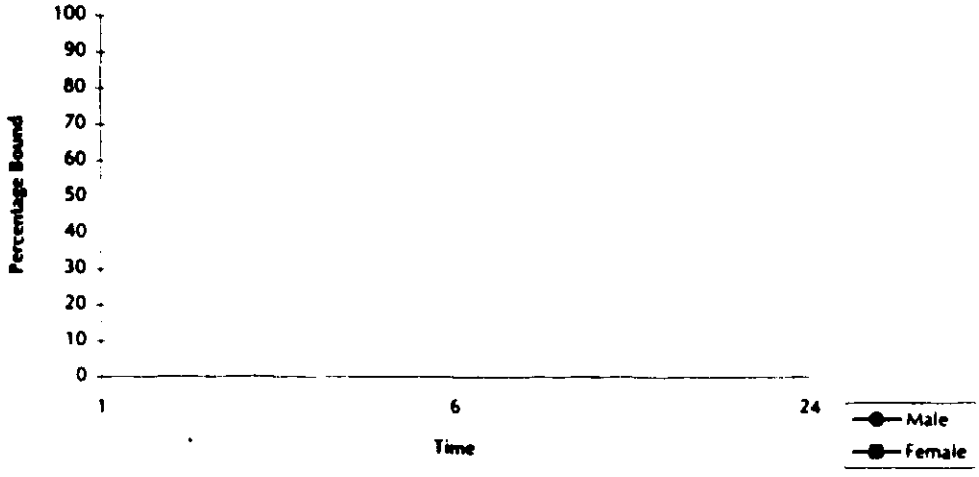


Figure 2 Protein binding of radiolabel in blood taken from rats treated with 200 μg/kg of latanoprost.

Whole body autoradiography studies were performed in two day-18 pregnant Lister rats. They were treated intravenously with 200 μg/kg of latanoprost. One rat was killed after 1 hr and the highest levels of radioactivity were associated with the contents of the intestinal tract, with moderate levels in the stomach contents, uterus, tongue, kidney cortex (inner renal cortex), kidney pyramid (urine), blood, lymph, nodes, bile ducts, liver, lungs and uveal tract. Low levels or radioactivity were observed in bone marrow, periosteum, brain and spinal cord, adrenal, pituitary, thyroid, thymus, Harderian gland, intra-orbital lachrymal gland, salivary glands, mucosa of the gastrointestinal tract, ovaries, muscle, pancreas, skin (both pigmented and non-pigmented), spleen and tooth pulp. In addition to these tissues, low levels of radioactivity were also found in the mammary tissue, placentae and evenly distributed throughout the fetuses.

By 24 hr high levels of radioactivity were detected and moderate levels were observed in the contents of the intestinal tract and kidney cortex. Low levels of activity were observed in the placentae and no detectable levels were observed in the fetuses or mammary tissue.

Conclusion:

Qualitatively, these studies confirm that like other prostaglandins, latanoprost and/or its free acid have half-lives of between 10 and 50 min, that radio activity is extensively excreted in bile and that radio activity is associated with organs of excretion. Bioavailability of latanoprost could not be estimated because in these preliminary experiments the values of AUC for the oral route of administration was greater than the iv route.

Metabolism of [13,14-^{3}H]-13,14-dihydro-17-phenyl-18,19,20-trinor-PGF$_2\alpha$-isoprpyl ester in the rat after a single intravenous or oral administration

Report Number: 9400105; Study site ; Report Date: November 1994; Date started: 6/93; Species: rat; Strain: ; N. 3 for oral and 4 for intravenous; Gender: M/F; Male weight: unspecified; Female weight: unspecified; Study duration: 1 dose; Doses evaluated: 200μg/kg; Route: p.o., i.v.; Dose volume: unspecified; Rate of Dosing: unspecified; Vehicle: saline; Lot: B 179109; label: JS 431303; GLP: yes; Reference: 1.36:10748

Latanoprost was converted to the free acid which is extensively metabolized through β-oxidation before being excreted in the urine of females or the feces of males.

Tritium labeled latanoprost, Plasma levels and excretion of radioactivity following ocular and intravenous administration to the rabbit

Report Number: 9400424; Study site Report Date: August 1994; Date started: ; Species: rabbit; Strain: Dutch Belted; N: 6; Gender: M/F; Study duration: 1 dose; Doses evaluated: 10 μg/animal and 200 μg /kg ; Route: ocular, i.v.; Dose volume: 30 μl for ocular & unspecified for i.v.; Rate of Dosing: 5 ml/min; Vehicle:

Lot: labeled B189203 & B019205; GLP: n; Reference: 1.37:10819

Latanoprost was labeled in [13,14-^{3}H] position and the dosing apparatus was flushed with latanoprost prior to administration into the ear vein.

The collection times were as follows:

Urine: Pre-dose, 0 to 6 , 6 to 12 12 to 24 24 to 48, 48 to 96, 120 to 144 hr after dosing.

Feces: 0 to 12, 12, to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120 and 120 to 144

hr after dosing.

Blood: 5, 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 24, 48, 72, 96, 120 and 144 hr after dosing.

Again the sponsor has not designed the study to optimize the detection of a half-life that is relatively short, however, from the i.v. and ocular initial data they have calculated the following parameters (table 4):

Table 43 Pharmacokinetic parameters in plasma following ocular or intravenous administration to the rabbit.

Parameter	Ocular (10 μg)	Intravenous (200 μg/kg)
$C_{5\,min}$ (ng equiv/ml)	18.36±4.238	704.0±107.0
Initial phase $t_{½}$ (hr)	0.373±0.174	0.259±0.026
Terminal elimination $t_{½}$ (hr)	2.371±1.224	117.4±24.6
AUC estimate over 1st phase (ng equiv. hr/ml)	5.808±1.359	298.3±21.11
AUC over the total time (ng equiv. hr/ml)	7.149±1.612	752.3±76.06
Cl_p (using AUC up to 1.5 hr) (ml/min/kg)	Not Determined	12.80±0.88
Cl_p (total AUC utilized) ml/min/kg	Not Determined	5.098±0.526
Vd (using AUC up to 1.5 hr) (l/kg)	Not Determined	0.286±0.023
Vd (total AUC utilized)) (l/kg)	Not Determined	50.97±6.067
Overall recovery of radioactivity (%)	103.7	102.4

The majority of radioactivity following intravenous administration was eliminated within the first 24 hr by the kidney for both sexes, 49.15% (males) and 67.90% (females). Following ocular administration no apparent gender differences were observed for renal or fecal elimination. The mean urinary elimination was 74.10% and the majority was eliminated within the first 24 hr.

Conclusion: These studies show that radioactivity following administration of tritium labeled latanoprost could be detected in the plasma and excreta, primarily in urine of rabbits whether administered topically to the eye or intravenously. The clearance and volume of distribution could not be compared for the two routes of administration because these parameters were not obtained for the ocular route of administration.

Metabolism of [13,14-^{3}H]-latanoprost in the rabbit after intravenous or topical administration on the eye

Report Number: 9400531; Study site:
Report Date: October 199413,14; Date started: ; Species: rabbit; Strain: Dutch Belted; N: 3; Gender: M/F; Study duration: 1 dose; Doses evaluated: i.v. 0.2 mg/kg; Route: ocular, i.v.; Dose volume: unspecified; Rate of Dosing: unspecified; Vehicle:

Lot: B189203, B019205; labeled 9110015; GLP: yes; Reference: 1.37:10926

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

The biological samples were taken from "Tritium labeled latanoprost, Plasma levels and excretion of radioactivity following ocular and intravenous administration to the rabbit," Report Number 9400424. In that study there were 3 male and 3 female rabbits per route of administration, however, the sponsor reports that after intravenous or topical administration to the eye 82.8±9.2% (n=11) and 96.8±15.2% (n=10) of the total administered dose, respectively, was recovered within 15 min.

The times of blood collection after administration were 5, 15, 30, 45, 60, 90 and 120 minutes and the calculated pharmacokinetic parameters are presented in table 5.

Table 5 Pharmacokinetic parameters for latanoprost free acid following ocular or intravenous administration of latanoprost to rabbits.

Parameter	Ocular[a] (10 μg)	Intravenous[b] (200 μg/kg)
Weight (kg)	2.96±0.21	2.46±0.1
Dose (μg/animal)	560±33	9.4±0.5
C_o (ng equiv./ml)	Not determined	627±178
$C_{5\,min}$ (ng equiv./ml) Maximum value measured	12.6±2.3	Not determined
Initial phase $t_{½}$ (min)	4.6±5.1	9.24±3.21
Terminal elimination $t_{½}$ (hr)	1.42±0.27	Not determined
$AUC_{120\,min}$ (ng equiv. hr/ml)	3.01±0.46	147±25
Cl_p (ml/min/kg)	8.0±2.8	30.0±4.6
V (l/kg)	0.39±0.28	0.39±0.11

Ref.: 1.37:10941

a. n=3 males and 2 females

b. n=3 males and 3 females

In the rabbit latanoprost is rapidly converted to the free acid and it's two major metabolites found in urine were the 1,2,3,4-tetranor of the free acid of latanoprost in the form of the δ-lactone and the acid (fig 3) according to retention times on HPLC and after derivatisation, according to retention times and mass spectra on GC-MS analysis. There were no obvious differences in the metabolic patterns following intravenous and topical administration and no differences between genders.

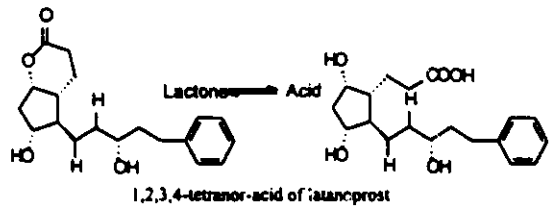


Figure 3 The structures of latanoprost free acid metabolism.

(^{3}H)-PhXA41: Absorption, distribution and excretion following oral, intravenous and

ocular administration to the cynomolgus monkey

Report Number: 9300006; Study site

Report Date: January 1993; Date started: 8/8/91; Species: monkey; Strain: cynomolgus ; N: 3; Gender: M/F; Male weight: 2.00-2.60 kg; Female weight: 2.15-2.40 kg; Study duration: 1 dose; Doses evaluated: 500μg/kg for p.o. and i.v. and 6 μg/eye topically; Route: i.v., p.o., ocular; Dose Volume: oral ca 0.625 ml/kg. i.v.

Lot: B069108, B079108 & B089108; GLP: yes; Reference: 1.34:9793

This is a GLP absorption, distribution and excretion study following oral, intravenous and ocular administration of [9-^{3}H]-13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF$_{2\alpha}$-1-isopropyl ester to the cynomolgus monkey. The tritium label is on the 9 position. 42 ml of blood was taken from each monkey for pharmacokinetic studies. No overt signs of pharmacology or toxicology were observed

The times of sampling for these studies were:

Urine: Pre-dose, 0 to 0.5 , 0.5 to 1, 1 to 1.5, 1.5 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 24, 24 to 48, 40 to 72, 72 to 96 and 96 to 120 hr after dosing

Feces: 0 to 8, 8, to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120 and 120 to 144 hr after dosing

- and blood from the femoral vein -

Blood: 1, 3, 5, 10, 15, 20 and 30 min, 1, 1.5, 2, 4, 8, and 24 hr after dosing

The experimental design of this study is adequate to characterize a compound that has short $t_{1/2}$, however, when the 24 hr samples were lyophilizated no radioactivity was associated with the residue, therefore, volatile radioactivity is probably associated with water.

Most of the activity excreted was recovered within the first 24 hr and the majority of that was recovered between 1.5 and 4 hr after dosing. Using these data one can

estimate the fate of the radio activity.

Results of studies of excretion of radiolabel are presented in table 6. The total values represent unexpectedly low recovery , when compared to rabbits (Report Number: 9400424). There were no substantial gender differences observed.

Table 6 The percent of administered dose of radioactivity excreted following a single dose of ^{3}H-latanoprost.

Route	Dose (μg/kg)	Urine	Feces	Cage Wash	Total
Intravenous	500	29	20	12	61
Oral	500	33	30	9	72
Ocular	12*	31	20	11	62

Ref. table 7.15 1.34:09845

* The actual dose delivered was 9.7 ± 1.7 μg.

Estimates of phar nacokinetic parameters (table 7) Show that clearance and volume of distribution are similar regardless of route of administration and the half-life is between 0.5 and 1 hour.

Table 7 Estimated Pharmacokinetic Parameters in Cynomologus Monkeys Administered Latanoprost by Various Routes (mean±SD (presumable))

Parameter	Intravenous (500 μg/kg)	Oral (500 μg/kg)	Ocular (12 μg)
C_{max} (ng equiv/ml)	774@ 1 min	353±125 @ 0.6 hr	7.5±0.9 @0.11 hr
Initial phase $t_{½}$ (hr)	0.493[a]	1.14±0.52[b]	0.506±0.052[a]
AUC estimate over 1st phase (ng equiv. hr/ml)	635±135	647±308	6.0±1.5
Cl_p (ml/min)	30±5	31±11	27±4
Vd (L)	1.28±0.21	1.45±1.28	1.17±0.17

A. Time range 0.083-2.00 hr
b. Time range 0.33-8.00 hr

At 5 min after intravenous administration detectable amounts of radioactivity were found in all tissues except the iris and lens of the eye. Most of the activity was found in the kidney (10.67 μg equiv./g), prostate (9.56 μg equiv./g) and liver (3.62 μg equiv./g). At

this time the urinary bladder also contained significant amounts of radioactivity (2.28 μg equiv./g). Apart from the above tissues and the GI contents, seminal vesicles, lungs small intestine and stomach, all other tissues sampled contained less than those in blood.

Of particular note, the retina/choroid, conjunctiva, cornea and eyelid) contained moderate levels of radioactivity.

Apart for the dosing site, ocular administration conferred tissue distribution similar to intravenous administration.

Using autoradiographic techniques the highest levels of radioactivity were associated the cornea (including the conjunctiva) 30 min after ocular administration of latanoprost. Moderate radioactivity was present in the ciliary body and humor of the anterior chamber and the anterior part of the sclera. Low levels of radioactivity were present in the iris.

The sponsor also preformed both Ex Vivo and In Vitro plasma and erythrocyte binding studies. Ex Vivo binding at 5 min was 28% to erythrocytes and 73% to plasma proteins. In Vitro binding studies in rat, monkey and man showed erythrocytes binding in rat ca 22%, in monkeys ca 17% and in man ca 12%, and plasma protein binding was ca 79% in rat, ca 87% in monkeys and ca 97% in man.

Conclusion: While the sponsor used adequate sampling times to characterize a short half-life compound the radiolabel selected exchanges with water. Therefore, the results can not be quantitatively evaluated. Qualitatively, the data show that latanoprost has a $t_{½}$ in monkeys of between 0.5 and 1 hour regardless of the route of administration, with a clearance of about 30 ml/min and a volume of distribution of about 1.3 L. They have also shown that Ex Vivo radiolabel binding to erythrocytes was 28% and to plasma protein was 73%, 5 min after exposure. In Vitro binding in man these values were ca 12% for erythrocytes binding and ca 97% for plasma protein binding.

Tissue distribution of [9b-^{3}H]-PhXA41 In the cynomologus monkey after topical administration on the eye, studied by whole body autoradiography

Report Number: L411 C054 R 001; Study site . Report Date: December 1994; Date started: unspecified; Species: monkey; Strain: cynomolgus ; N: 2; Gender: M; Weight: 3.86 & 4.42 kg; Study duration: 2 doses; Doses evaluated: 6μg; Route: ocular; Dose volume: 10 μl; Vehicle: . Lot: unspecified but 408783 for labeled material; GLP: no; Reference: 1.35:10061

The formulation differs from the clinical formulation by the presence of a surfactant

and less disodium phosphate.

One monkey was administered test material in one eye 2 hr before sacrifice and in the contralateral eye 30 min. before sacrifice. The other monkey was treated in one eye 24 hr and in the other eye 6 hr before sacrifice.

This study shows that when radio labeled latanoprost is administered to the eye radiolabel is associated with the corneas, anterior chamber, the iris and the ciliary muscle. Radiolabel was also observed in the esophagus.

Metabolism of latanoprost in the cynomolgus monkey after single intravenous, oral or topical administration on the eye

All data on the performance of the animal experiments were reported in the study entitled "**(^{3}H)-PhXA41: Absorption, distribution and excretion following oral, intravenous and ocular administration to the cynomolgus monkey**" Report No. 930006.

Report Number: L 411 C056 R001; Study site : . Report Date: December 1994; Species: monkey; Strain: cynomolgus ; N: 3; Gender: M/F; Male weight: ; Female weight: ; Study duration: 1 dose; Doses evaluated: 0.5 mg/kg for p.o. and i.v. and 6 μg/eye; Route: ocular, i.v., p.o.; Dose Volume :; Lot: B 069106 & labeled 069108 , 079108 & 089108; GLP: yes; Reference: 1.35:10112

Latanoprost was labeled at the 9 position with tritium.

Regardless of the route of administration latanoprost is rapidly hydrolyzes to the free acid (fig 4) and is further metabolized by β-oxidation to the 1,2-dinor and then to the 1,2,3,4-tetranor metabolite of the free acid.

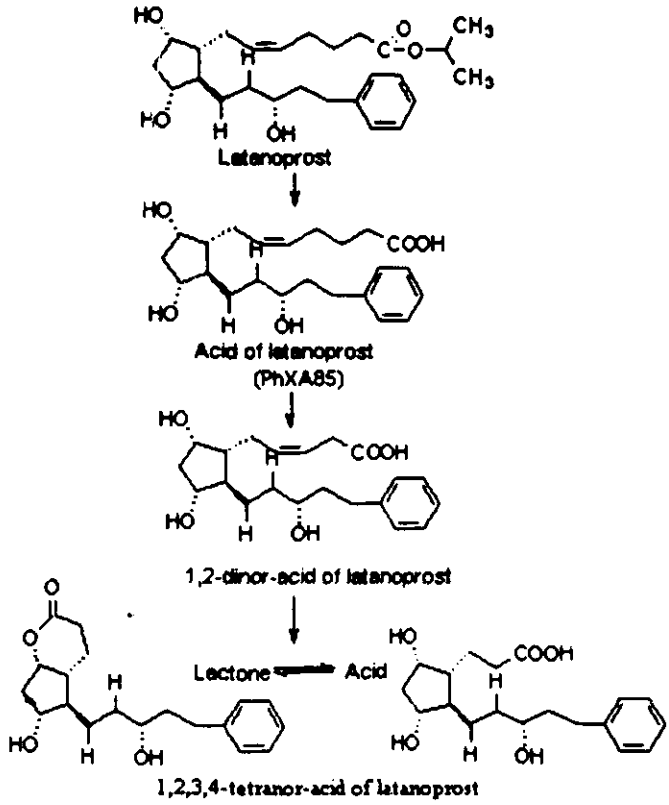


Figure 4. The metabolism of latanoprost in the monkey when administered orally, intravenously or topically to the eye.

The plasma profile after i.v., oral as well as topical, administration to the eye shows that the ester moiety of latanoprost is rapidly hydrolyzed to the free acid. From the retention times of the free acid and the amount of radioactivity it was possible to estimate the half-life following i.v. administration to be about 10 minutes (fig 5). And similarly for ocular administration the half-life is about 20 min. With time one less and two more polar metabolites appeared. One hour after administration the radioactivity in plasma had become too low to be detected by with on line radioactivity detection. There was also evidence that by one hour the tritium label had completely exchanged with water (Report No. 9300006).

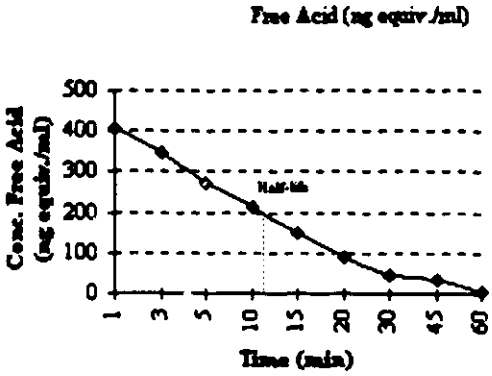


Figure 5 Calculated concentration of {^{3}H] latanoprost free acid following intravenous administration of 500 μg/kg to male and female monkeys (n=3/sex).

Conclusion: Latanoprost is a prodrug that is rapidly hydrolyzed to the corresponding free acid regardless of the route of administration. In plasma the free acid has a half-life of about 10 min. after intravenous and about 20 min. after ocular administration. The drug was eliminated from the body through urine and feces after complete metabolism, probably by β-oxidation in the liver to the 1,2-dinor metabolite of the free acid and further metabolized to the 1,2,3,4-tetranor metabolite.

The ocular pharmacokinetics and metabolism of [^{3}H]-13,14-dihydro-17-phenyl-18,19,20-trinor-PGF$_{2\alpha}$-isopropyl ester in the rabbits after topical administration

Report Number: 9400260; Study site: [illegible] Report Date: December 1993; Species: rabbit; Strain: Dutch Belted; N: 4; Gender: F; Female weight: 1.4 to 2.4 kg; Study duration: 1 dose; Doses evaluated: 50μg/ml; Route: ocular both eyes; Dose volume: 20 μl;

[illegible] Lot: B9110015 & S 431303; GLP: yes; Reference: 1.36:10791

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

Number of animals and the time they were killed:

Number of rabbits	Time killed (hr)
4	0.25
4	0.5
4	1
4	4
4	6
4	24
1	0.25
1	0.5
1	1
1	4
1	6
1	24

Twenty μl of labeled test material solution was applied to both eyes of rabbits and the eyes were enucleated and dissected as follows:

Right eye: Eye lids, cornea, iris, ciliary body, conjunctiva and choroid.

Left eye: Eye lids, cornea, iris, vitreous, conjunctiva, anterior sclera, choroid and lens. Ciliary body was collected in all animals except from the 4 hr group.

The various parts of the right eye were pooled and used to study the metabolic profiles. The different parts from the left eye, including tear fluid and plasma, were used for the determination of total radioactivity.

Eyes from one animal were enucleated at each time point to determine the total radioactivity of the whole eye globe.

Radio activity was determined directly by liquid scintillation counting after total combustion of the tissue samples. For extraction and separation of latanoprost the

different parts of the eye tissues were mixed with 3 ml of ethanol and homogenized, centrifuged and aliquots of the supernatant counted by liquid scintillation.

Since the tritium label on latanoprost exchanges with water it difficult to discuss the disposition of much beyond 15 to 30 min., so in general it has been shown that topically applied latanoprost results in rapid hydrolysis with subsequent appearance of the free acid in the iris-ciliary body.

Tissue distribution of tritium labeled latanoprost in the cynomolgus monkey after topical administration on the eyes studied by whole body autoradiography

Report Number: 9400106; Study site : Department of Toxicology, Physiology and Medical Biophysics Biomedical Center University of Uppsala and Pharmacia Ophthamics Uppsala, Sweden, and Hazleton, UK; Report Date: November 1994; Date started: unspecified; Species: monkey; Strain: cynomolgus ; N: 2; Gender: M/F; Male weight: ; Female weight: ; Study duration: 21 day; Doses evaluated: 6.4μg; Route: ocular; Dose volume: 10 μl; Vehicle: 13/14 labeled Latanoprost - 0.183 mg; Benzalkonium chloride - 0.224; Polysorbate 80 - 1.50 mg; Sodium chloride - 4.10 mg; Monosodium phosphate-1-hydrate - 4.60 mg; $Na_2PO_4 \cdot 2H_2O$ - 5.94 mg; H O for injection - 1.00 ml; Lot: B249305; GLP: yes; Reference: 1.35:10076

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

Administration of 6.4 μg of labeled latanoprost to the eyes of cynomolgus monkeys daily for 21 days, shows the presence of radioactivity in the cornea which gradually appears in the iris, anterior chamber and ciliary body. The estimated elimination half-life was between 3-4 hours.

HPLC investigations showed the predominate peak present in the eye to be the free acid. In the stomach both latanoprost and its free acid were observed, while in the small intestine and bile the main peak corresponded to the 1,2-dinor latanoprost and other more polar metabolites.

Tritium labeled latanoprost (^{3}H)-PhXA41: Absorption and excretion following repeated ocular administration to the cynomolgus monkey

Report Number: 9400459; Study site

Report Date: 10/5/94; Species: monkey; Strain: cynomolgus ; N: 2; Gender: M/F; Study duration: 21 day; Doses evaluated: 12μg; Route: ocular; Dose volume: 10 μl;

1.35:9947

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

Labeled in the 13 and 14 position, 48 to 65 ml of blood was drawn from the monkeys on day 21 and additional 9 to 15 ml was taken over the next 3 days. The excretion study provide a low mass balance which was attributed to exchange of tritium with water. This study showed that radio labeled material was rapidly absorbed and that a small amount of unidentified labeled material accumulated in the eye.

The mechanism of [13,14-^{3}H]-latanoprost in the cynomolgus monkey after repeated topical administration on the eye

Report Number: 9400110; Study site: Report Date: October 1994; Date started: February 1994; Species: monkey; Strain: cynomolgus ; Study duration: 21 day; Doses evaluated: 12μg; Route: ocular; Dose volume: ; Vehicle: see 9400459; Lot: B TRQ ; GLP: yes; Reference: 1.35:10145

9-^{3}H labeled latanoprost

Plasma samples were taken on day 1 and 21, at 5 and 30 min, on day 10 at 5 min. and on day 21 at 2 and 48 hr after ocular administration.

Urine samples were collected during day 2 and day 20 after the first ocular administration and feces samples were collected during day 6 and day 20 after the first ocular administration.

No measurable latanoprost was found in plasma 5 min after ocular administration.

The amount of radioactivity as tritiated water in the plasma 2 hr after the 21st administration of latanoprost on the eye was 46% of the total radioactivity of the plasma. At 48 hr after the 21st administration the radioactivity of the plasma was too low to make an estimation of the amount of tritiated water.

In urine neither latanoprost, its free acid nor the 15-keto metabolite of the free acid were detected. The major peak was the tetranor metabolite.

In feces the dinor and tetranor metabolites were the major peaks detected.

Conclusion: Latanoprost when applied to eye of monkeys is rapidly hydrolyzed to latanoprost free acid which appears in plasma within 5 min. At 30 min the predominate metabolite was the 15-keto and by 2 hr 46% of the radioactivity is found as tritiated water.

Tritium labeled latanoprost, Plasma levels and excretion of radioactivity following intravenous administration to the dog

Report Number: 9400423; Study site
Report Date: August 1994; Date started: March 24, 1992; Species: dog; N: 6; Gender: M/F; Male weight: 9.85 - 11.50; Female weight: 8.45 - 9.55; Study duration: 1 dose; Doses evaluated: 40 μg/kg; Route: i.v.; Dose volume: 1 ml/kg; Dose Volume: unspecified; Rate of Dosing: slow bolus; Vehicle: saline (pg. 11041); Lot: 179203, 18923 & 17109; GLP: no; Reference: 1.37:10978

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

This is a *non-GLP* study (GLP in UK and Japan) designed to follow the fate of tritium labeled latanoprost following slow bolus intravenous administration.

The collection times were as follows:

Urine:	Pre-dose, 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 96, 120 to 144 hr after dosing.
Feces:	0 to 12, 12, to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120 and 120 to 144 hr after dosing.
Blood:	5, 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 24, 48, 72, 96, 120 and 144 hr after dosing.

Again the sponsor has not designed the study to optimize the detection of a half-life that is relatively short, however, from initial data they have calculated the following parameters (table 8):

Table 8 Estimated Pharmacokinetic Plasma Parameters in Male and Female Dogs Following Intravenous Administration of 40 μg/kg of Latanoprost as Determined for up to 1.5 hr After Dosing

Parameter	Intravenous (mean±SD)
C_{max} (ng equiv/ml)	49.95@ 5 min
Initial phase $t_{½}$ (hr)	0.429±0.030 hr
AUC estimate over 1st phase (ng equiv. hr/ml)	30.25±2.33
Cl_p (ml/min)	18.64±0.95
Vd (L)	0.692±0.050

The above data had been pooled for both genders, however, it is not possible to determine if there are any gender differences during the early sampling periods.

Metabolism of [13,14-3H]-latanoprost in the dog after intravenous administration

Report Number: 9400104; Study site :
Report Date: October 1994; Date started: ; Species: dog; N: 3; Gender: M/F; Study duration: 1 dose; Doses evaluated: ca. 40 μg/kg; Route: i.v.; Vehicle: saline; Lot: B 17179709 & 431303; GLP: yes; Reference: 1.37:11073

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

Samples were obtained from **"Tritium labeled latanoprost, Plasma levels and excretion of radioactivity following intravenous administration to the dog"** Report No. 9400423.

Latanoprost is rapidly hydrolyzed following intravenous administration to the free acid. The free acid is rapidly eliminated from plasma with a half-life of 4 min. Most of the radioactivity was recovered in urine with some of the metabolites identified as latanoprost free acid, 1,2-dinor of the free acid and the 1,2,3,4-tetranor of the free acid (as free acid and gamma-lactone). These metabolites were also found in feces.

A study on corneal permeability and metabolism of 12,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF$_2$α-1-isopropyl ester in vitro

Report Number: L411 C042; Study site Report Date: December 1991; Species: pig; Doses evaluated: 9.2, 18.8μM; Route: In vitro; Vehicle: Glutathione bicarbonate ringer solution; Lot: unspecified; GLP: no; Reference: 1.34:9749

9β-^{3}H labeled latanoprost was used in these experiments.

In an In Vitro porcine assay where corneas were mounted in a incubation chamber, latanoprost was quantitatively hydrolyzed to the free acid and no further metabolism was observed.

Metabolism of [9-^{3}H]-13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF$_{2\alpha}$-1-isopropyl ester by 15-hydroxy prostaglandin dehydrogenase and porcine ocular tissues.

Report Number: L411 S043; Study site: Report Date: December 1991; Date started: unspecified; Species: pig; Doses evaluated: 10μg/ml; Route: In vitro; Vehicle: Phosphate buffer; Lot: unspecified; GLP: n; Reference: 1.34:9762

9β-^{3}H labeled latanoprost was used in these experiments.

Various eye tissues of pigs have low 15-hydroxy prostaglandin dehydrogenase (15-PGDH) activity and high Δ^{13}-reductase in the cornea the sponsor evaluated the ability of the porcine eye to metabolize latanoprost.

Because latanoprost does not possess a double bond at the 13, 14 position it is not a good substrate for oxidation of the 15 hydroxyl by 15-PGDH or Δ^{13}-reductase. Cytosolic fractions or homogenates from conjunctiva, iris with ciliary body, retina with choroid, lens and cornea showed no further metabolism beyond the hydrolysis to the free acid.

Hydrolysis of [9-^{3}H]-13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF$_{2\alpha}$-1-isopropyl ester by human plasma and porcine corneal epithelium in vitro

Report Number: L411 C050 R001; Study site : Report Date: April 1992; Date started: unspecified; Species: human & porcine; Route: in vitro; Dose volume: ; Vehicle: Porcine epithelium - phosphate buffer; Lot: IJ1434/H and 408790; GLP: yes; Reference: 1.34:9776

.9β-^{3}H labeled latanoprost was used in these experiments.

Twenty μl of latanoprost (176 μg/20 μl) were mixed with either 20 ml of human plasma or porcine corneal epithelium homogenate and samples were withdrawn at 0, 1, 5, 10, 30 and 60 min. After extraction with ethyl acetate the samples were analyzed by reversed phase-

high pressure chromatography with on line radioactivity detection.

Latanoprost is hydrolyzed to latanoprost free acid in both human plasma and porcine corneal epithelium (fig 6) at approximately the same rate of hydrolysis. However, 7.6 and 4.6 % of unidentified material was observed at 5 and 10 min. of incubation, respectively, in the porcine epithelium preparation.

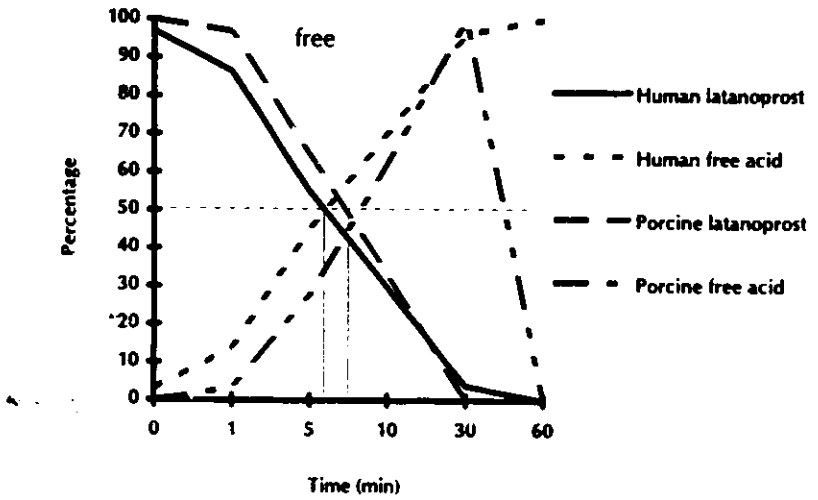


Figure 6 The hydrolysis of latanoprost and appearance of free acid In Vitro in human plasma and porcine corneal epithelium

Conclusion:

Human plasma and porcine corneal epithelium metabolize latanoprost similarly.

Induction/inhibition of hepatic cytochrome P-450 in the rat

Report Number: 9300779; Study site: ; Report Date: 11/10/1993; Date started: 2/19/1993; Species: rat; Strain: ; N: 4; Gender: M/F; Study duration: 91 day; Doses evaluated: 0, 2, 20, 200μg/kg; Route: p.o.; Vehicle: not specified; Lot: unspecified; GLP: yes; Reference: 1.36:10699

Male and female rats were dosed daily for 13 weeks with an unspecified vehicle, 2, 20 or 200 μg/kg of latanoprost daily. Evaluation of total P450 and isoforms showed that there were no differences observed between controls or males and females for total

P450, ethoxycourin O-dealkylase, ethoxyresorufin O-dealkylase, pentoxyresorufin-O-dealkylase or lauric acid 12-hydroxylase activity.

Extraction and separation of tritium labeled latanoprost (PhXA41) and its metabolites in plasma, urine and feces

Report Number: 9400068; Study sit. Report Date: March 1994; Date started: ; Species: rat, rabbit, monkey; Reference: 1.37:11109

[13,14-^{3}H]-latanoprost labeled was used in these experiments.

A methods development study in which material was obtained from rabbits and monkey pharmacokinetic studies and rat studies were spiked to demonstrate that test material and its products could be extracted and separated.

Bioavailability of latanoprost in different formulations

Report Number: 9400268; Study site Report Date: Sept. 1994; Date started: ; Species: cat; Strain: ; N: 6; Gender: F; Weight: unspecified; Study duration: 1 dose; Doses evaluated: 1.2μg; Route: ocular; Dose volume: 20 μl; Vehicle: various; Lot: ij 1444 & ij 1435; GLP: no; Reference: 1.37:10968

The objective of this non-GLP study was to compare the effects of different formulations of buffered saline solutions of latanoprost on the miotic response of cats eyes. The experimental design was not adequate to meet the objectives of a well designed bioassay.

The concentration of latanoprost in the various formulations was designed to be 60 μg/ml, however, the values of the range of found concentrations differed by 18 %.

The design of the test was not adequate to bioassay the potency of the test material in formulations evaluated. The method used only evaluated one concentration of test material, so that the most that could be determined was that were or were no differences in the response of the pupil of cats to single dose of latanoprost.

There were no statistical differences between the maximal difference in pupil diameter of the treated eye and the contralateral control eye for any of the formulations evaluated [varying concentrations of polysorbate 80 (0, 0.015 and 0.15 %), benzalkonium chloride (0, 0.01 and 0.02 %) and disodium EDTA (0, 0.05 and 0.1 %)].

Bioanalysis of the acid of latanoprost (PhXA85) by radioimmunoassay

Report Number: 9400174; Study site
Date: August 1994; Reference: 1.37:11137 Report

A radioimmunoassay for the free acid of latanoprost was developed. When plasma samples for humans, monkeys, rats, and mice were spiked with the free acid the accuracy of the assay varied from 87.5 to 102.6% and the coefficient of variation for the precision of the assay varied from 8.3 to 19.8%.

Limit of detection 30 pg/ml and the limit of quantitation is 60 pg/ml.

Determination of immunoreactive PhXA85 (free acid of PhXA41) in plasma samples collected from toxicological study with PhXA41 (Hazleton, study no. 397/503)

Report Number: 9400311; Study site Report Date: November 1994; Date started: unspecified; Species: monkey; Strain: cynomolgus ; N: 5; Gender: M/F; Study duration: 365 day; Doses evaluated: 20, 50 and 100μg; Route: ocular; Lot: 429158 & 431308; GLP: yes; Reference: 1.38:11347

The data show that as the dose applied to the eye is increased, the detectable concentration of the latanoprost free acid increases in plasma.

Determination of immunoreactive PhXA85 (free acid of PhXA41) in plasma samples collected from toxicological study with PhXA41 (Hazleton, study no. 397/518)

Report Number: 9400302; Study site: Report Date: November 1994; Date started: week 24 1993; Species: monkey; Strain: cynomolgus ; N: 5; Gender: M/F; Study duration: 365 day; Doses evaluated: 1 and 3μg administered twice-a-day; Route: ocular; Dose volume: 30 μl; Lot: 429158 & 431308; GLP: yes; Reference: 1.38:11363

Performed as part of study Report Number: 9400426; Study site:

Report Date: August 1004; Date started: 11/18/91; Species: monkey; Strain: cynomolgus ; N: ; Gender: M/F; Male weight: 1.96 - 3.15 kg; Female weight: 1.95 - 2.82 kg; Study duration: 365 day; Doses evaluated: 0, 1 and

Plasma levels of the free acid of latanoprost were not detectable at 5 or 30 min. following ocular administration of 1 μg, however, levels ranging between 474 to 645

pg/ml were detected at 5 min. following 3 μg applied to the eye. At 30 min. following application of the 3 μg dose plasma level were be low the level of quantitation (60 μg/ml).

28 Day oral (gavage administration) toxicokinetic study in the mouse

Report Number: 9400730; Study site:
Report Date: November 1994; Date started: 4/7/94; Species: mouse; Strain: Crl:CD-1(ICR)BR; N: 3; Gender: M/F; Male weight: 24.8 - 33.7; Female weight: 22.0 - 27.9; Study duration: 28 day; Doses evaluated: 200μg/kg; Route: p.o.; Dose volume: 5 ml/kg; Vehicle: saline; Lot: 9401F07; GLP: n; Reference: 1.37:11197

Toxicokinetic data appear in report no. 9400398.

[13,14-^{3}H] latanoprost free acid was used in the study.

This study is the dosing portion of the toxicokinetic evaluation of latanoprost, Report No. 9400398 which immediately follows.

Determination of immunoreactive PhXA85 (free acid of PhXA41) in mouse samples collected from toxicokinetic study with PhXA41

Report Number: 9400398; Stu : Report Date: November 1994; Date started: 4/7/94; Species: mouse; Strain: Crl:CD-1(ICR)BR; N: 3; Gender: M/F; Male weight: 24.8 - 33.7g; Female weight: 22.0 - 27.9g; Study duration: 28 day; Doses evaluated: 200μg/kg; Route: p.o.; Dose volume: 5 ml/kg; Vehicle: saline; Lot: 9401F07; GLP: yes; Reference: 1.38:11248

5 (report no. 9400730).

Blood samples were collected at 5, 10, 15 and 30 min and 1, 2, 6, and 24 hr after dosing on days 1 and 28 from three animals per treatment group.

Because of the short half-life of this material and the reported ability of the label to exchange with water the results obtained from this study are difficult to evaluate.

The females at both the day 1 and day 28 observation times had higher plasma levels of latanoprost free acid ranging between 117 to 167 % of the male plasma levels (table 9). And the levels for day 28 were 101 to 179 % of the male day 1 levels and 159 to 212 % of the female day 1 levels.

Table 9 The Plasma Concentration of Latanoprost Free Acid (pg/ml) in Mice at Various Times after Treatment with 200 μg/kg p.o. Latanoprost Daily.

	Concentration of latanoprost free acid (pg/ml)			
Day 1 Males	5 min	10 min	15 min	30 min
Male 1	892	1394	1189	702
Male 2	1158	979	808	718
Male 3	857	1752	1303	855
mean	969	1375	1100	758
SD	165	387	259	84
SE	116	274	183	59
Day 1 Females				
Female 1	1705	2233	1679	1131
Female 2	1601	1378	905	1244
Female 3	1541	1090	1279	1082
mean	1616	1567	1288	1152
SD	83	594	387	83
SE	59	420	272	59
% of male	167	114	117	152
Day 28 Males				
	5 min	10 min	15 min	30 min
Male 1	1535	2070	1380	1206
Male 2	2062	1878	1512	1511
Male 3	2155	1611	1813	1081
mean	1917	1853	1568	1266
SD	334	230	222	222
SE	236	163	157	156

Day 28 Females				
Female 1	4349	2891	1793	2109
Female 2	3669	3323	2143	2026
Female 3	2280	2220	2223	2289
mean	3433	2811	2053	2141
SD	1054	556	229	1349
SE	746	393	162	95
% of male	179	152	131	169
% day 1 M	198	135	142	167
% day 1 F	212	179	159	186

These data show that females mice have higher plasma levels of latanoprost free acid than males following oral administration of 200 μg/kg of latanoprost. They also demonstrate that plasma levels are greater after 28 days of administration.

28 Day oral (gavage administration) toxicokinetic study in the rat

Report Number: 9400729; Study site

Report Date: November 1994; Species: rat; Strain: Crl:CD(SD)BR; N: 3; Gender: M/F; Male weight: 200.7 - 235.5 g; Female weight: 150.5 -187.1 g; Study duration: 28 day; Doses evaluated: 200μg/kg; Route: p.o.; Dose volume: 5 ml/kg; Vehicle: Saline; Lot: 9401E07; GLP: n; Reference: 1.38:11260

Toxicokinetic data appear in report no. 9400396.

[13,14-^{3}H] latanoprost free acid was used in the study.

This study is the dosing portion of the toxicokinetic evaluation of latanoprost, Report No. 9400396 which immediately follows.

No treatment related or deaths were noted.

Determination of immunoreactive PhXA85 (free acid of PhXA41) in rat plasma samples collected from toxicokinetic study with PhXA41

Report Number: 9400396; Study site Report Date: November 1994; Date started: unspecified; Species: rat; Strain: Crl:CD(SD)BR; N: 3; Gender: M/F; Male weight: 200.7 - 235.5g; Female weight: 150.5 -187.1g; Study duration: 28 day; Doses evaluated: 200μg/kg; Route: p.o.; Dose volume: 5 ml/kg; Vehicle: Saline; Lot: 9401E07; GLP: yes; Reference: 1.38:11309

oort no. 9400729)

Blood samples were collected at 5, 10, 15 and 30 min and 1, 2, 6, and 24 hr after dosing on days 1 and 28 from three animals per treatment group.

Plasma levels of latanoprost free acid for females in the day 1 observation times were lower than similarly treated males and ranged between 67 to 83% of male concentrations (table 10). For day 28 females the levels were between 88 and 164 % of the male levels. In all but the day 28 30 min plasma level for females, the plasma levels in day 28 animals were lower than day 1 levels, ranging from 43 to 80 % of day 1 levels (127 % for 30 min female).

Table 10 The Plasma Concentration of Latanoprost Free Acid (pg/ml) in Rats at Various Times after Treatment with 200 μg/kg p.o. Latanoprost Daily.

Day 1 males	Concentration of latanoprost free acid (pg/ml)			
	5 min	10 min	15 min	30 min
Male 1	1504	952	670	858
Male 2	610	922	1028	570
Male 3	964	1118	994	286
mean	1026	997	897	571
SD	450	106	198	286
SE	318	75	140	202
Day 1 females				
Female 1	742	628	904	222
Female 2	686	878	404	482
Female 3	642	976	635	580
mean	690	827	648	428

SD	50	179	250	185
SE	35	127	177	131
% of male	67	83	72	75
Day 28 Males				
	5 min	10 min	15 min	30 min
Male 1	506	629	421	447
Male 2	272	789	446	256
Male 3	535	732	527	294
mean	438	717	465	332
SE	102	57	39	71
SD	144	81	55	101
Day 28 Females				
Female 1	244	377	536	464
Female 2	538	647	406	499
Female 3	841	969	285	674
mean	541	664	409	546
SE	211	210	89	80
SD	299	296	126	113
% of male	124	93	88	164
% day 1 M	43	72	52	58
% day 1 F	78	80	63	127

These data show that females rat have generally lower plasma levels of latanoprost free acid following oral administration of 200 μg/kg of latanoprost. They also demonstrate the plasma levels are generally lower after 28 days of administration.

Determination of immunoreactive PhXA85 (free acid of PhXA41) in plasma samples collected from toxicological study with PhXA41

Report Number: 9400304; Study site: Report Date: November 1994; Date started: January; Species: rat; Strain: Crl:CD(SD)BR; N: 10; Gender: M/F; Male weight: 189-240 g; Female weight: 136-185 g; Study duration: 91 day; Doses evaluated: 2, 20 and 200μg/kg; Route: p.o.; Vehicle: unspecified; Lot: 429158 & 431308; GLP: yes; Reference: 1.38:11322

[13,14-^{3}H] latanoprost

Samples taken from study number 9400367

Twenty four hours after the last dose of latanoprost in a 13 week rat toxicology study no plasma levels of latanoprost free acid could be detected (limit of detection was 30 pg/ml).

Determination of immunoreactive PhXA85 (free acid of PhXA41) in rat plasma samples collected from toxicological study with PhXA41

Report Number: 9400397; Study site: Report Date: October 1994; Date started: unspecified; Species: rat; Strain: Crl:CD(SD)BR; N: 10; Study duration: 735 day; Doses evaluated: 2, 20 and 200μg/kg; Route: p.o.; Dose volume: 5 ml/kg; Vehicle: ; Lot: 429158 & 431308; GLP: yes; Reference: 1.38:11334

Supports study number 9400614, the rat carcinogenicity study. Blood samples were taken from the first 10 surviving animals on week 97 week for females and 104 for males at 1 hour after the daily administration of latanoprost. Levels of PhXA85, the free acid of latanoprost, were determined by radioimmunoassay.

The mean plasma levels of PhXA85, the free acid of latanoprost, in male and female rats on week 104 and 97, respectively, at 1 hour after the daily administration of latanoprost.

Gender	Mean (pg/ml) ± SEM	
	20 μg/kg	200 μg/kg
Male	111.1 ± 22.1	473.4 ± 129.1
Female	48.7 ± 8*	359 ± 43.8

* Under the quantitation limit

Genotoxicity:

Study to determine the ability of PhXA41 to induce mutation in four histidine-requiring strains of Salmonella typhimurinum and two tryptophan-requiring strains of Escherichia coli

Report Number: L411 S017; Study site:
Report Date: June 1994; Date started: 12/18/90; Species: S. typhimurinum & E. coli; Strain: see table below ; Doses evaluated: Two studies were performed: range finding concentrations were 9, 40, 200, 1000 and 5000 μg/plate and the study concentrations were 1.28, 6.4, 32, 160 & 800 or 50, 100, 200, 400 or 800 μg/plate; Vehicle: DMSO; Lot: IJ 1375; GLP: yes; Reference: 1.34:9546

Latanoprost did not induce mutation in Salmonella typhimurium in strains TA 98, 100, 1535 and 1537 or in Escherichia coli in strains WP2 pkM 101 and WP2 uvrA. pkM 101 at the concentrations of 1.28 to 800 μg/plate in the absence and presence of S-9.

Table 11 and 12 show the bacterial strains used in this study and the types of mutations and the results of positive control used in these experiments.

Table 11 Bacterial strains

Species	Strain
S. typhimurium	TA98
S.typhimurium	TA100
S.typhimurium	TA1535
S.typhimurium	TA1537
E. coli	Wp2 pKM101
E.coli	WP2 uvrA- pKM101

Table 12 Positive controls and results expressed as a multiple of the vehicle control revertant colonies.

Positive Control	Strain(s)	S-9	Concentration μg/plate	Results (times vehicle control revertants)
2-Nitrofluorene (2NF)	TA98	no	50.0	119

Sodium azide (NaN_3)	TA100, TA1535	no	2.0	6 & 58, respectively
9-Aminoacridine (AAC)	TA1537	no	50.0	430
4-Nitroquinoline-1-oxide (NQO)	WP2 pKM101 & WP2 uvrA-pKM101	no	2.0	9 & 13, respectively
2-aminoanthracene (AAN)	All[a]	yes	5.0	68, 11, 32, 1 & 7, respectively

a TA98, TA100, TA1535, TA1537, Wp2 pKM101 & WP2 uvrA-pKM101

Study to evaluate the potential of PhXA41 to induce micronuclei in the polychromatic erythrocytes of CD-1 Mice

Report Number: L411 S023; Study site: .

Report Date: 5/31/91; Date started: 5/2/91; Species: mouse; Strain: out-bred CD-1; Doses evaluated: range finding 75.42, 116, 178.5, 274.6, 422.5, 650, 1000 and 1538 and 2367 mg/kg Study 200, 400 and 800 mg/kg; Route:; Vehicle

Lot: IJ1447; GLP: yes; Reference: 1.34:9673

Latanoprost was suspended in water with the acid of Tween 80 and carboxymethyl cellulose, and administered intraperitoneally (25ml/kg) to groups of male and female albino mice (15/sex/group). A range-finding study, conducted prior to the definitive study, indicated that mortalities occurred at doses of 1000 mg/kg and above. The doses used in the main portion of the study were 200, 400 and 800 mg/kg and 40 mg/kg of cyclophosphamide as the positive control. The negative control group received the vehicle. Five animals per sex per group were sacrificed at 24 , 48, and 72 hrs after treatment. Femurs were removed, and bone marrow was aspirated, slides were prepared and stained for microscopic reading of the proportion of polychromic erythrocytes, and the number of micronuclei.

Latanoprost did not produce an increase in the incidence of micronucleated polychromic erythrocytes, while the positive control produced statically significant increases in the micronuclei. Treatment with latanoprost resulted in a decrease in the ratio of polychromatic to normochromatic erythrocytes, indicating possible bone marrow toxicity.

Study to determine the ability of PhXA41 to induce mutations to 6-thioguanine resistance in mouse lymphoma L5178Y cells using a fluctuation assay

Report Number: L411 S024 R 001; Study site:

Report Date: Study to determine the ability of PhXA41 to induce mutations to 6-thioguanine resistance in mouse lymphoma L5178Y cells using a fluctuation assay; Date started: 5/10/91; Doses evaluated: 0.316, 1, 3.16, 10, 31.6, 100, 316, and 1000 and 25, 50, 100, 150, 200 AND 250 μg/ml; Vehicle: Lot: IJ 1447; GLP: n; Reference: 1.34:9596

Cultures of wild type mouse lymphoma L5178Y cells were plated in growth medium to confirm cell viability, and were then incubated with various concentrations of test compound, negative control

, either with or without S-9 metabolic activation. Latanoprost failed to demonstrate an ability to induce mutation in L5178Y mouse lymphoma cells, while the positive controls increased the mutation frequency.

Study to evaluate the chromosome damaging potential of PhXA41 by its effects on cultured human lymphocytes using an in vitro cytogenetics assay

Report Number: L411 S027 R001; Study site.

Report Date: May 1994; Date started: 7/31/91; Species: human; Doses evaluated: 16.89, 22.53, 30.03, 40.05, 53.39, 71.19, 94.92, 126.6, 168.8, 225, 300 and 400 μg/ml; Vehicle: Lot: IJ 1447; GLP: yes; Reference: 1.34:9626

In the absence of S-9, latanoprost was associated with a significant increase in chromosomal structural aberrations, including chromatid exchanges. In the presence of S-9, the frequency of aberratants cells increased in one experiment, but not in another. Both positive controls also produced increases in the proportion of cells with chromosomal aberrations.

Study to evaluate the potential of PhXA41 to induce unscheduled DNA synthesis in rat liver using an in vivo/in vitro procedure

Report Number: 9400244; Study site: .

Report Date: Study to evaluate the potential of PhXA41 to induce unscheduled DNA synthesis in rat liver using an in vivo/in vitro procedure; Date started: 11/4/93; Species: rat; Strain: Wistar Doses evaluated: Range finding 550, 850, 1300, and 2000; full study 632.5 and 2000 mg/kg; Vehicle: TWEEN 80; Lot: 9110015; GLP: n; Reference: 1.34:9705

Latanoprost was evaluated in Wistar rats that were treated orally 632.5 or 2000 mg/kg. The rats were killed at either 2-4 hr after treatment or 12-14 hr after treatment.

At doses up to 2000 mg/kg, p.o. of latanoprost there was no evidence of unscheduled DNA in hepatocytes harvested either 2-4 or 12-14 hr after administration. However, it should be

noted that the sponsor did not analyze the amount of test material delivered.

Summaries of Genotoxicity Studies:

Latanoprost was evaluated for genotoxicity potential in a battery of mutagenicity tests and found to have no genotoxic activity in Ames S. typhimurium/E .coli, mouse micronuclei test, mouse lymphoma (L5178Y) test or an unscheduled DNA test. In human lymphocytes in culture in the absence of metabolic activation by S-9 latanoprost induced chromosome aberrations were observed, and in the mouse micronuclei test there was an indication of bone marrow toxicity.

Animal Carcinogenicity studies:

Oral (gavage administration) carcinogenicity study in the rat

Report Number: 940061-; Study site:
Report Date: September 1994; Date started: 8/19/91; Species: rat; Strain: Crl:CD(SD)BR; N: 50; Gender: M/F; Doses evaluated: 0, 0, 2, 20, 200 μg/kg; Dose volume: 5 ml/kg; Route: p.o.; Vehicle: saline; Lot: ; GLP: yes; Reference: 1.26:5894

Rationale for dose selection: The selected dose levels were based on human therapeutic doses and previous toxicity and pharmacokinetic studies. The high dose was approximately 3000 times the human therapeutic level and approached the limit of solubility in aqueous based solutions.

The rationale for determining the multiple of the human dose is not supported by either the toxicology data or the pharmacokinetic data presented. The doses evaluated in the toxicology studies were not the maximally tolerated doses and the pharmacokinetic studies were flawed because they were done at time periods that could not adequately characterize the kinetics of a short acting compound, and they used radio labeled compounds that exchanged label with water.

So the high dose selected for this study is based on the solubility of latanoprost in saline.

Because latanoprost is extensively metabolized by the liver it is most appropriate for comparison of safety assessment between species to express the dose in terms of body surface area instead of on a weight of test material/kg of body weight basis. For the current study a 200 μg/kg dose would be 910 $\mu g/m^2$ when expressed on a body surface area or 492 times the maximum expected human dose (1.85 $\mu g/m^2$).

Males were killed of 104 weeks of treatment and females were killed after 97 weeks of treatment.

Result:

There were no biologically meaningful differences between treated and control rats in weight gain, food consumption, terminal hematology, survival (table 14) and clinical signs. The spectrum of nonneoplastic findings in treated animals was similar to that found in the control animals. Likewise, there was no biologically meaningful difference between the control and the treated rats with respect to neoplastic lesions.

Table 14 Survival of rats to 97 wee for females and 104 weeks for males (ref 1.26:4923)

Dose (μg/kg)	Survival (percentage)	
	Male	Female
0	18(36)	20(40)
0	28(56)*	20(40)
2	26(52)*	18(36)
20	24(48)	19(38)
200	18(36)	14(28)

* P≤0.5 when compared to control group 1

Because of incidences of ovarian cysts observed in reproductive studies and possible bone marrow toxicity observed in the Mouse Micronuclei Test (Study No. L411 S023) these parameters were reviewed in detail and presented in table 15. No effect of treatment could be observed for either of these parameters.

Table 15 Necropsy and Histopathology Results from Rat Carcinogenicity Study

Organ and keyword(s) or phrase		Male					Female				
	Dose μg/kg	0	2	20	200	0	0	2	20	200	0
Ovary (Necropsy)	Number Examined	0	0	0	0	0	50	50	50	50	50
cyst	Number Observed						12	11	7	15	5
Ovary (Non-neoplastic histology -decedents)	Number Examined	0	0	0	0	0	30	32	31	36	29

cyst	Number Observed						11	13	5	16	6
Ovary (Non-neoplastic histology - terminal)	Number Examined	0	0	0	0	0	20 (20)*	6 (18)	4 (19)	14 (14)	20 (20)
cyst	Number Observed						9	6	4	10	8
Ovary (Neoplastic histology - all)	Number Examined	0	0	0	0	0	50*	38*	35*	50*	49*
B-cystadenoma	Number Observed						0	0	0	1	1
B-tubulostromal adenoma	Number Observed						0	0	0	0	1
Ovary (Neoplastic histology - terminal)	Number Examined	0	0	0	0	0	20 (20)	6 (18)	4 (19)	14 (14)	20 (20)
B-tubulostromal adenoma	Number Observed						0	0	0	0	1
Femur Marrow (Non-neoplastic histology - decedents)	Number Examined	32	24	26	32	22	29	32	31	36	30
Hyperplasia	Number Observed	9	8	6	4	8	8	8	12	10	7
Femur Marrow (Non-neoplastic histology - terminal)	Number Examined	18 (18)	0 (26)	0 (24)	18 (18)	28 (28)	20 (20)	0 (18)	0 (19)	14 (14)	20 (20)
Hyperplasia	Number Observed	0	0	0	1	7	2	0	0	3	6

a. Number of animals surviving
* 50 animals started

Conclusion:

Oral administration of latanoprost to male rats for 104 weeks and females for 97 weeks produced no evidence of either toxicity or differences from control rats in incidence or types of neoplastic lesions.

80 week oral (gavage administration) carcinogenicity study in the mouse

Report Number: 9400620; Study site:
Report Date: October 1994; Date started: 9/24/91; Species: mouse; Strain: Crl:CD-1(ICR)BR; N: 51; Gender: M/F; Doses evaluated: 0, 0, 2, 20, 200 μg/kg; Route: p.o.; Vehicle: 0.9% Saline; Lot: ; GLP: yes; Reference: 1.22:4343

Rationale for dose selection: The selected dose levels were based on human therapeutic doses and previous toxicity and pharmacokinetic studies. The high dose was

approximately 3000 times the human therapeutic level and approached the limit of solubility in aqueous based solutions.

The rationale for determining the multiple of the human dose is not supported by either the toxicology data or the pharmacokinetic data presented. The doses evaluated in the toxicology studies were not the maximally tolerated doses and the pharmacokinetic studies were flawed because they were done at time periods that could not adequately characterize the kinetics of a short acting compound, and they used radio labeled compounds that exchanged label with water.

So the high dose selected for this study is based on the solubility of latanoprost in saline.

Because latanoprost is extensively metabolized by the liver it is most appropriate for comparison of safety assessment between species to express the dose in terms of body surface area instead of on a weight of test material/kg of body weight basis. For the current study a 200 $\mu g/kg$ dose would be 546 $\mu g/m^2$ when expressed on a body surface area or 295 time the maximum expected human dose (1.85 $\mu g/m^2$).

Animals were killed after treatment of the males for 87 week and females for 91 weeks because they reached approximately 50% survival.

There were no biologically meaningful differences between treated and control mice in weight gain, food consumption hematology, survival (table 16) and clinical signs. The spectrum of nonneoplastic findings in treated animals was similar to that found in the control animals. Likewise, there was no biologically meaningful difference between the control and the treated mice with respect to neoplastic lesions.

Table 16 Survival of mice to 91 weeks for females and 87 weeks for males (ref 1.22:4343)

Dose (μg/kg)	Survival (percentage)	
	Male	Female
0	29(51)	32(59)
0	29(55)	32(59)
2	26(49)	28(51)
20	22(39)	33(65)
200	29(53)	33(63)

Because ovarian cysts were observed in reproductive studies and possible bone marrow toxicity observed in the Mouse Micronuclei Test (Study No. L411 S023) these parameters were reviewed in detail . The data for the ovaries (table 17) show no effect of treatment could be observed and observations of note were made for the bone marrow.

Table 17 Necropsy and Histopathology Results from Mouse Carcinogenicity Study

Organ and keyword(s) or phrase		Male					Female				
	Dose µg/kg	0	2	20	200	0	0	2	20	200	0
Ovary (Necropsy)	Number Examined	51	51	51	51	51	51	51	51	51	51
cyst	Number Observed						43	39	41	36	41
Ovary (Non-neoplastic histology - decedents)	Number Examined	0	0	0	0	0	21	26	18	19	21
cyst	Number Observed						16	22	15	17	17
Ovary (Non-neoplastic histology - terminal)	Number Examined	0	0	0	0	0	30 (30)[a]	23 (25)	28 (33)	32 (32)	30 (30)
cyst	Number Observed						29	20	27	27	29
Ovary (Neoplastic histology - all)	Number Examined	0	0	0	0	0	51*	47*	46*	51*	51*
B-cyctadenoma	Number Observed						0	0	1	0	1
B-Luteoma	Number Observed						0	1	0	0	1
Femur Marrow (Non-neoplastic histology - all)	Number Examined	51	26	32	32	51	51	26	18	51	51
Marrow necrosis	Number Observed	0	0	0	0	0	1	0	0	0	1
Marrow Atrophy	Number Observed	1	0	0	0	0	8	0	1	1	1
Marrow hyperplasia	Number Observed	14	9	13	19	20	10	12	7	21	21
Sternum marrow	Number Examined	51	29	37	51	51	51	28	20	51	51
Marrow hyperplasia	Number Observed	14	10	10	18	20	10	11	7	20	19

a. Number of animals surviving

* 51 animals started

ref.: 1:22:4506

Conclusion:

Oral administration of latanoprost to male mice for 91 weeks and females for 87 weeks produced no evidence of either toxicity or differences from control rats in incidence or types of neoplastic lesions.

Miscellaneous Studies:

Octanol-water partition of some $PGF_{2\alpha}$ derivatives

Report Number: 9300041; Study site
Report Date: February 1993; Lot: unspecified; GLP: no; Reference: 1.37:11152

Substance	log P
Latanoprost	4.35
latanoprost free acid	0.5

Test to determine the index of primary cutaneous irritation in the rabbit

Report Number: 9200028; Study site:
Report Date: April 1993; Date started: 12/12/91; Species: rabbit; Strain: New Zealand; N: 6; Gender: M; Male weight: 2.30-02.7 kg; Female weight: ; Study duration: 1 day; Doses evaluated: 35 & 100 (eye drops) and 40 (saline)μg/ml; Route: topical; Dose volume: 0.5; Vehicle: saline and an unspecified eye drop formulation; Lot: B049201, B059201, B109111; GLP: yes; Reference: 1.29:7603

A dose of 0.5 ml of latanoprost in either an unspecified eye drop formulation or saline was applied to intact and scarified skin and occluded for 24 hr. The dressings were removed and 30 and 48 hr later the application sites were evaluated for erythemia and edema according to the Draize scale.

The results show that the low dose eye drop formulation was slightly irritating, the high dose eye drop formulation was not irritation and the saline formulation was slightly irritating.

The sponsor did not take precautions to determine whether or not the dose of test material was delivered.

Evaluation of the potential to induce immediate hypersensitivity. Passive cutaneous anaphylaxis (PCA) and induced anaphylactic shock in the guinea pig.

Report Number: 9400059; Study site:
Report Date: 2/3/94; Date started: 1/14/93; Species: guinea pig; Strain: Hartley; N: 10/12; Gender: M; Doses evaluated: unspecified; Vehicle: saline; Lot: B059210/2; GLP: yes; Reference: 1.29:7534

anaphylaxis (PCA) in guinea pigs.

Anaphylactic shock was induced using the following protocol:

		Induction Phase- route i.p. Days 1*, 3, 5, 8, 10, & 12		Challenge Phase - route - i.v. Days 33 for groups 1 & 2 and day 36 for group 3	
Group Designation	N	Compound and Concentration	Dose Volume (ml/animal)	Compound and Concentration	Dose Volume (ml/animal)
Negative control (Group 1)	10	Saline for injection	0.5	Latanoprost (40 μg/ml)	1
Test article (Group 2)	10	Latanoprost (40 μg/ml)	0.5	Latanoprost (40 μg/ml)	1
Positive control (Group 3)	10	Ovalbumin	0.5	Ovalbumin (200 μg/ml on day 33) (10 mg/ml on day 36)	1

* On day 1 induction phase, 0.2 ml of adjuvant (aluminum hydroxide) was also injected immediately after injection of test or control article.
ref.: 1.29:7540

On day 26 serum from all animals was diluted (1 to 8, 1 to 32, 1 to 128 and 1 to 512) and administered intradermally using the following protocol:

Group Designation	N	Day 1 intradermal injections (4x0.1 ml)	Day 2 (1 - 18 hr) Intravenous unjection (1 ml)*
Test article (Group 41)	12	Serum dilutions form groups 1 and 2	Latanoprost (40 μg/ml)
Positive control (Group 5)	12	Serum dilutions from groups 1 and 3	Ovalbumin (600 μg/ml)**

* 0.5 ml of test or positive control article solution mixed with o.5 ml of 1% Evans Blue.

** Concentration before the mixing with Evans Blue

ref.: 1.29:7541

In both these test latanoprost showed no evidence of being able to induce an immediate hypersensitivity reaction, while the positive controls were capable of inducing an immediate hypersensitivity reaction.

Test to evaluate sensitizing potential in the guinea pig

Report Number: 9400529; Study site:
Report Date: March '93; Date started: 12/12/91; Species: guinea pig; Strain: Hartley; N: 10; Gender: M/F; Doses evaluated: induction - 3 series of 2 x 0.1 ml (0.1 mg/ml latanoprost); challenge - 0.5 ml; Route: i.d. & topical; Dose volume: ; Vehicle: Lot: B 059201; GLP: yes; Reference: 1.29:7471

It is difficult to determine exactly how this experiment was conducted, however, if appears the guinea pigs were divided into 4 groups of unknown numbers of animals. For sensitization , three groups were treated with a series of three intradermal injections of Freund's adjuvant, test material or Friend's adjuvant and test material and one group was treated topically with a 48 hr occlusive application (it appears that since the application was not irritation they painted with 0.5 ml of lauryl sulfate on day 8, no mention of whether nor not test material was also applied at this time). Eleven days later the animals were challenged by an unspecified route to an area that had not been previously exposed to the test material by an unspecified route. In both the sensitization and the challenge phases of this study the dose was not specified.

Signs of irritation were noted during the induction when administered by either the intradermal or topical routes of administration. There appears to be no evidence that latanoprost causes delayed hypersensitization.

PhXB20 (5,6 trans-13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester; 5.6 trans isomer of PhXA41) - single dose toxicity study by the intravenous route in the mouse

Report Number: 9200138; Study site:
Report Date: March 1993; Date started: 12/22/92; Species: mouse; Strain: OF1 (IOPS Caw); N: 5; Gender: M/F; Male weight: 30 - 35 g; Female weight: 21 - 24 g; Study duration: 1 dose; Doses evaluated: 1.7 mg/kg; Route: i.v.; Dose volume: 50 ml/kg; Dose Volume: 50 ml/kg; Rate of Dosing: 1 ml/min; Vehicle: saline; Lot: 199209; GLP: no; Reference: 1.30:7820

There were no deaths, differences in clinical signs, differences in body weight gain or macroscopic abnormalities noted at necropsy observed 14 days after an intravenous

administration of 1.7 mg/kg.

A major deficiency of this submission is the failure of the sponsor to ensure that the specified doses were actually delivered. This is a consequent of the test material adsorbing to material used in storage and/or dose administration; in fact there are several notations from the analytical reports that attribute a 20% loss of test material to adsorption. As expected with adsorption problems the deviation of found concentrations from expected concentrations were greatest with low concentrations. In many studies the sponsor instituted a procedure of flushing the dosing apparatus with test material prior to dosing animals, however, they provided no data to support the effectiveness of the procedure. Toxicologic studies of latanoprost have been performed in mice, rats, rabbits, dogs and monkeys (Table 18). The dog was the species that had least tolerance for latanoprost. The adverse effects were salivation miosis and vomiting. In long term monkey studies ocular administration of ocular administration of latanoprost induced a widening of the palpebral fissure in 27 out of 30 monkeys. No histopathological alterations could be detected and Müller's muscle as well as the other muscles of the eyelids appeared normal. These changes in the palpebral fissure were reversible within 3 to 6 months after termination of treatment.

Summary of Animal Studies:

Table 18 Animal Safety Studies

Species	Study name	Dosing duration	Route	Maximum Dose	Ref.
Mouse	Test to evaluate the acute toxicity following a single intravenous administration of 2.0 mg/kg in the mouse	1 dose	i.v.	2.0 mg/kg	1.13:428
Mouse	Single dose oral (gavage) toxicity study in the mouse	1 dose	p.o.	50 mg/kg	1.13.379
Mouse	14 day oral (gavage administration) tolerance study in mouse	14 day	p.o.	200 μg/kg	1.17:2220
Mouse	28 day oral (gavage) sub-acute toxicity in the mouse	28 day	p.o.	200 μg/kg	1.18:2252
Mouse	28 day oral (gavage) sub-chronic toxicity study in the mouse	28 day	p.o.	10 mg/kg	1.18:2366

Mouse	13 week oral (gavage administration) sub-chronic toxicity study in the mouse	91 day	p.o.	200 μg/kg	1.18:2502
Rat	Test to evaluate the acute toxicity following a single intravenous administration of 2.0 mg/kg in the rat	1 dose	i.v.	2.0 mg/kg	1.13:456
Rat	4 week intravenous dose range-finding study in the rat	28 day	i.v.	340 μg/kg	1.20:3203
Rat	13 week intravenous study in the rat	91 day	i.v.	250 μg/kg	1.20:3419
Rat	Single dose oral (gavage) toxicity study in the rat	1 dose	p.o.	50 mg/kg	1.13:447
Rat	29 day oral (gavage) sub-chronic toxicity study in the rat	28 day	p.o.	200 μg/kg	1.19:2722
Rat	29 day oral (gavage) sub-chronic toxicity study in the rat	28 day	p.o.	10 mg/kg	1.19:2822
Rat	13 week oral (gavage administration) sub-chronic toxicity study in the rat	91 day	p.o.	200 μg/kg	1.19:2942
Rabbit	4 week ocular toxicity in the rabbit	28 day	ocular	25 μg	1.14:515
Rabbit	PhXA41 in different vehicles - 4 week ocular tolerance study in the rabbit	28 day	ocular	1 drop of a 59 μg/ml solution	1.29:7636
Rabbit	52 Week ocular toxicity study in the rabbit	365 day	ocular	100 μg	1.14:704
Dog	4 week intravenous dose range-finding study in the beagle dog	28 day	i.v.	340 μg/kg	1.21:3814
Dog	13 Week intravenous toxicity study in the beagle dog	91 day	i.v.	100 μg/kg	1.21:3952
Monkey	52 Week ocular toxicity study in the cynomologus monkeys	365 day	ocular	50 μg	1.15:1157
Monkey	52 Week ocular toxicity study in the cynomologus monkey	365 day	ocular	3 μg	1.16:1774

In a model of cutaneous irritation in rabbits latanoprost in saline the solutions were only slightly irritating. In guinea pig models of immediate hypersensitivity, passive cutaneous anaphlaxis or anaphlaxis, latanoprost was inactive. Nor was there any evidence of latanoprost inducing a delayed hypersensitivity reaction in guinea pig. One notable adverse event was the observation in monkeys of enhanced eye pigmentation. As can be seen (fig 7) incidence of slight or greater increase in pigmentation can be observed by 8 weeks of administration and there seems to be no or little relationship to dose.

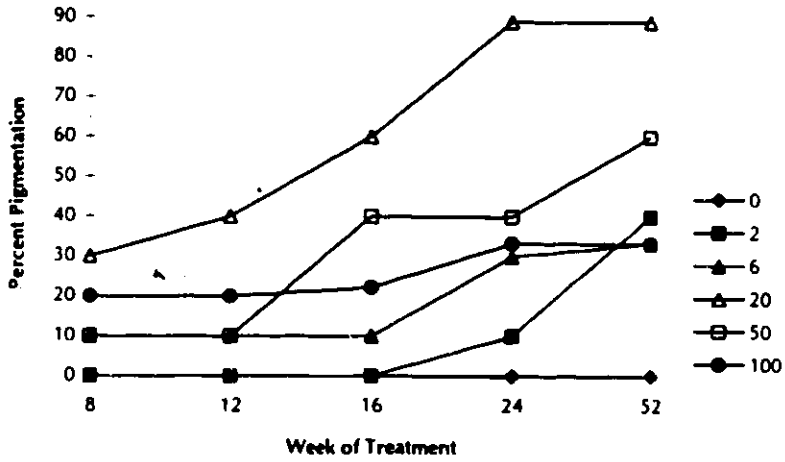


Figure 7 The incidence of slight or greater enhanced pigmentation from two 52 week cynomolgus monkey studies with latanoprost administered ocularly (doses are total daily dose in μg)[ref.: 1.15:1157 (9400425) & 1.16:1774 (900426)]

Attempts to determine the mechanism of this slight or greater increase in pigmentation using histologic and immunohistologic techniques were indeterminate. The effects of latanoprost on reproductive function and progeny were evaluated in rats and rabbits (table 19)

Table 19 Effects of Latanoprost in Reproductive Toxicology Studies

Species	Study	Route	Maximum Dose	Ref.

Rat	PhXA41- Dose range-finding fertility and reproduction study by intravenous route in the female rat	i.v.	300 μg/kg	1.30:7981
Rat	PhXA41- Dose range-finding fertility and reproduction study by intravenous route in the male rat	i.v.	300 μg/kg	1.30:7855
Rat	Fertility study by intravenous route in the rat (segment I)	i.v.	250 μg/kg	1.30:8108
Rat	PhXA41 - Dose range-finding study by intravenous route in the pregnant rat	i.v.	300 μg/kg	1.31:8349
Rat	Teratology study by intravenous route in the rat (Segment II)	i.v.	250 μg/kg	1.31:8451
Rabbit	PhXA41 - Dose range-finding study by intravenous route in the pregnant rabbit	i.v.	300 μg/kg	1.32:8635
Rabbit	Teratology study by intravenous route in the rabbit (Segment II)	i.v.	5 μg/kg	1.32:8738
Rat	Dose range-finding peri- and post-natal study (Segment III) by intravenous route in the rat	i.v.	100 μg/kg	1.32:8957
Rat	Developmental toxicity study by intravenous route in the rat (Segment III)	i.v.	250 μg/kg	1.33:9149

Latanoprost has been evaluated for its effect of reproduction following intravenous administration in rats (Seg. I, II and III) and rabbits (Seg. II and III). In rabbits an incidence of 1 of 6 dams had no viable fetuses at a dose that was 32 times the human dose on a body surface area basis, and the highest nonembryocidal dose in rabbits was 6 times the human dose on a body surface area basis. In rats no evidence of impaired fertility in either males or female at doses that are lethal to males was observed at doses up to 570 times the human dose. There are no adequate and well-controlled studies in pregnant women. Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No teratogenic potential has been detected.

The Sponsor has attempted to evaluate the absorption, distribution, metabolism and excretion (ADME) of latanoprost by use of tritium labeled latanoprost or radioimmunoassay in several species. The use of the former method presents significant problems for

interpretation, because the tritium label, regardless of whether it was in the 9 or the 13,14 position, exchanges rapidly with water. Thus, quantitation of pharmacokinetic data derived from administration of tritium labeled latanoprost was most meaningful only within the first few minutes after administration. On the other hand the radioimmunoassay was specific for the free acid of latanoprost with an accuracy of the assay varied from 87.5 to 102.6% and the coefficient of variation for the precision of the assay varying from 8.3 to 19.8%. The limit of detection was 30 pg/ml and the limit of quantitation was 60 pg/ml. Qualitatively, in rats, dogs, mice, and cynomolgus monkeys, latanoprost is rapidly absorbed and hydrolyzed to the free acid. The free acid has an estimated plasma half-life of about 10 minutes and it is further oxidized and excreted in urine or feces. The metabolic pathway is presented in figure 8.

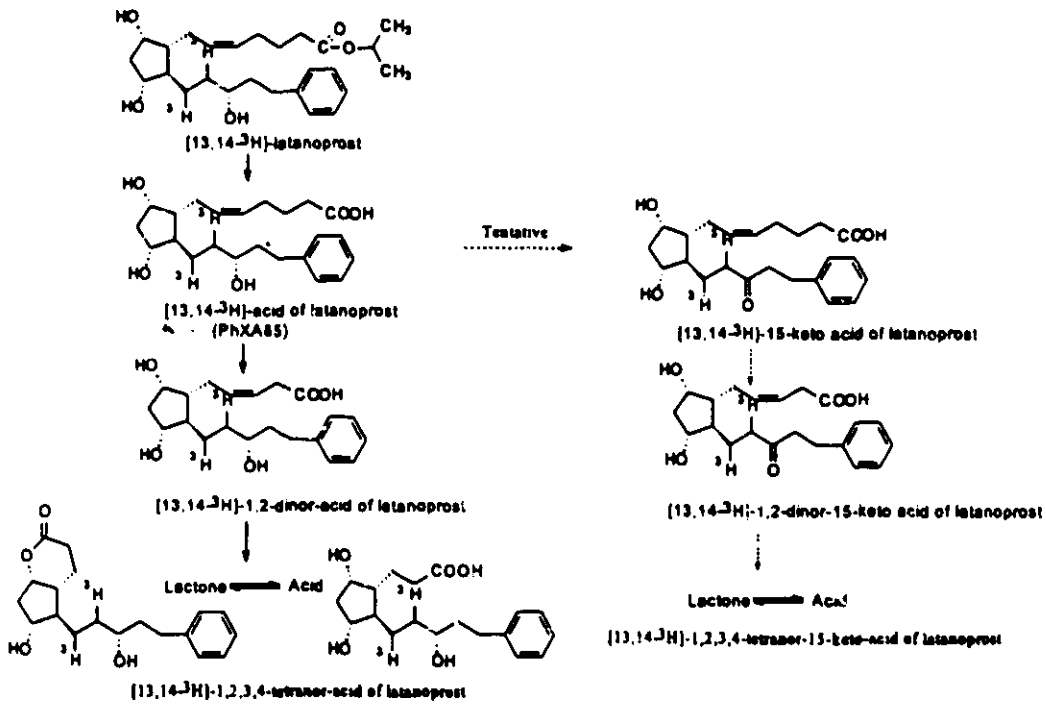


Figure 8 Metabolic pathway for latanoprost

Data derived from *In vitro* studies in porcine eyes show that the cornea hydrolyzes latanoprost to the free acid and no further metabolism was observed. Also since latanoprost does not possess a double bond at the 13, 14 position it is not a good substrate for oxidation

the 15 hydroxyl by 15-PGDH, and cytosolic fractions or homogenates from conjunctiva, iris with ciliary body, retina with choroid, lens and cornea showed no further metabolism. Therefore, the eye possesses a unique environment in which latanoprost is readily absorbed, metabolically activated to the free acid and not further metabolized. In conclusion, latanoprost is a prodrug that *In vivo* is rapidly hydrolyzed to the corresponding free acid regardless of the route of administration. In plasma the free acid has a half-life of about 10 min after intravenous and ocular administration. The drug was eliminated from the body by urine and feces after being completely metabolized, probably by β-oxidation in the liver to the 1,2-dinor metabolite of the free acid and further metabolized to the 1,2,3,4-tetranor metabolite.

Genotoxicity: Latanoprost was evaluated for genotoxicity potential in the following assays:

Study	Species & Strain	Doses Evaluated	Ref
Study to determine the ability of PhXA41 to induce mutation in four histidine-requiring strains of Salmonella typhimurinum and two tryptophan-requiring strains of Escherichia coli	S. typhimurinum & E. coli TA 98, 100, 1535 and 1537 WP2 pkM 101 and WP2 uvrA. pkM 101	Range finding 9, 40, 200, 1000 and 5000 Study 1.28, 6.4, 32, 160 & 800 or 50, 100, 200, 400 or 800 μg/plate	1.34:95 46
Study to evaluate the potential of PhXA41 to induce micronuclei in the polychromatic erythrocytes of CD-1 Mice	Mouse; out-bred CD-1	Range finding 75.42, 116, 178.5, 274.6, 422.5, 650 & 1000 and 1538 and 2367 Study 200, 400 and 800 mg/kg	1.34:96 73
Study to determine the ability of PhXA41 to induce mutations to 6-thioguanine resistance in mouse lymphoma L5178Y cells using a fluctuation assay	Mouse	0.316, 1, 3.16, 10, 31.6, 100, 316, and 1000 and 25, 50, 100, 150, 200 AND 250 μg/ml	1.34:95 96

Study to evaluate the chromosome damaging potential of PhXA41 by its effects on cultured human lymphocytes using an in vitro cytogenetics assay	Human	16.89, 22.53, 30.03, 40.05,53.39, 71.19, 94.92, 126.6, 168.8, 225, 300 and 400 μg/ml	1.34:96 26
Study to evaluate the potential of PhXA41 to induce unscheduled DNA synthesis in rat liver using an in vivo/in vitro procedure	Rat; Wistar	Range finding 550, 850, 1300, and 2000; full study 632.5 and 2000 mg/kg	*1.34:97 05*

Rat and Mouse Carcinogenicity Studies:

Dose selection: The sponsor was not able to reliably deliver the expected dose of test material to the animals. This failure was attributed to the adsorption of test material to the dosing apparatus. Attempts to remedy this problem by flushing the dosing apparatus with test material prior to dosing animals were not entirely successful. When they analyzed the various concentrations of test material they reported sizable differences between the amounts detected and expected. These differences were more pronounced at the lower concentrations of test material than a higher concentration (fig 9 & 10, Table 20).

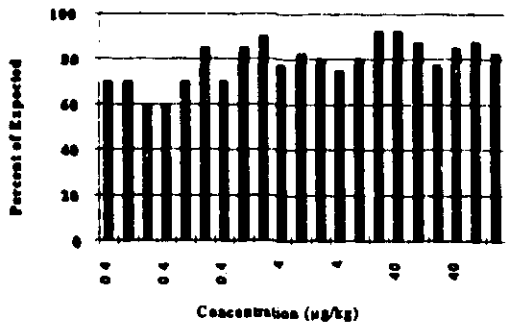


Figure 9 The expected concentration of test material for the mouse carcinogenicity study (vol. 1.22 pg. 4343)

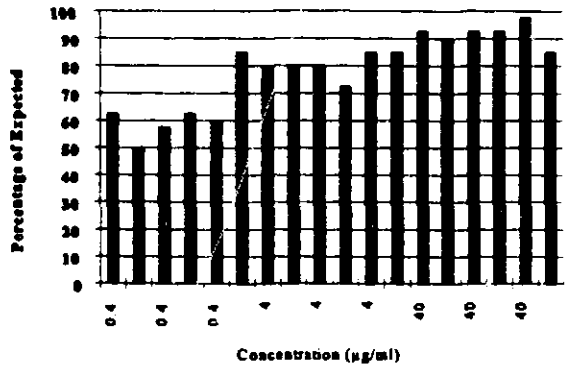


Figure 10 The expected concentration of test material for the rat carcinogenicity study (vol. 1.26 pg. 5894)

Table 20 The average percentage of the expected dose delivered in the mouse and rat carcinogenicity studies.

Dose (µg/kg)	Percentage of Expected	
	Mouse	Rat
Low (2)	62.9	69.3
Intermediate (20)	80.4	81.4
High (200)	91.7	86.4

Latanoprost is extensively metabolized by the liver, and the most appropriate way to compare doses between species is on a body surface area basis instead of a of body weight basis. For this comparison the following table (table 21) will be used:

Table 21 Representative Surface Area to Weight Ratios (km) for Various Species[a]

Species	Body Weight (kg)	Surface Area (m^2)	km Factor
Mouse	0.20	0.66	3.0
Rat	0.15	0.025	5.0

Monkey	3.0	0.24	12
Dog	8.0	0.40	25
Human	60	16	37

a. Freireich, E.J. *et al*, 1966. Quantitative comparison of toxicity of anticancer agents in mouse, rat, dog, monkey and man. Cancer Chemother. Repts. 50(4):219-244.

Ex.: To express a mg/kg dose in any given species as the equivalent mg/m^2 dose, multiply the dose by the appropriate km. In adult human 100 mg/kg is equivalent to 100 mg/kg x 37 kg/m^2 - 3700 mg/m^2

Latanoprost is administered topically to the eye and a conservative estimate of the maximum daily dose is to assume that all the administered drug substance were totally absorbed. The recommended dose is 1 drop in the affected eye once daily so the maximum human dose is 2 drops daily. This makes the total maximum exposure a maximum possible of 3.0 μg (50 $\mu g/ml$ x 0.03 ml/drop x 2 drops), the maximum possible dose would be 50 ng/kg for 60 kg patient, which is equivalent to 1.85 $\mu g/m^2$.

In order to estimate the relative safety of latanoprost studied in animals to humans the maximally tolerated dose or alternately the highest does evaluated was converted to a dose expressed in $\mu g/m^2$ and divided by the estimated human exposure, expressed similarly. These values are presented in table 22.

In 13 week studies in rats and dogs when latanoprost is administered by the intravenous route the safety ratios were 80 and 120, respectively, and when by the oral route to rats the ratio was 460. Likewise, in carcinogenicity studies in both mice rats (treated for between 87 to 91 wks) and rats (treated for between 97 to 104 wks) the relative exposure ratio was large, 300 to 490. However, in the rabbit teratology studies of latanoprost the no effect embryo toxicity dose was 1 $\mu g/kg$ and this represents only a 6 fold difference in dose when compared to humans.

Table 22 The ratios of the dose in animals expressed as $\mu g/m^2$ to the maximal possible dose in a 60 kg patient (1.85 $\mu g/m^2$)

Study	Species	Maximally tolerated dose or highest dose tested[a] ($\mu g/kg$)	Dose ($\mu g/m^2$)*	Ratio of dose expressed as body surface area to a 60 kg patient.(1.85 $\mu g/m^2$)
Carcinogenicity	Mouse	200[a]	546	295
	Rat	200[a]	910	492
13 Week i.v.	Rat	35	156	84
13 Week p.o.	Rat	200[a]	850	459
13 Week i.v.	Dog	10	220	119
52 week ocular	Rabbit	100[a]	1200	649
52 Week ocular	monkey	6[a]	72	39
52 Week ocular	monkey	50[a]	600	324
		1[b] (lowest nonembryocidal dose)	11	6
Teratology (Seg II) dose-range finding study	Rabbit	5	60	32
Teratology (Seg II) study	Rabbit	1[b]	11	6
Fertility (Seg. I)	Rat	250[c]	1062	594

* Calculated as [((Dose($\mu g/kg$) X Mean % of dose delivered)÷100) X km Factor from table 21] ÷ 1.85 (human dose expressed in $\mu g/m^2$)

b The no effect dose evaluated.

c Lethal to males

Levels of PhXA85, the free acid of latanoprost, were determined by radioimmunoassay and the results shown in table 23.

Table 23 The mean plasma levels of PhXA85, the free acid of latanoprost, in male and female rats on week 104 and 97, respectively, at 1 hour after the daily administration of latanoprost (ref. 1.38:11334).

Gender	Mean (pg/ml) ± SEM	
	20 μg/kg	200 μg/kg
Male	111.1 ± 22.1	473.4 ± 129.1
Female	48.7 ± 8*	359 ± 43.8

* Below the quantitation limit

While the above results are not directly comparable to results obtained in human studies (table 24) one can see that rat plasma level of the free acid of latanoprost 1 hr after oral administration was greater than 18 times the human plasma concentrations at peak levels (359 rat pg/ml ÷ 20 human pg/ml).[1]

Table 24 Plasma levels of latanoprost or its free acid in humans subjects or patients.

Route	C_{max}	Time	Method
topicalone (3 μg)	53 pg/ml	5-15 min	radio labeled latanoprost (study No. 9400107)
topical daily for 1 yr in 10 patients (3 μg)	6/10 - <30 pg/ml 1/10 - 32 pg/ml 1/10 - 45 pg/ml 1/10 - 54 pg/ml 1/10 - 67 pg/ml (mean = 20 pg/ml)	5 min after administration	Radioimmunoassay (IRA) Limit of quantitation 60 pg/ml and limit of detection 30 pg/ml (study No. 9400109)

Results (Neoplastic and nonneoplastic): Latanoprost was evaluated in rats and mice in a carcinogenicity bioassay at doses of 2, 20 and 200 μg/kg administered orally. No drug related effects were seen in either species. These studies were not adequate to characterize the carcinogenicity potential of the test material because the animals could have tolerated higher doses, however, the studies were adequate to characterize the risk of carcinogenicity at the ophthalmic dose used in humans.

The results of these studies were presented to the Executive Carcinogenic Assessment Committee and they concurred with the conclusions that label reflect that the doses evaluated did not adequately assess the carcinogenicity potential of latanoprost.

Proposed Labeling: Animal Studies:

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Latanoprost was well-tolerated at intravenous doses of 1 μg/kg/day in the dog and 35 μg/kg/day in the rat for 13 weeks. These doses are approximately 16 and 560 times the recommended human dose given ocularly. In animal studies latanoprost has not been found to have sensitizing properties.

In the eye, no toxic effects have been detected with doses of up to 100 μg/eye/day in rabbits or monkeys. In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. Increased pigmentation of the iris has also been reported in humans with hazel eyes during chronic treatment with latanoprost. The results from a large pre-clinical program demonstrated that the effect is unlikely to be associated with proliferation of melanocytes, and neither naevi nor freckles in the eye have changed during chronic treatment with latanoprost. It appears that the mechanism of increased pigmentation is due to stimulation of melanin production in melanocytes of the iris. The change in iris color occurs slowly and may not be noticeable for several months and may be irreversible.

In chronic ocular toxicity studies, administration of latanoprost at a dose of 6 μg/eye/day (4 times the daily human dose) has also been shown to induce increased palpebral fissures. This effect is reversible and occurs at doses above the clinical dose. This effect has not been observed in humans.

Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction did not affect the retinal blood vessels as determined by fluorescein angiography.

Recommended Labeling

In chronic ocular toxicity studies, administration of latanoprost at a dose of 6 μg/eye/day (3 times the daily human dose) has also been shown to induce increased palpebral fissures. This effect is reversible and occurs at doses above the clinical dose. This effect has not been observed in humans.

No change except for last paragraph. *Chronic treatment with latanoprost in monkey ~~eyes, which~~ that had undergone extracapsular lens extraction did not affect the retinal blood vessels as determined by fluorescein angiography.*

Genotoxicity:

Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus test. Chromosome aberrations were observed In Vitro with human lymphocytes, however, similar effects were observed with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, suggesting that this is a class effect. Additional In Vitro and In Vivo studies on unscheduled DNA synthesis in rats were negative.

Recommended Labeling:

Latanoprost was not mutagenic in S. typhimurinum strains TA 98, 100, 1535 and 1537 or E. coli strains WP2 pkM 101 and WP2 uvrA. pkM 101, or in a micronucleus test using mouse lymphoma L5178Y cells. Chromosome aberrations were observed in vitro with human lymphocytes, however, similar effects were observed with prostaglandin $F_2\alpha$, a naturally occurring prostaglandin, suggesting that this is a class effect. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were negative.

Carcinogenicity:

"Latanoprost was not carcinogenic in either mice or rats when administered at doses of up to 200 μg/kg/day (6700 times the recommended human dose) for up to 20 and 24 months, respectively."

Recommended Labeling:

The carcinogenic potential following long term administration of latanoprost has not been fully characterized. Latanoprost has been evaluated by oral administration in mice (87 weeks for males and 91 weeks for females) and rats (104 weeks for males and 97 weeks for females) at doses up to 170 $\mu g\ kg^{-1}\ day^{-1}$, however, no toxicity was seen in these studies and higher doses could have been used. If 5 % of the highest dose evaluated in rodents (170 $\mu g\ kg^{-1}\ day^{-1}$) was absorbed and the total ocular dose in patients was also completely absorbed then the ratio of the doses in μg/kg in rodents to a 50 kg patient would be greater than 100.

Reproduction:

Latanoprost has not been found to have any effect on male or female fertility in animal studies. A systemic dose 100 times the clinical dose has been shown to induce abortions in rabbits but not in rats. No teratogenic potential has been detected.

Recommended

Include in Pregnancy Teratogenic Effects/Pregnancy Category.

Pregnancy Teratogenic Effects/Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 825 times the clinical dose (based on 0.06 μg/kg - 50 kg human) and have revealed no evidence of impaired fertility or harm to the fetus due to latanoprost. A systemic dose of 100 times the clinical dose has been shown to induce abortion in rabbits but not in rats. There are, however, no adequate and well- controlled studies in pregnant women. Because reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Recommended:

Pregnancy Teratogenic Effects/Pregnancy Category C Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 1 of 6 dams had no viable fetuses at a dose that was 32 times the human dose, and the highest nonembryocidal dose in rabbits was 6 time the human dose. In rats no evidence of impaired fertility in either males or female at doses that are lethal to males was observed at doses up to 570 times the 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.

No teratogenic potential has been detected.

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, caution should be exercised when XALATAN is administered to a nursing woman.*

Recommendation:

No changes

David A. Shriver, Ph.D.
Pharmacologist

cc:

HFD-340
HFD-540
HFD-540/PHARM/SHRIVER
HFD-540/MO/CARRERAS
HFD-540-CHEM/TSO
HFD-540/PMS/CHAPMAN
HFD-540/SPHARM/AJACOBS

Concurrence Only:

HFD-540/DD/JWILKIN 2/19/96
HFD-540/SPHARM/AJACOBS 1/11/96

N20597.001

- Appendix-

JUL 23 199

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

IND: (Original Submission dated March 22, 1991)

Drug: Eye Drop Solution

Sponsor:

Number of Vol.s: Four

Date CDER Received: March 22, 1991

Date Assigned: April 1, 1991

Date 1st Draft Completed: May 13, 1991

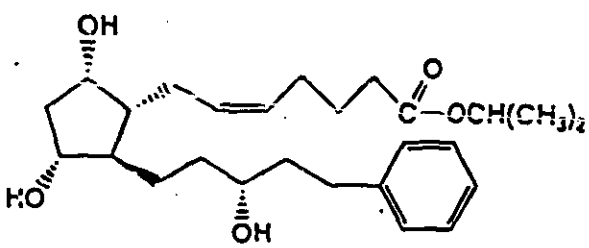
Date Accepted by Supervisor: July 10, 1991

Review Objective: To review an IND submitted for use of Eye Drop Solution for the treatment of ocular hypertension.

Category: Ophthalmic Antihypertensive

Dosage Form and Route of Administration: Solution for ocular administration.

Chemical Structure:



Composition:

Ingredients	Complete Formula	Batch Formula
Active Ingredients		
13,14-dihydro-15(R)-17-phenyl-18, 19, 20,-trinor $PGF_2\alpha$ isopropylester	60 ug	60 mg
Other Ingredients		

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Proposed Clinical Studies:

Number and Types of Subjects:
Forty subjects divided into twenty subjects with normal intraocular pressure and 20 with ocular hypertension. Males and females 20-80 years of age will be tested.

Dosage and Duration of Administration and Evaluations to be Performed:
The study-drug will be administered topically from a dropper bottle in volumes of approximately 35 ul per drop to both eyes twice daily for 5 days. Patients will be instructed to place one drop of a 60 ug/ml solution in each eye, 2 x/day x 5 days. Exact dosage will consist of 2.1 ug of drug per one 35 ul drop and 8.4 ug per day for 4 drops. Parameters scheduled for measurement will consist of the following: aqueous humor flow rate, intraocular pressure, outflow facility, permeability, hyperemia and adverse reactions.

Patient Consent Form: The sponsor states that informed consent will be obtained from all subjects. A copy of the informed consent form was submitted to the IND for evaluation.

Preclinical Studies: All preclinical pharmacodynamic, pharmacokinetic and toxicological studies submitted to this IND will be reviewed in the following tabular format.

Pharmacodynamic and Pharmacokinetic Studies with PhXA34

Study Type	Species/ Strain	Sex & # Animals Per Group	Route of Admin.	Doses	Duration of Admin.	Laboratory; Proj. Rpt. No., Study Start Date	Result and Conclusions
Pharmacodynamics (Intraocular Pressure)	Cat and Monkey	Sex not indicated; 12 cats; 6 monkeys	Topical to the eye	cats received 0.3-3 ug; Monkeys received 1-10 ug	Single and 5 Day Dosing		1) Cats: PhXA34 displayed mi otic effects at doses of 3 ug. The drug did not reduce intraocular pressure or cause superficial irritation of the eye. 2) Monkey: PhXA34 significantly reduced intraocular pressure after a single dose of 1-10 ug. PhXA34 at 10 once daily for 5 days also reduced intraocular pressure.
Pharmacodynamics (Conjunctival hyperemia)	Rabbit and Hamster	Sex not indicated; 6 rabbits	Topical to the eye	0.1-0.5 ug in the rabbit and 10^{-7} to 10^{-5} M in the Hamster Cheek pouch preparation.	Single Dose		1) Rabbit: PhXA34 produced a "barely detectable hyperemia" in the conjunctiva of the eye when applied a dose of 0.1-0.5 ug. 2) Hamster Cheek Pouch: PhXA34 had little vasodilator effect at concentrations of 10^{-7} to 10^{-5} M.
Pharmacodynamics (Blood aqueous barrier)	Rabbit	Sex not indicated; 6 rabbit	Topical to the eye	14 ug	2 x daily for 7 weeks		1) PhXA34 produced no adverse effect on the blood-aqueous barrier as shown by the normal protein concentration of the aqueous humor after continous treatment with PhXA34. The protein concentration of th aqueous humor in rabbits dosed with 14 ug PhXA34 2x daily, for 7 weeks was 21 $\pm$ 1 mg/100 ml in the drug treated eye and 19 $\pm$ 2 mg/100 ml in the control eye.

Pharmacodynamic and Pharmacokinetic Studies With PhXA34

Study Type	Species/Strain	Sex & # Animals Per Group	Route of Admin.	Doses	Duration of Admin.	Laboratory; Proj. Rpt. No., Study Start Date	Result and Conclusions
Pharmacodynamics (Aqueous humor dynamics)	Cynomolgus Monkey	Sex not indicated; 5	Topical to the eye	10 ug	5 days		1) Results showed a tendency towards an incr in total outflow facility between the drug treat eye and the contralateral control eye after 5 da topical dosing with 10 ug PhXA34 per day. Re indicated increased uveoscleral out flow (e.g., t total uveoscleral outflow of drug treated eyes w 40% higher than that of the contralateral contr eyes). Total outflow of aqueous humor also ten to increase in treated eyes versus controls. Trabecular outflow of aqueous humor was not increased by PhXA34. According to the sponso the ability of PhXA34 to lower intraocular press is based on an increased uveoscleral outflow.
Pharmacodynamics (Microcirculation in the eye)	Cynomolgus Monkey	Sex not indicated; 5	Topical to the eye	10 ug	Single Dose using radioactive labelled microspheres		1) Regional blood flow determined 60 and 150 minutes after topical application of drug showed increase in blood flow to the anterior sclera including the episcleral tissue and the ciliary body 150 minutes after drug application.
Pharmacodynamics (Capillary Permeability)	Cynomolgus Monkey	Sex not indicated; 5	Topical to the eye	10 ug	Single Dose		1) The extravascular plasma equivalent albumin space showed no significant difference between drug treated and control eyes in any of the ocular tissues studied, indicating that the drug had no appreciable effect on capillary permeability. There was no effect even in the conjunctiva or anterior sclera. PhXA34 had minimal vascular effects in th eye with the exception of the anterior sclera and ciliary body where a moderate increase in bloc flo occurred.

Pharmacodynamic and Pharmacokinetic Studies With PhXA34

Study Type	Species/Strain	Sex and # Animals Per Group	Route of Admin.	Doses	Duration of Admin.		Results and Conclusions
High Dose Pharmacology	Rat	Sex not indicated; 10	Intravenous	0.01, 0.1, 1.0, 10, 100 & 1000 ug/kg of PhXA34 & DH100A*	During a 15 minute period		1) Blood Pressure: After injection, increased a higher doses of both drugs. Thirty-sixty minut after the 1000 ug/kg dose blood pressure wa decreased. 2) Blood Gases, Blood Acid/Base Balance, Cen Venous Pressure: No drug related effect. 3) Mortality: 1/5 deaths with each substance a dose of 1000 ug/kg. DH100A caused cardiac arrest while PhXA34 caused ventricular fibrillat and death. 4) EKG: Each drug at doses of 100-1000 ug/kg produced changes in the EKG i.e., P-R shortenin or Q-T prolongation, ventricular premature beats or minor bundle branch blocks. 5) The "no-effect" dose level of PhXA34 was 1 ug/kg.
High Dose Pharmacology	Cynomolgus Monkey	Sex not indicated; 4	Intravenous	1, 10, 100 & 500 ug/kg	Single Dose		1) No drug related effect on blood pressure, hea rate or EKG. 2) An increase in respiratory rate occurred at 50 ug/kg.
General Pharmacodynamics	Cynomolgus Monkey	Sex not indicated; 5	Intravenous	0.6, 2.0, 6.0 and 60 ug/kg	Single Dose		1) "Coronary blood flow to the heart showed a dose-related increase; blood flow to the lungs decreased and blood flow to the diaphragm increased at doses of 6 and 60 ug/kg. Concomitantly, there was an increase in intrathoracic inspiration-expiration pressure difference as measured in the esophagus and increase in respiratory rate." According to the sponsor, this indicates in spontaneous breathing animals, some degree of bronchial constriction. Slight changes were also observed afte a dose of 2 ug/kg.

*DH100A = 17-phenyl-18, 19, 20, -trinor-PGF$_{2\alpha}$-1-isopropyl ester) the parent compound which in the body is partly metabolized to PhXA34/PhXA41 (without ester r 4.

Pharmacodynamic and Pharmacokinetic Studies With PhXA34

Study Type	Species/ Strain	Sex & # Animals Per Group	Route of Admin.	Doses	Duration of Admin.	Laboratory; Proj. Rpt. No.; Study Start Date	Result and Conclusions
Corneal permeability and metabolism	Porcine cornea (In vitro)	Sex and # of animals used for tissue samples not indicated	In vitro System	Tritium labelled DH100A & PhXA34 used; doses tested not indicated	Single Dose		1) The permeability coefficient calculated for DH100A was 5.9 x 10^{-6} cm/sec. The permeability coefficient figures for PhXA34 were 7.1% and 5.1 ± 0.7 x 10^{-6} cm/sec. 2) A low level of metabolism of DH100A to the 15-dihydro form was seen after 240 min. of incubation on both sides of the cornea (<6%).
Pharmacokinetics (Metabolism in the eye)	Porcine ocular tissues (In vitro)	Sex and # animals used for tissue samples not indicated	In vitro System	Tritium labelled prostaglandin ($PGF_{2\alpha}$) & tritium labelled DH100A*	Single Dose		1) $PGF_{2\alpha}$ Metabolic Capacity: cornea (4.8%) > retina and choroid (4.1%) > iris with ciliary body (3.5%) > conjunctiva (2.8%) > lens (0.7%) > whole eye (0.5%). 2) DH100A Metabolic Capacity: Conjunctiva (2.3%) > cornea (1.7%) = iris with ciliary body (1.7%) > retina with choroid (1.5%) > lens (1.3%). *) Conclusion: "Intraocular tissues poorly metabolize prostaglandins. Any metabolism of PhXA34/PhXA41 is very unlikely."
Pharmacokinetics (Metabolism in the eye)	Porcine lung & Kidney (In vitro)	Sex and # of animals used for tissue samples not indicated	In vitro System	Tritium labelled DH100A*	Single Dose		1) In Porcine lung Tissues: "Incubation for 120 to 240 min. resulted in complete conversion of DH100A to 2 major metabolites, namely the 15-keto-17-phenyl-18, 19, 20- + trinor-$PGF_{2\alpha}$ (about 70% after 240 min. incubation) + 15-keto-13, 14,-dihydro-17-phenyl-18, 19, 20-trinor-$PGF_{2\alpha}$ (13% after 240 min. incubation) and some unidentified metabolites. 2) In Porcine Kidney: After 240 min. of incubation, the major products were 15-keto-13, 14-dihydro-17-phenyl-18, 19, 20-trinor-$PGF_{2\alpha}$ and 13, 14,-dihydro-17-phenyl-18, 19, 20-trinor-$PGF_{2\alpha}$. 3) Human In Vivo Data: According to the sponsor, Granstorm (1975) reported 13, 14-dihydro-17-phenyl-18, 19, 20-trinor-$PGF_{2\alpha}$ to be a metabolite of DH100A & is a circulating metabolite in blood.
Pharmacokinetics (Metabolism & Excretion)	Cyno-molgus Monkey	Sex not indicated; 3	Intravenous	50 ug/kg of tritium labelled PhXA34	Single Dose		1) Results of this study showed that "PhXA34 is rapidly hydrolyed in the blood, totally metabolized and excreted mainly in the liver."

DH100A = 17-phenyl-18, 19, 20, -trinor-$PGF_{2\alpha}$-1-isopropyl ester, the parent compound which in the body is partly metabolized to

Toxicology Studies Conducted with PhXA34/PhX4A and DH100A

Study Type	Species/Strain	Sex & # Animals Per Group	Route of Admin.	Doses mg/kg/day	Duration of Admin.	Laboratory; Proj. Rpt. No. Study Start Date	Result and Conclusions
Acute Systemic Toxicity	OF1 mice aged 5-7 weeks old	6 males & 6 females	Intravenous	2.0 mg/kg of PhXA34	Single Dose		1) No drug induced mortality or pathological changes at a dose of 2.0 mg/kg.
Acute Systemic Toxicity	Sprague Dawley rat aged 5-7 weeks old						1) No drug induced mortality or pathological changes observed at a doses of 2.0 mg/kg.
Acute Systemic Toxicity	OF1 mice aged 5-7 weeks old						1) No drug induced mortality or pathological changes observed at a dose of 2.0 mg/kg
Acute Systemic Toxicity	Sprague Dawley rat aged 5-7 weeks old						1) No drug induced mortality or pathological changes observed

Toxicology Studies Conducted wi

Study Type	Species/Strain	Sex & # Animals Per Group	Route of Admin.	Doses	Duration of Admin.		Result and Conclusions
Four Week Ocular Tolerance	Hy/CRN Pigmented Rabbits	5 males & 5 females per group	Topical to the eye as drops; only the right eye received drug treatment; the left eye served as an individual control	1, 5, and 25 ug of PhXA34; an additional group received the placebo and served as a control	Twice daily for 35 days		1) there were no deaths and no drug related changes in the following parameters: clinical signs, body weight gain, ocular irritancy or pupillary and corneal reflexes, corneal thickness or intra ocular pressure, hematology, clinical chemistry or gross and histopathology. 2) Treatment of pigmented rabbits ocularly for 35 days with 1, 5 or 25 ug of PhXA34 twice daily to one eye produced no local ocular or systemic toxicity.

Genetic Toxicology Studies Conduced with PhXA34

Study Type	Test System [a]	End Point	Doses [b] ug/plate	Laboratory; Proj. Rpt. No.; Study Start Date	Results and Conclusions
In Vitro Mutagenicity	S. Typhimurium (TA 98, TA 100, TA 1535, & TA 1537); E. Coli WP2pkM101 & WP uvrA-Pk M101	Point Mutation	1) PhXA34: a) without metabolic activation (0.8, 4, 20, 31.25, 62.50, 100, 125, 250, & 500 ug/plate. b) with metabolic activation (4, 20, 100, 125, 250, 500, 1000, 2000 & 2500 ug/plate. 2) Positive Contr ls consisted of 2-nitrofluorene, sodium azide, 9-amino-acridine, 4-nitro-quinoline 1-oxide & 2-aminoanthracene at final concentrations of 50, 2, 50, 2 & 5 ug/plate respectively.		1) PhXA34 did not induce mutation in Salmonella typhimurium in strains TA 98, 100, 1535, and 1537 or in Escherichia coli in strains WP2 Pk M101 and WP uvrA- Pk M 101 at the concentrations tested in these experiments.
	S. Typhimurium (TA 98, TA 100, TA 1535, TA 1537); E. coli WP2 pk M101 and WP2 uvrA-Pk M101		1) PhXA41 a) with and without metabolic activation at 1.28, 6.40, 32.0. 50, 100, 160, 200, 400 and 800 ug/plate. 2) The same positive controls and concentrations used in mutagenicity study # L411S013 were used in this study.		1) PhXA41 did not induce mutation in Salmonella Typhimurium in strains TA 98, 100, 1535, and 1537 or in Escherichia coli in strains WP 2 pk M 101 and Wp uvrA pk M 101 at the concentrations tested in this experiment.

a) Assays were conduced in the presence and absence of metabolic activation by an Arochor 1254 induced rat liver post-mitochondrial fraction (S-9).
b) Drugs were dissolved in DMSO.

Comments and Evaluation

1) The drug proposed for use in the present IND (i.e., PhXA41), is a prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogue. According to the sponsor, "it is the active epimer of PhXA34, a mixture containing two epimers (15R and 15S) in equal proportion. PhXA41 is contained within PhXA34 at a proportion of about 50/50 with the less active 15-S epimer."

2) In animal models used to conduct comparative pharmacological studies of PhXA41, the active epimer and the less active epimer, it was found that PhXA41 exerted 60-70% stronger pharmacological activity than PhXA34 (the epimeric mixture).

3) The pharmacology/toxicology data base submitted in support of this IND, includes pharmacodynamic/pharmacokinetic, acute systemic, ocular toxicity and mutagenicity studies on PhXA34 and PhXA41. With respect to toxicology, these studies showed the following: no drug induced mortality in rat acute i.v. systemic toxicity studies at 2 mg/kg of PhXA34 or PhXA41 and no local ocular or systemic toxicity in rabbits dosesd ocularly with 1, 5, or 25 ug of PhXA34 2x/day times 35 days. Results of testing PhXA34 or PhXA41 for mutagenicity in four strains of Salmonella typhimurium and two strains of Escherichia coli were negative for mutagenicity.

4) The sponsor states that "in a 4 week ocular toxicity test in rabbits performed with PhXA41 with a maximum dose of 50 ug per eye/day no clinical abnormalities could be detected." The sponsor however neglected to submit this study to the IND for pharmacology/toxicology evaluation. The sponsor should be requested to submit this study to the IND for evaluation.

5) No preclinical reproductive toxicity data has been submitted to this IND. The sponsor should be requested to perform segments I, II and III reproduction studies and submit the results to the IND for evaluation.

6) According to the sponsor, "PhXA34 has been tested clinically in Sweden, U.S.A. and Japan in a total of 96 persons (0.3-10 ug/application) without side effects related to the drug other than mild or moderate conjunctival hyperemia depending on the dose (10 ug). The sponsor also states "a comparison of the intraocular pressure lowering effect of 3 different doses of PhXA41 with that of 3 doses of PhXA34 in healthy human volunteers is in progress in Sweden." Final results of these studies have not been submitted to the IND for evaluation.

Recommendation:

A) Non-initiation of clinical trials until the sponsor submits the following and the results are found to support safety of use of PhXA41 upon ocular application.

1) the four week rabbit ocular toxicity study using PhXA41 up to a maximum dose of 50 ug per eye/day.

or

2) the results of clinical studies using doses equal or greater than those proposed for use in the currently proposed clinical trials.

Norma J. Browder

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Pharmacologist, DAIDP/HFD-520

cc: Orig: NDA 36,523
HFD-520
HFD-520/mo/Chambers
HFD-521/cso/Huntley
HFD-520/chem/De Camp
jpg:6/3/91; 6/12/91

HFD-520/pharm/Browder
HFD-520/micro/Sheldon
init. by REOsterberg 7/10/91
b36523.00

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Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

IND:

DRUG: PhXA41 Eye Drop Solution

CATEGORY: Anti-Glaucoma

SPONSOR:

NUMBER OF VOLUMES: 8

DATE OF SUBMISSION: October 5, 1992

DATE CDER RECEIVED: October 13, 1992

DATE ASSIGNED: May 4, 1994

DATE REVIEW STARTED: October 20, 1994

DATE FIRST DRAFT COMPLETED: December 22, 1994

DATE REVIEW ACCEPTED BY SUPERVISOR: January 25, 1995

EVALUATION OVERVIEW

PhXA41 is a synthetic prostaglandin F-2-alpha analogue isopropyl ester which has been reported to reduce the intraocular pressure in both monkeys and humans. The compound can exist as two epimers (15R and 15S), and the equimolar mixture of both epimers is known as PhXA34. PhXA41, the active epimer, is an esterified prodrug which is hydrolyzed to the biologically active form in the cornea. PhXA41 Eye Drop Solution is manufactured by The formulation contains 50 mcg/ml of PhXA41 in PhXA41 has been tested in clinical trials in England, Japan, Sweden, and the United States. The purpose of this submission is to justify Phase III clinical trials with this formulation in glaucoma patients.

PRECLINICAL STUDIES

The GLP studies described below were conducted according the GLP guidelines. Dosing solutions were analyzed for potency, animals were housed under the appropriate environmental conditions, etc. In some studies, no signs of toxicity were seen, but solubility limitations precluded the use of any higher doses.

1. Acute Intravenous Toxicity Study in Mice

This was a GLP study conducted by from October 22, 1990 to January 17, 1991 (protocol signing to final report).

A single dose of the compound was administered intravenously at a dose of 2 mg/kg (50 ml/kg) to 6 male and 6 female OF1 mice. The vehicle was not described. The mice were observed daily for 14 days and were then sacrificed with carbon dioxide, and subjected to a gross necropsy.

There were no deaths and no clinical signs of toxicity in this study.

2. Acute Intravenous Toxicity in Rats

This was a GLP study conducted by from October 22, 1990 to January 23, 1991.

A single dose of the compound was administered intravenously at a dose of 2 mg/kg (50 ml/kg) to 6 male and 6 female Sprague-Dawley rats. The vehicle was not described. The rats were observed daily for 14 days and were then sacrificed with carbon dioxide, and subjected to a gross necropsy.

There were no deaths and no clinical signs of toxicity.

3. Acute Oral Toxicity in Mice

This was a GLP study conducted by

A single dose of the compound was administered orally to Charles-River albino mice (3/sex/group) in doses of 0.1, 1, 10, or 50 mg/kg. The vehicle for the test substance was Neutralolja TG8/10; the volume administered was 4.4 ml/kg for the high-dose group and 4 ml/kg for all of the other groups. There was no control group in this study. The animals were observed for 14 days and were then sacrificed by pentobarbital and exsanguination.

There were no deaths in this study. Wetness around the urogenital area and soft or loose feces were observed, but since there was no control group, it was not possible to determine if the effects were

due to the test substance or to the vehicle. (The chemical nature of the vehicle was not described, but it is thought to be an oil).

4. Acute Oral Toxicity in Rats

This was a GLP study conducted by . The study was conducted in Charles-River (Sprague-Dawley) rats, but at one point in the summary, the report incorrectly refers to mice.

A single dose of the compound was administered orally to rats (3/sex/group) in doses of 0.1, 1, 10, or 50 mg/kg. The same vehicle (Neutralolja) was used as in the previous study, and again the volume was 4.4 ml/kg for the high-dose group and 4 ml/kg for the other groups.

There were no deaths or clinical signs of toxicity in this study.

5. Four Week Intravenous Study in Rats

This was a GLP study conducted by from May 14, 1991 to June 17, 1992.

PhXA41 was administered intravenously to Sprague-Dawley rats (5/sex/group) at doses of 0, 1, 10, 100, or 340 mcg/kg/day for 28 days. The vehicle was saline for injection and the volumes administered ranged from 1.0-7.1 ml/kg due to solubility limitations. Evaluations for treatment-related effects were based on observations, body weights, food consumption, hematology, serum chemistry, gross pathology, organ weights, and microscopic histopathologic examination.

No changes occurred in this study that could be related to treatment.

6. Four Week Intravenous Study in Dogs

This was a GLP study conducted by

PhXA41 was administered intravenously to Beagle dogs (one male, one female per group) in doses of 0, 1, 10, 100, or 340 mcg/kg/day for 28 days. The compound was administered in saline for injection in volumes ranging from 1.0-7.1 ml/kg. The effects of the compound were evaluated based on the same parameters as in the rat study (#5) above.

There were no deaths in the study. Animals in the 100 and 340 mcg/kg groups developed miosis, salivation, vomiting, diarrhea, and increases in alanine aminotransferase.

7. Four Week Oral (Saline) Study in Mice

This was a GLP study conducted by

PhXA41 dissolved in sterile physiological saline was administered by gavage to albino mice (6/sex/group) at doses of 0, 2, 20, or 200 mcg/kg/day for 28 days in a volume of 5 ml/kg. Evaluations for treatment-related effects were based on observations, body weights, food consumption, gross pathology, and the weight of the stomach. No clinical chemistries or microscopic examinations were performed.

There were five deaths in the study, but the deaths were not related to treatment. Four of the five mortalities occurred in the low-dose group, and were attributed to dosing accidents. There were no treatment-related changes in any of the parameters measured in this study.

8. Four Week Oral (Saline) Study in Rats

This was a GLP study conducted by

PhXA41 dissolved in sterile physiological saline was administered by gavage to Sprague-Dawley rats (5/sex/group) at doses of 0, 2, 20, or 200 mcg/kg/day for 28 days in a volume of 5 ml/kg. Evaluations for treatment-related effects were based on observations, body weights, food consumption, gross pathology, and the weight of the stomach. No clinical chemistries or microscopic examinations were performed.

There were no deaths and no treatment-related changes in this study.

9. Four Week Oral (Oil) Study in Mice

This was a GLP study conducted by

PhXA41 was administered by gavage to albino mice (6/sex/group) in doses of 0, 0.01, 0.1, 1, or 10 mg/kg/day for 28 days. The vehicle was Neutraloja TG8/10 (which permitted the higher doses). The volume administered was 4 ml/kg in all groups. The effects produced by the compound were evaluated based on the same parameters as described in studies 7 and 8 above.

There were nine deaths in this study, all of which were attributed to dosing accidents. (The distribution of mortalities across groups supports this conclusion). Treatment-related occurrences of anogenital/urogenital staining were seen in the high-dose group. There were no other treatment-related changes.

10. Four Week Oral (Oil) Study in Rats

This was a GLP study conducted by

PhXA41 was administered by gavage to Sprague-Dawley rats (5/sex/group) in doses of 0, 0.01, 0.1, 1, or 10 mg/kg/day for 28 days. The vehicle was Neutraloja TG8/10, and all doses were

administered in a constant volume which was alternately reported to be either 4 or 5 ml/kg. The effects produced by the compound were evaluated based on the same parameters as described in studies 7, 8, and 9.

There were three deaths in the study, one of which occurred in the high-dose group. All three deaths were attributed to dosing accidents. No treatment-related effects were seen in any of the parameters investigated.

11. Four Week Ocular Study in Rabbits

This was a GLP study conducted by

NOTE: Pages 6 through 11 of this report have not been submitted to the FDA. These six pages contain key information on the test article, the test system, and the dosing procedure (according to the table of contents).

From the report summary and the remainder of the report it was possible to determine that the compound was instilled into the right eye of pigmented rabbits twice daily for four weeks. The left (untreated) eye was used for comparison. There were four groups of animals, each containing 5 males and 5 females. Each application consisted of approximately 30 microliters containing doses of 0 (placebo), 1, 5, or 25 micrograms, so that the total daily doses were 0, 2, 10, or 50 mcg/day.

Ophthalmological examinations were conducted before the start of the study, and after four weeks of treatment. Effects on the eyes were evaluated using a slit lamp and indirect ophthalmoscopy, with a mydriatic agent being used during examination of the fundus and posterior segments. Ophthalmic pachymetry (corneal thickness) and tonometry (intraocular pressure) were measured under anesthesia.

The amount of ocular irritation occurring in the cornea, iris, and conjunctiva was evaluated weekly using a grading system that scored opacity, ulceration, granulation, congestion, chemosis, discharge, enanthema, and photomotor (pupillary) reflex.

Possible systemic effects were evaluated based on observations, body weights, hematology including coagulation, clinical chemistry, gross macroscopic pathology, and histologic microscopic examination of selected tissues.

There was one death in the study, but it was a result of the bleeding procedure (blood clots were found at necropsy in the neck tissue surrounding the jugular vein in this animal).

Ophthalmological examinations and ocular irritation evaluations revealed no differences between control and treated groups. No

treatment-related effects occurred in any of the parameters used to evaluate systemic toxicity.

12. One Year Ocular Study in Rabbits

This was a GLP study conducted by . This study used PhXA34, an epimeric mixture containing 50% PhXA41. (The previous 11 studies used PhXA41).

An eyedrop formulation of PhXA34 was instilled into the conjunctival sac of the right eye of Dutch belted rabbits (15/sex/group) in doses of 0, 10, 25, or 50 micrograms twice daily, for total doses of 0, 20, 50, or 100 mcg/day. The placebo and high-dose formulations were administered as two drops (approximately 30 microliters each) twice daily, while the low and mid-dose groups were given one drop twice daily. Five animals of each sex from each group were sacrificed after six months of dosing, while the remaining rabbits were dosed for one year.

Ophthalmic examinations were conducted using a direct ophthalmoscope and included examination of the vitreous humor, lens, optic disc, and fundus. Tonometry and pachymetry were also performed. Ocular irritation was graded using the standard Draize scoring system. Potential systemic toxicity was evaluated based on observations, body weights, food consumption, hematology, clinical chemistry, gross macroscopic pathology, organ weights, and microscopic histopathologic examination.

There were five deaths in the study, but none of the deaths were treatment-relat . The deaths were distributed across groups, and four of the five mortalities were due to technical difficulties encountered during blood collection. Slight decreases in food consumption were seen in some high-dose animals, but body weights were not affected. Increases in serum creatinine and blood urea nitrogen occurred in high-dose females, but not in males.

One control animal and three high-dose animals developed small lens opacities or focal cataracts. The sponsors ophthalmologist concluded that these were of no toxicologic significance. Tonometry measurements indicated that the intraocular pressures were generally slightly higher in the treated (right) eyes than in the untreated eyes. There appeared to be slight increases in the corneal thickness among the treated groups of animals as compared to the control group, however the interpretation of this data was complicated because of considerable variation in the predose values. Paradoxically, a comparison of the left (untreated) eye and the right (treated) eye, revealed that the left cornea was slightly thicker than the right in all groups including the control group. Some minor irritation in the form of a redness and a clear discharge, was seen around the eyelids and conjunctiva in some treated animals.

THERE WAS NO STUDY 13 IN THIS SUBMISSION

At this point in the sponsors summary, a description of a one year ocular study in monkeys was presented. Eyedrops containing PhXA41 were applied to one eye of cynomolgus monkeys (5/sex/group) twice daily for one year. Each group of animals received the vehicle in one eye. The other eye received either no treatment (control group) or PhXA41 in total doses of 20, 50, or 100 mcg/day.

Increases in the pigmentation of the iris occurred in about one-half of the animals treated with PhXA41. The iris in the treated eye became somewhat darker than the iris in the contralateral control eye. The pigmentation changes were accompanied by an increase in the palpebral fissure, i.e. the eyelids appeared to be more open in the treated eye than in the control eye.

14. Intravenous Reproductive Fertility Study in Male Rats

This was a GLP study conducted by

PhXA41 was administered intravenously to male Sprague-Dawley rats (6/group) at doses of 0 (saline), 5, 50, or 300 mcg/kg/day for 71 days before mating and then up until necropsy.

NOTE: The sponsors summary report erroneously states that a dose of 1 mcg/kg was also used in this study, which in fact, was not the case.

Male rats were mated with untreated females. After the mating period, the males were sacrificed and the weights of the testes and epididymides were recorded. The females were sacrificed on day 20 of gestation, and the ovaries and uterus were removed. Ovarian weights were recorded, as were the numbers of live and dead fetuses, resorption sites, and corpora lutea. Fetuses received an external examination.

Analyses of the dosing solutions gave recoveries of approximately 73-84% of the labeled claim.

No treatment-related effects were seen in this study.

15. Intravenous Reproductive Fertility Study in Female Rats

This was a GLP study conducted by

PhXA41 was administered intravenously to female Sprague-Dawley rats (6/group) in doses of 0 (saline), 5, 50, or 300 mcg/kg/day.

NOTE: The sponsors submission describes two different dosing regimens for this study, only one of which, can be correct. The protocol and the summary of the report, give the duration of dosing as 15 days before mating, throughout mating, and

until day 7 of gestation. However, in the body of the report, the duration of dosing is given as days 6-15 of gestation.

Female rats were mated with untreated males. The females were sacrificed on day 20 of gestation, and the ovaries and uterus were removed. Ovarian weights were recorded, as were the numbers of live and dead fetuses, resorption sites, and corpora lutea. Fetuses received an external examination.

As had been the case in the preceding study, the potency of the dosing solutions was only about 80% of label claim. Two of the high-dose animals died. No clinical signs were seen in these two animals, but the deaths were probably related to treatment. In the surviving animals, there were no treatment-related effects on any of the reproductive parameters evaluated.

16. Intravenous Reproductive Range Finding Study in Pregnant Rats

This was a GLP study conducted by

PhXA41 was administered intravenously to pregnant Sprague-Dawley rats (6/group) in doses of 0 (saline), 0.1, 1.0, 5, 50, or 300 mcg/kg/day during days 6-15 of gestation. On day 20 of gestation, the animals were sacrificed, and the uterus and ovaries were removed and examined. The number of corpora lutea were recorded, as were the number of embryonic/fetal deaths, and the number of live fetuses. Fetuses were weighed, sexed, and examined externally for abnormalities.

Potency analyses were again only about 80% of claim. There were no effects in either the dams or the offspring that were considered to be treatment-related. One fetus with a cleft palate was observed in the 1 mcg/kg group, but this was thought to be an incidental finding. An increased incidence of early resorptions occurred in most treated groups, [illegible] not the high-dose group.

17. Intravenous Ran[illegible] ding Study in Pregnant Rabbits

This was a GLP study conducted by

PhXA41 was administered intravenously to pregnant New Zealand albino rabbits (6/group) in doses of 0 (saline), 0.1, 1.0, 5, 50, or 300 mcg/kg/day during days 6-18 of gestation. On day 29 of gestation, the animals were sacrificed, and the uterus and ovaries were removed and examined. The number of corpora lutea were recorded, as were the number of embryonic/fetal deaths, and the number of live fetuses. Fetuses were weighed, and examined externally for abnormalities.

The dosing solutions assayed at about 80% of label claim. There were no maternal deaths, but increased respiration, muscular

tremors, and motor incoordination were observed in dams from the high-dose group. Multiple ovarian cysts were found in two dams from the 50 mcg/kg group, and in four animals from the 300 mcg/kg group. All animals in the 50 and 300 mcg/kg groups underwent total litter resorption early in gestation. In the group that received 5 mcg/kg, there was an increase in the number of resorptions, and one animal in the group, aborted on day 19 of gestation There were no fetal abnormalities in the 0.1, 1.0, or 5 mcg/kg groups.

THERE WAS NO STUDY 18 IN THIS SUBMISSION

At this point in the sponsors summary, a description of a range-finding prenatal/postnatal (Segment III) study in rats was presented. PhXA41 was administered intravenously in doses of 0, 1, 3, 10, or 100 mcg/kg/day to mated female Sprague-Dawley rats (8/group) from day 15 of gestation until weaning of the offspring.

One dam in the high-dose group delivered only stillborn pups, and three other live litters in this group, died during the first week postpartum. Two litters from the 10 mcg/kg group, and one litter from the 3 mcg/kg group also died. In addition, some of the mated females were found to be not pregnant.

19. Bacterial Mutation (Ames) Assay

This was a GLP study conducted by

PhXA41 was tested in four strains of Salmonella typhimurium (TA98, TA100, TA1535, and TA1537) and in two strains of Escherichia coli (WP2 pKM101 and WP2 uvrA- pKM101) for its ability to induce reverse mutations. A metabolic activation system (S-9) was prepared containing cofactors and the 9000 x g supernate of a liver homogenate obtained from rats that had been treated with Arochlor 1254.

In the range finding portion of the study, PhXA41 was tested in amounts ranging from 8-5000 mcg/plate. Cytotoxicity (thinning of the background bacterial lawn) was seen at the higher amounts. In the definitive portion of the study, amounts of 1.28-800 mcg/plate were tested both in the absence and in the presence of S-9. The solvent (DMSO) was used as the negative control and five different positive controls were also used.

PhXA41 did not induce mutations in this assay, either with or without S-9. The positive controls were mutagenic.

20. Mouse Lymphoma Assay

This was a GLP study conducted by .

Cultures of wild type mouse lymphoma L5178Y cells were plated in growth medium to confirm cell viability, and were then incubated

with various concentrations of test compound, negative control, or positive control, either with or without S-9. PhXA41 was added to make final concentrations ranging from 1-250 mcg/ml with S-9, and 1-200 mcg/ml without S-9. The solvent (DMSO) was used as the negative control. The positive controls were benzo(a)pyrene with S-9, and 4-nitroquinolone-1-oxide without S-9. Solutions of 6-thioguanine were added and the cell cultures were incubated for seven days to allow expression of mutation at the HGPRT locus, i.e. resistance to 6-thioguanine.

Concentrations of PhXA41 greater than 100 mcg/ml resulted in poor cell survival, but PhXA41 was not mutagenic at any of the concentrations tested. The positive controls were mutagenic in this assay.

21. In Vivo Mouse Micronucleus Test

This was a GLP study conducted by

PhXA41 was suspended in water with the aid of Tween 80 and carboxymethylcellulose, and administered intraperitoneally (25 ml/kg) to groups of male and female albino mice (15/sex/group). A range-finding study, done prior to the definitive study, indicated that mortalities occurred at doses of 1000 mg/kg and above. The doses used in the main portion of the study were 200, 400, and 800 mg/kg. The negative control group received the vehicle, while the positive control group received cyclophosphamide. Five animals per sex per group were sacrificed at 24, 48, and 72 hours after treatment. Femurs were removed, and bone marrow was aspirated, mixed with a small amount of fetal bovine serum, and centrifuged. Slides were prepared and stained for microscopic reading of the proportion of polychromatic erythrocytes and the number of micronuclei.

PhXA41 did not produce an increase in the incidence of micronucleated polychromatic erythrocytes, while the positive control produced statistically significant increases in micronuclei. Treatment with PhXA41 resulted in a decrease in the ratio of polychromatic to normochromatic erythrocytes, indicating possible bone marrow toxicity.

22. In Vitro Human Cytogenetics Assay

This was a GLP study conducted by

Blood samples were obtained from a male and a female volunteer, and each specimen was subdivided and cultured in a buffered medium. Phytohemaagglutinin was added to stimulate lymphocyte division. PhXA41 was added in a range of concentrations, either with or without S-9. The solvent (DMSO) was used as the negative control. Cyclophosphamide with S-9, and methyl methanesulfonate without S-9, were used as positive controls. The treatment periods were 20

hours in the absence of S-9, three hours in presence of S-9 followed by 17 hours of recovery, or three hours in the presence of S-9 followed by 41 hours of recovery. Colchicine was added to arrest dividing cells in metaphase. The lymphocytes were harvested, fixed, and stained with Giemsa stain for microscopic chromosomal evaluation.

Based on the results of a preliminary range-finding experiment, the doses selected for cytogenetic analysis were 100-160 mcg/ml in the absence of S-9, and 280-340 mcg/ml in the presence of S-9.

In the absence of S-9, PhXA41 was associated with a significant increase in chromosomal structural aberrations, including chromatid exchanges. In the presence of S-9, the frequency of aberrant cells increased in one experiment, but not in another. Both positive controls also produced increases in the proportion of cells with chromosomal aberrations.

IN ADDITION TO THE TOXICOLOGY STUDIES DESCRIBED ABOVE, TWO CARCINOGENICITY STUDIES (ONE IN MICE AND ONE IN RATS) HAVE BEEN CONDUCTED BY THE SPONSOR. THE REPORTS OF THESE STUDIES WERE NOT INCLUDED IN THIS SUBMISSION.

PHARMACODYNAMIC STUDIES

The following efficacy and pharmacology information was obtained from one study conducted at the Huntingdon Research Center in England, and from a series of studies conducted at the Glaucoma Research Unit of Kabi Pharmacia in Sweden.

1. In New Zealand albino rabbits, PhXA41 in doses up to 1 mcg/eye resulted in moderate conjunctival hyperemia. When PhXA41 was given in combination with either pilocarpine or dipivefrin, the hyperemia was somewhat less. No significant effects on intraocular pressure (IOP) were produced by PhXA41, either alone or in combination with either of the other glaucoma drugs.

2. Topical formulations of PhXA41 in buffered saline were applied to one eye of either female cats or cynomolgus monkeys (drop size 10-20 microliters). The effects on the diameter of the pupil, and on IOP were measured, with oxibuprocain being used for local anesthesia. The contralateral eye served as a control. In cats, PhXA41 (0.3-3 mcg), caused pupillary constriction and no effect on IOP. In monkeys, PhXA41 (1-9.5 mcg) caused pupillary dilation and a decrease in IOP.

3. The effects of PhXA41 on the integrity of retinal blood vessels was studied in cynomolgus monkeys. The animals were anesthetized, and the extracapsular crystalline lens was extracted from the right eye by irrigation/aspiration. Antibiotics were applied to the eye

to prevent infection, and the animals were allowed to recover for three months. After the recovery period, treatment with PhXA41 was started. PhXA41, in a dose of 10 mcg/day, was administered topically to both eyes once daily for six months. At various times during the six month treatment period, the monkeys were anesthetized for eye examinations and fluorescein angiography. The pupils were dilated with a mydriatic agent, and the eyes were examined using a slit lamp microscope. Fluorescein was injected into a hind leg, and angiograms were taken using a fundic camera.

The clinical eye examinations detected a slight fibrinoid reaction in the lens capsule of some of the aphakic eyes. No clinical disturbances in the fundus were seen. Reading of the angiograms showed that there was no leakage of fluorescein from the retinal blood vessels including the perifoveal capillary network, in any of the phakic or aphakic eyes. There was no evidence of macular edema.

4. Cynomolgus monkeys were also used to evaluate the effects of PhXA41 on regional blood flow, capillary permeability, and aqueous humor dynamics in the eye. In an experiment in which erythrocytes were labeled with Cr51, PhXA41 (6 mcg) was associated with increased blood flow to the anterior and posterior sclera, but the other vascular effects in the eye were relatively minor. In another experiment in which albumin was labeled with radioactive iodine, PhXA41 was associated with increased uveoscleral outflow, but the effects on trabecular outflow were relatively minor.

5. The effects produced by PhXA41 on certain cardiovascular and pulmonary parameters were also studied. In one experiment, four cynomolgus monkeys were trained, during a period of acclimation, to accept chair restraint. The experimental setup allowed for intravenous infusion, and for recording of respiration rate, heart rate, blood pressure, and electrocardiogram. After an equilibration period, intravenous infusions of either vehicle or PhXA41 (1, 10, 100, and 500 mcg/kg) were made. Slight increases in heart rate and respiration rate, and some minor changes in the EKG occurred after PhXA41. There were essentially no effects on systolic, diastolic, or mean blood pressures.

In another experiment, the effects on regional blood flow and airway resistance were studied. Cynomolgus monkeys were anesthetized and a catheter was inserted into the left ventricle of the heart via the brachial artery. Regional blood flow was estimated using radioactively labeled microspheres which were injected into the left ventricle at various times before and after the intravenous administration of PhXA41. Changes in airway resistance were estimated from the intrathoracic inspiration-expiration pressure difference and the respiration rate. PhXA41 (6 mcg/kg) was associated with an increased respiration rate, and an increase in the inspiration-expiration pressure difference, suggesting an increase in airway resistance. Changes in regional

blood flow were variable and relatively minor.

PHARMACOKINETIC STUDIES

The following pharmacokinetic information was obtained from one ADME study conducted by and from a series of PK studies conducted at the Glaucoma Research Unit of

1. In vitro corneal preparations were used to evaluate the penetration and metabolism of PhXA41 in the eye. Porcine eyes were obtained from a slaughter house, kept on ice, and quickly dissected. Corneas with a small amount of sclera were mounted in incubation chambers containing buffered nutrient media. Tritiated PhXA41 was added to the incubation compartment on the epithelial side of the cornea, and samples were withdrawn from the other compartment (endothelial side) at various time intervals up to four hours.

Approximately 10% of the labeled PhXA41 passed across the cornea in four hours. On the epithelial side of the cornea, PhXA41 existed as the isopropyl ester. On the endothelial side, it existed as the free acid, indicating that the cornea was capable of hydrolyzing PhXA41.

2. In another experiment, the ability of various portions of the porcine eye to hydrolyze PhXA41 was studied. Sufficient esterase activity was found in cornea, conjuntiva, iris, retina, and lens to hydrolyze tritiated PhXA41 to the corresponding free acid. No further metabolism of the free acid occurred in these tissues.

3. When tritiated PhXA41 was incubated with human plasma in vitro, the ester was completely hydrolyzed to the free acid within one hour.

4. Whole body autoradiography was used to examine tissue distribution of PhXA41. Tritiated PhXA41, in an eyedrop formulation, was applied to both eyes of two cynomolgus monkeys. Radioactivity was detected in the cornea, sclera, anterior chamber, iris, ciliary muscle, eyelid, and lacrimal duct. Some radioactivity was also found in the gastrointestinal tract, liver, kidneys, and urinary bladder.

5. In another study, tritiated PhXA41 was administered to cynomolgus monkeys by three different routes (intravenous, oral, ocular), to evaluate the absorption, distribution, and excretion of the compound.

PhXA41 was rapidly absorbed after oral and ocular administration, with peak blood levels occurring within one hour of dosing. After

intravenous administration, plasma radioactivity declined rapidly with a half-life of approximately 30 minutes. PhXA41 was distributed into kidney, liver, gastrointestinal tract, prostate, seminal vesicles, eye structures, and many other tissues. After ocular dosing, the compound distributed to the cornea, retina, choroid, conjunctiva, and eyelid. PhXA41 was bound to plasma proteins and to erythrocytes. PhXA41 was eliminated in urine and feces after all three routes of administration.

CONCLUSIONS/RECOMMENDATIONS TO SPONSOR

The use of prostaglandins represents a novel approach to the treatment of glaucoma, but the instillation of prostaglandin analogues into the eye is not without some risk. Mild to moderate conjunctival hyperemia occurred following the ocular administration of PhXA41 in both albino and pigmented rabbits. This formulation was also associated with some conjunctival hyperemia in the previous clinical trials in humans. In a one year ocular study in cynomolgus monkeys, changes occurred in pigmentation of the iris. In the one year rabbit ocular study, "small lens opacities or focal cataracts" were seen in one control animal and in three high-dose animals. Also, measurement of intraocular pressures in the one year rabbit study, indicated that the pressures were usually slightly higher in the treated eye as compared to the untreated eye, (which would be an undesirable effect in glaucoma patients).

In the ocular safety studies reported in this submission, PhXA41 or PhXA34 was administered to Dutch belted (pigmented) rabbits in doses of up to 50 or 100 mcg/day for one month or one year. However the only data reported for albino rabbits, was from a short-term, pharmacodynamic evaluation in which the highest dose was only 1 mcg/eye. It is suggested that some additional ocular safety data be developed in albino rabbits using doses comparable to those that will be used in humans, i.e. at least 50 micrograms.

It is requested that the pages missing from the four week rabbit ocular study (Study 11, pages 6-11) be submitted to this IND. It is also requested that a written statement be submitted to the IND to reconcile the contradictory descriptions of the dosing regimen given in the rat reproductive fertility report (Study 15).

Full reports should be submitted to the FDA of any other animal studies that have been completed with PhXA41, and not yet reported. These include, at least, the monkey one year ocular study, the rat Segment III range-finding study, the mouse carcinogenicity study, and the rat carcinogenicity study.

The Phase III clinical trials should be delayed until after the above requested data has been reviewed.

If and when the Phase III trials with PhXA41 are conducted, they should exclude pregnant women, because of the potential abortifacient properties of prostaglandin F-2-alpha analogues. If nonpregnant women of childbearing potential are to be included in the clinical trial, then additional teratogenicity and reproductive toxicology studies should be conducted according to the latest ICH guidelines.

Because of the ocular effects seen in the animal studies with the compound (conjunctival hyperemia, lens opacities, pigmentation changes, variable responses on intraocular pressure), the subjects in any clinical trials with PhXA41, must receive frequent and comprehensive eye exams by a qualified ophthalmologist. The intraocular pressure must be monitored regularly because the risks associated with the compound will be outweighed only if the intraocular pressure is effectively lowered and the glaucoma is brought under control.

Kenneth Seethaler

Kenneth Seethaler, Ph.D., D.A.B.T.
Pharmacologist, HFD-520

cc: Original IND
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/Chem/B.Shetty
HFD-540
HFD-540/DD/J.Wilkin
HFD-540/SPharm/S.Alam
HFD-540/MO/J.Bull
HFD-540/CSO/K.Chapman

Concurrence Only:
HFD-520/DD/L.Gavrilovich
HFD-520/SPharm/R.Osterberg

550

Holmes

DIVISION OF DERMATOLOGICAL AND OPHTHALMIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-597 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 11/3/95
Updated 2/6/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	6/14/95	6/16/95	6/23/95
AMENDMENT	7/6/95	7/13/95	7/20/95
AMENDMENT	7/21/95	7/24/95	8/3/95
AMENDMENT	8/18/95	8/23/95	9/1/95
AMENDMENT	8/25/95	8/28/95	9/1/95
AMENDMENT	10/27/95	10/30/95	12/7/95
AMENDMENT	12/22/95	12/26/95	1/8/96
AMENDMENT	1/23/96	1/24/95	---

NAME & ADDRESS OF APPLICANT: Pharmacia, Inc.
7001 Post Road
Dublin, OH 43017

DRUG PRODUCT NAME

Proprietary:	Xalatan
Nonproprietary/USAN:	Latanoprost
Code Names/#'s:	PHXA41, XA41
Chemical Type/	1-P
Therapeutic Class:	**prostaglandin**

ANDA Suitability Petition/DESI/Patent Status:
The applicant is the exclusive licensee or the assignee of the following patents:

US 4,599,353, expires 7/8/03, method and composition
US 5,296,504, expires 3/22/11, method and composition
US 5,422,368, expires 3/24/11, composition and use

PHARMACOLOGICAL CATEGORY/INDICATION:
Prostaglandin, anti-hypertensive/glaucoma

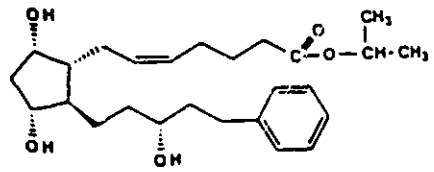
DOSAGE FORM: Sterile solution
STRENGTHS: 0.005% or 50 ug/mL
ROUTE OF ADMINISTRATION: Topical/Ocular
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name:

Isopropyl-(Z)-7[(1R, 2R, 3R, 5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenyl-1-pentyl]cyclo-pentyl]-5-heptenoate
CAS Registry number: 130209-82-4

Structural formula:



Molecular formula: $C_{26}H_{40}O_5$

Relative molecular mass: 432.58 g/mol

SUPPORTING DOCUMENTS:

IND Pharmacia Inc., PHXA Eye Drop Solution

DMF #	TYPE	SPONSOR	LETTER

RELATED DOCUMENTS (if applicable):

IND
Phone/fax:

CONSULTS:

Environmental Assessment consulted to HFD-004 on 6/28/95.
Trade Name consult, 7/24/95
Compliance statement, 10/17/95

REMARKS/COMMENTS:

Latanoprost is a prostaglandin $F_2\alpha$ analogue, a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humor. Latanoprost is an isopropyl ester pro-drug which has to be hydrolyzed to the acid form to become biologically active.

Latanoprost is a new molecular entity. Xalatan (latanoprost) Ophthalmic Solution, 0.005% has not been commercially marketed in any country. It is a new class of antiglaucoma agent.

CONCLUSIONS & RECOMMENDATIONS:

The application is **approvable** for manufacturing and controls under section 505 of the Act. All manufacturing facilities are in GMP compliance as of 10/7/95. Method validation submitted on 1/29/95. However a signed FONSI has not been received from HFD-004.

However, the sponsor should be notified of the following minor deficiencies, which may be satisfied by post-approval commitments or in the final labeling:

1. The product should be shipped under refrigeration. The drug product should protected from exposure to 40°C at any length of time during transportation.

2. Initiate a label extraction study as soon as possible and submitt the results in an amendment.

3. Provide updated stability data for the production batches (9502R01A, 500 L; 9502R02A, 1000 L; and 9502R03A, 500 L) as soon as possible.

4. For light protection, it is recommended to add caution statement such as "keep container in carton after each use" (in the package insert, on the bottle, and on the carton).

5. Add controls for 15-(S)-latanoprost and 5,6-trans-latanoprost in the release and stability specifications, and report the results in the stability studies.

6. Add the resolution between latanoprost and 5,6-trans-latanoprost in the system suitability specification for

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-597
HFD-540/Division File
HFD-540/Tso
HFD-540/Carreras
HFD-540/Shriver
HFD-160/Cooney
HFD-540/Chapman
HFD-540/WHDeCamp WD 2/2/96
HFD-540/Sheinin
HFD-530/Holmes

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

Index 550

NDA #: 20-597 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 3/26/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	2/14/96	2/15/96	
AMENDMENT	2/19/96	2/20/96	
AMENDMENT	2/21/96	2/23/96	
AMENDMENT	2/22/96	2/23/96	
AMENDMENT	3/7/96	3/8/96	

NAME & ADDRESS OF APPLICANT: Pharmacia, Inc.
7001 Post Road
Dublin, OH 43017

DRUG PRODUCT NAME

Proprietary:	Xalatan
Nonproprietary/USAN:	Latanoprost
Code Names/#'s:	PHXA41, XA41
Chemical Type/	1-P
Therapeutic Class:	**prostaglandin**

ANDA Suitability Petition/DESI/Patent Status:
The applicant is the exclusive licensee or the assignee of the following patents:

US 4,599,353, expires 7/8/03, method and composition
US 5,296,504, expires 3/22/11, method and composition
US 5,422,368, expires 3/24/11, composition and use

PHARMACOLOGICAL CATEGORY/INDICATION:
Prostaglandin, anti-hypertensive/glaucoma

DOSAGE FORM: Sterile solution
STRENGTHS: 0.005% or 50 ug/mL
ROUTE OF ADMINISTRATION: Topical/Ocular
DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

RELATED DOCUMENTS (if applicable):

Phone/fax:

COMMENTS

Environmental Assessment consulted to HFD-004 on 6/28/95 for review. Deficiencies were found and communicated to the sponsor. Amendment date 2/22/96 covers the response to the EA deficiencies. This amendment is consulted to HFD-004 for reviewed on 3/6/96. Final EA review and FONSI are signed.

Trade Name acceptable.

Compliance status acceptable as of 10/17/95

Method validation sent to Chicago District and Division of Drug Analysis on 1/2 /96

Amendment 2/14/96: Nine months stability for three production batches to support the proposed expiry,

Amendment 2/19/96: Representative . chromatograms for assay of latanoprost ee production batches on stability,

Amendment 2/21/96: Light stability of the drug product packaged in the proposed labeled container closure system,

Amendment 2/22/96: Response to the EA deficiencies.

Amendment 3/7/96: Result of 8 weeks consumption test.

CONCLUSIONS & RECOMMENDATIONS:

The application is **APPROVABLE** for manufacturing and controls under section 505 of the Act. The application may be approved for an expiry of 18 month.

However minor deficiencies remain from the chemist review #1 dated 11/3/95 revised on 2/6/96.

1. Provide label extraction as soon as possible.

2. Provide updated stability data for the production batches (9502R01A, 500 L; 9502R02A, 1000 L; and 9502R03A, 500 L) as soon as possible.

3. Add controls for 15-(S)-latanoprost and 5,6-trans-latanoprost in the release and stability specifications, and report the results in the stability studies.

4. Add the resolution between latanoprost and 5,6-trans-latanoprost in the system suitability specification for

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-597
HFD-550/Division File
HFD-550/Tso
HFD-550/Carreras
HFD-550/Shriver
HFD-160/Cooney
HFD-550/Holmes
HFD-550/Yaciw 7/1/96

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-597

XALATAN™

(latanoprost)

STERILE OPHTHALMIC SOLUTION

50 μg/mL

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC
AND OPHTHALMIC DRUG PRODUCTS (HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-597

XALATAN™

(latanoprost)

STERILE OPHTHALMIC SOLUTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **XALATAN™**, **Pharmacia, Inc.** has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Latanoprost is a synthetic drug which will be administered topically for the treatment of glaucoma and ocular hypertension. The drug substance will be manufactured [illegible] and the drug product will be manufactured at Automatic Liquid Packaging Inc., Woodstock, IL. The finished drug product will be used in hospitals, clinics and homes.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Information regarding disposal of production waste and returned goods is included in

c.c. original NDA 20-597/JHolmes copy to NDA/HFD-550
HFD-357/EA File NDA #20-597
HFD-357/Docket File
HFD-205/FOI COPY

environmental assessment. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

3/15/96 Nancy B. Sager
DATE PREPARED BY
Nancy B. Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

3/15/96 Roger L. Williams
DATE CONCURRED
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-597 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 4/22/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	3/19/96		
AMENDMENT	4/1/96	4/2/96	4/10/96
AMENDMENT	4/3/96	4/4/96	4/10/96
AMENDMENT	4/15/96	4/16/96	4/19/96

NAME & ADDRESS OF APPLICANT: Pharmacia Inc.
7001 Post Road
Dublin, OH 43017

DRUG PRODUCT NAME

Proprietary:	Xalatan
Nonproprietary/USAN:	Latanoprost
Code Names/#'s:	PHXA41, XA41
Chemical Type/	1 P
Therapeutic Class:	**prostaglandin**

ANDA Suitability Petition/DESI/Patent Status:
The applicant is the exclusive licensee or the assignee of the following patents:

US 4,599,353, expired 7/8/03, method and composition
US 5,296,504, expired 3/22/11, method and composition
US 5,422,368. expired 3/24/11, composition and use

PHARMACOLOGICAL CATEGORY/INDICATION:
Prostagladin, Anti-hypertensive/glaucoma

DOSAGE FORM: Sterile solution
STRENGTHS: 0.005% or 50 ug/mL
ROUTE OF ADMINISTRATION: Topical/Ocular
DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name:

RELATED DOCUMENT:

Chemist's review #1 dated 2/6/96
Chemist's review #2, dated 3/26/96

REMARKS/COMMENTS:

Amendment dated 4/1/96 is a response to the impurities specifications requirement for impurity 15(S)-isomer and 5,6-trans isomer. In this amendment the label extraction study report is also included. Amendment dated 3/19/96 is the revised bottle and carton labels. Amendment 4/3/96 and 4/15/96 are a copy of the revised draft package insert.

CONCLUSIONS & RECOMMENDATIONS:

The application remains **approvable** for manufacturing and controls under section 505 of the Act. However, the sponsor should be notified to continue monitoring the 5,6-trans isomer and 15(S) epimer in the stability study for the three validation batches (9502R01A, 9502R02A, and 9502R03A) and submitting the result in the Annual Report. The application may be approved for 18 months expiry.

Su C. TSo, Ph.D
Review Chemist

cc: Orig. NDA 20-597
HFD-550/Division File
HFD-550/Tso
HFD-550/Carraras
HFD-540/Shriver
HFD-160/Cooney
HFD-550/Holmes
HFD-550/Patel HB Patel 4-24-96

Consult #468 (HFD-540)

XALATAN Latanoprost Ophthalmic Solution 0.005 %

A review revealed several names which sound like or look like the proposed name: Zilantel, Zileuton, Salantel, Salatar, Salagen, Xylophan. Due to differences in dosage form, marketing status (RX vs OTC), or usage, the Committee does not believe there is a significant potential for confusion involving any of these names and the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Ruth Mills, Chair 8/19/95

NOTE: The Committee believes the established name for this product is -

Latanoprost Ophthalmic Solution

[Delete "Sterile"]

COMPLETED

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-597

XALATAN™

(latanoprost)

Eye Drops

50 μg/mL

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS (HFD-550)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: March 14, 1996

SUMMARY:

A FONSI is recommended.

Latanoprost is a synthetic drug which will be administered topically for the treatment of glaucoma and ocular hypertension. An abbreviated EA was submitted pursuant to 21 CFR § 25.31a(b)(3). There is no evidence that extraordinary circumstances exist that would require the submission of additional environmental information. It is estimated that 1.25 kg of active moiety will be used in the U.S per year.

Precautions taken at the sites of manufacture and the methods of disposal are expected to minimize occupational exposures and environmental release.

ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated:	04/07/1995
Consult #1:	06/28/1995
Review #1:	01/25/1996
EA dated:	02/15/1999[sic]
Consult #2:	03/06/1996

Contact: Joanne Holmes

2. **Name of applicant/petitioner:**

Pharmacia Inc.

3. **Address:**

P.O. Box 16529
Columbus Ohio 43216-6529

RESPONSE TO DEFICIENCIES IDENTIFIED IN REVIEW #1:

1. General Issues:

Since this is an ophthalmic product an abbreviated EA pursuant to 25.31a(b)(3) may be submitted. You have the option of converting this to an abbreviated EA. If you convert this to an abbreviated EA you do not have to respond to the deficiencies for those sections of the EA not required in an abbreviated EA. If you retain the EA format you have to address all deficiencies. The deficiencies that you would be able to delete if the abbreviated format is used are identified.

To convert your document to an abbreviated format you should delete all information in format item 5 after the molecular weight for latanoprost (much of this information is fate and

effect information), identify the drug product exipients in format item 6, including CAS registration numbers and delete information from format items 7-11 and 15. For format items 7-11 and 15, a reference to abbreviated format 21 CFR § 25.31a(b)(3) should be provided. Appendix I should not be deleted from the EA.

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements is available from the Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855, 301-594-1012; FAX on Demand, 1-800-342-2722, Document # 0803; or via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.VDA.GOV).

RESPONSE: An abbreviated EA in an acceptable format has been submitted. **ADEQUATE**

2. Format item 2: Please confirm that the applicant is still Pharmacia Inc. or make appropriate revisions.

RESPONSE: They confirmed Pharmacia is the applicant. **ADEQUATE**

3. Format item 4: There is no indication as to whether proprietary intermediates are used in the process. If no proprietary intermediated are used this should be stated. If proprietary intermediates are used, information regarding the manufacturing site must be provided. If the proprietary intermediates are manufactured at sites other than those currently identified in the EA, information regarding the manufacturing site should be included in format item 6.

RESPONSE: No proprietary intermediates are purchased for use in the synthesis of the drug substance. **ADEQUATE**

4. Format item 5: Any drug substance impurities that are found at environmentally relevant levels should be identified. If there are no such impurities this should be stated. An MSDS for the drug substance should be included in the non-confidential EA.

RESPONSE: Impurity information has been provided in a confidential appendix. The levels do not raise any environmental concerns. **ADEQUATE**

5. Format item 6:

   a. It is stated in section C that returned goods will be incinerated. The EA should also include the license or permit number, the issuing authority, the EPA or issuing authority's identification number, and if any, the license or permit expiration dates of the currently used disposal contractors/facilities.

   RESPONSE: The requested information has been provided. **ADEQUATE**

   b. No statement regarding the effect of approval on compliance with current emission requirements could be located for the U.S. facility.

   RESPONSE: A statement has been provided. **ADEQUATE**

   c. No calculated estimate of quantities of latanoprost that are expected to enter the environment is provided although on page 17 it is indicated that /year of latanoprost will be used per year and on page 8 the annual production is estimated as per year. Please clarify the marketing projections and provide an estimate of the environmental concentration [see Industry Guidance]. If you provide an abbreviated EA you do not have to provide a calculated estimate but you still must clarify the marketing projections since an estimate of the maximum yearly market volume is required for an abbreviate EA under 25.31a(b)(3).

RESPONSE: The estimates have been clarified. A maximum of /year is expected to be used, which is equivalent to These quantities/concentrations do not raise any environmental concerns. **ADEQUATE**

6. Format item 7:

No information detailing the methods used to determine the following physical/chemical properties or information to support the general statements made about these properties were provided: solubility, octanol/water partition coefficient, abiotic degradation, soil adsorption/mobility and sediment/soil concentrations. The information to support the claims should be provided (e.g., test reports). Alternatively you may convert this EA to an abbreviated format which is allowed under 25.31a(b)(3) as indicated in deficiency 1. If you choose to resubmit as an abbreviated EA, you do not have to address this deficiency.

RESPONSE: These deficiencies were not addressed since they converted to an abbreviated format. **ADEQUATE**

Endorsements:

HFD-357/NBSager 3/15/96

HFD-003/RLWilliams 3/15/96

CC: Original NDA 20-597/JHolmes copy to NDA/HFD-550

EA File 20597

File: 20597e02.rns

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-597

XALATAN™

(latanoprost)

STERILE OPHTHALMIC SOLUTION

50 μg/mL

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC
AND OPHTHALMIC DRUG PRODUCTS (HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-597

XALATAN™

(latanoprost)

STERILE OPHTHALMIC SOLUTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **XALATAN™**, **Pharmacia, Inc.** has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Latanoprost is a synthetic drug which will be administered topically for the treatment of glaucoma and ocular hypertension. The drug substance will be manufactured and the drug product will be manufactured at Automatic Liquid Packaging Inc., Woodstock, IL. The finished drug product will be used in hospitals, clinics and homes.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Information regarding disposal of production waste and returned goods is included in

environmental assessment. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

3/15/96 Nancy B. Sager
DATE PREPARED BY
Nancy B. Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

3/15/96 Roger L. Williams
DATE CONCURRED
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

Environmental Assessment for Xalatan™ Eye Drops 50 μg/ml

Pharmacia AB
Uppsala - SWEDEN
Corporate R&D
Pharmaceuticals

Author:
Brorson, T.

Pharmacia Inc.
Abbreviated Environmental Assessment
XALATAN™ (latanoprost) Eye Drops 50 μg/mL

TABLE OF CONTENTS

ABBREVIATED ENVIRONMENTAL ASSESSMENT
XALATAN™ Eye Drops 50 μg/mL

1. DATE

February 15, 1999

2. NAME OF APPLICANT

Pharmacia Inc.

3. ADDRESS OF APPLICANT

P.O. Box 16529
Columbus, Ohio 43216-6529

4. DESCRIPTION OF PROPOSED ACTION

4.1 Request for Approval - Need for Action

This Abbreviated Environmental Assessment is being submitted in support of NDA 20-597 in the U.S. for XALATAN™ Eye Drops 50 μg/mL in accordance with 21 CFR § 25.31a(b)(3).

The active component of XALATAN is latanoprost. Latanoprost is a new synthetic prostaglandin $F_{2\alpha}$ analogue intended for treatment of glaucoma patients and patients with ocular hypertension. Latanoprost reduces the intraocular pressure and is well tolerated by patients.

The product will be prescribed by doctors and is intended for outpatient treatment. An estimated 2×10^6 to 3×10^6 patients in the U.S. require treatments for glaucoma (Hoskins Jr. and Kass, 1989).

4.2 Locations where the new drug substance and drug product will be produced and the type of environment present and adjacent to manufacturing locations

4. DESCRIPTION OF PROPOSED ACTION (continued)

4.2 a. (continued)

b) Pharmaceutical production in the U.S.

XALATAN will be formulated, filled, packaged and labeled by ALP (Automatic Liquid Packaging Inc., 2200 W. Lake Shore Drive, Woodstock, IL 60098). The ALP facilities are situated in the Rolling Hills Industrial Park in Woodstock. The plant includes one building (350,000 sq. ft.) containing areas for production, storage (raw materials, finished products), R & D, water purification, control laboratories, administration, etc. The total area of the site is 22 acres. The surroundings of the plant are rural. The location is, however, intended for industrial purposes. The climate is seasonal.

The ALP plant does not fall under the U.S. Environmental Protection Act. The wastewater discharges are in accordance with the "Ordinance Enacting A General Pretreatment Program, Regulating Use of Sewers and Providing Penalties for Violations Thereof in the City of Woodstock" (Ordinance No. 2299; approved 06-18-91). Hazardous waste is handled in accordance with the Unifer Hazardous Waste Manifest (20-FS-C6), hazardous waste ILD 984778613, State of Illinois Environmental Protection Agency. The manufacture of XALATAN at ALP will have no effect on their compliance with their current emissions requirements (see Attachment 2).

No protected or sensitive environments, endangered or exotic species, or historic archaeological areas are considered to be impacted by the pharmaceutical production of XALATAN in the U.S.

c) Storage and distribution in the U.S.

XALATAN will be sold to physicians, hospitals, pharmacies and drug wholesalers by Pharmacia Inc., Dublin, Ohio. Storage and distribution will be either from their facility located at Pharmacia Inc., P.O. Box 597, 8484 US 70 West, Clayton, NC 27520-0597, or from the Upjohn facility, 7000 Portage Road, Kalamazoo, MI 49001.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

b) Impurities

Information concerning possible impurities in latanoprost is provided in *Confidential* Appendix 1.

c) Pharmaceutical production in the U.S.

The chemical substances used in the manufacture of XALATAN are the active ingredient, latanoprost,

d) Materials for assembling of the XALATAN product

Materials for assembling of the XALATAN

an

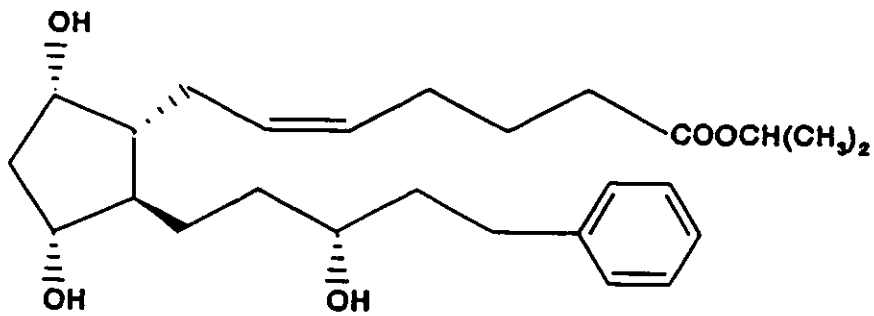
I. LATANOPROST

SUBSTANCE IDENTIFICATION, CHEMICAL AND PHYSICAL PROPERTIES

Chemical Name: Isopropyl-(Z)-7[(1R, 2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclo-pentyl]-5-heptenoate

Generic Name: Latanoprost

Structure:



CAS Registry Number:	130209-82-4
Molecular Formula:	$C_{26}H_{40}O_5$
Appearance:	a colorless to slightly yellow, odorless oil
Boiling Point:	no evidence of boiling or decomposition was observed at up to the maximum temperature of the apparatus, 280°C
Melting Point:	not applicable.
Molecular Weight:	432.58
Log Octanol/Water Partition Coefficient:	4.35 (pH 7.4) - latanoprost 0.52 (pH 7.4) - acid of latanoprost
Water Solubility:	practically insoluble; approx. 50 mg/L.
Solubility in Organic Solvents:	freely soluble in octanol, ethanol, methanol, isopropanol, ethylacetate, dichloromethane, chloroform, and acetone; very soluble in acetonitrile.

II. BENZALKONIUM CHLORIDE SOLUTION NF (50%)

SUBSTANCE IDENTIFICATION, CHEMICAL AND PHYSICAL PROPERTIES

Chemical Name:	Alkyl dimethyl benzyl ammonium chloride
Synonyms:	Benzalkonium chloride (BKC) is a trivial name for a series of quarternary ammonium salts containing one or two alkyl groups ranging from C_8 to C_{18}. Synonyms are, for example: Alkyl dimethylbenzyl ammonium chloride; Ammonyx; Bionol; Bio-Quat; BTC; Germinol; Paralkan, and Triton K-60.
Composition:	Benzalkonium chloride solution NF (50%) consists of Dodecyl dimethyl benzyl ammonium chloride (approx. 65%) and Tetradecyl dimethyl benzyl ammonium chloride (approx. 35%).
CAS Registry Number:	8001-54-5
Molecular Formula:	$C_9H_{13}NClR$ (R= $C_{12}H_{25}$ or $C_{14}H_{29}$)
Appearance:	clear and colorless to slightly yellow, viscous solution
Density:	approx. 0.98 g/mL (20°C)
Molecular Weight:	283 - 424
Solubility:	Benzalkonium chloride solution NF (50%) is miscible with water or lower alcohols, such as methanol, ethanol and propanol at all ratios. The compound is neither miscible with benzene nor ether.

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6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The introduction of substances into the environment has been subdivided into three areas:

A. Introduction of substances into the environment by the manufacture, storage and transportation of the product.

   I. Bulk production

   II. Pharmaceutical production in the U.S.

B. Introduction of substances into the environment by the use of the product.

C. Introduction of substances into the environment by disposal of the product.

A. Introduction of substances into the environment by the manufacture, storage and transportation of the product

I. Bulk production

a) Air Emissions

Air emissions during the different synthesis steps at include solvents

b) Wastewater Discharges

Discharge to effluent wastewater streams during the synthesis of latanoprost and its intermediates includes mother liquors, washing water, and aqueous phases of extraction. The process wastewater normally contains inorganic salts, dissolved organic material and non-miscible solvents.

Wastewater is pre-treated on-site (pH adjustment and sedimentation) and then treated at the municipal wastewater treatment plant. The wastewater license includes limits for 31 different parameters (heavy metals, cyanide, ammonia, COD, pH, oil, salts etc). Wastewater is sampled after pre-treatment and analyzed at the on-site environmental laboratory. COD, oil and total Ni are analyzed once a day; total salt, SO_4^{2-}, CN^-, $N\text{-}NH_4^+$, $N\text{-}NH_3$ and phenol are analyzed three times per day; non-miscible solvents and pH are analyzed twelve times per day.

Sludge from the balancing is dewatered and incinerated at a permitted waste incinerator.

A. (continued)

I. **Bulk production in**

c) Spill Control Procedures

Solvents are stored, transferred (closed vessel), and mixed in rooms equipped with explosion-proof wiring and ventilation at required rates.

All employees working with latanoprost are trained in the procedures for handling a spill. A supply of containment drums and adsorbent materials are kept in the storage area.

d) Hazardous and Non-Hazardous Waste Emissions

There are four categories of waste generated during the manufacturing and cleaning processes: solid hazardous waste, liquid hazardous waste, solid non-hazardous waste and liquid non-hazardous waste.

1. *Solid Hazardous Waste*

All solid materials (filter residues, by-products, packaging materials, clothing and gloves etc) that are potentially contaminated by latanoprost, or its intermediates, are sent off for incineration.

2. *Liquid Hazardous Waste*

Liquid hazardous waste (e.g. solvent mixtures that cannot be regenerated, chlorinated compounds, certain mother liquors) is sent for incineration.

All handling of hazardous waste is in accordance with applicable regulatory requirements. Shipments are properly manifested and reported as required by the regulating agencies. The final destruction of the hazardous waste by incineration is carried out by

3. *Solid Non-Hazardous Waste*

Non-hazardous waste is collected in containers at the plant and then processed at the municipal incineration plant.

4. *Liquid Non-Hazardous Waste*

Some mother liquors and cleaning waters are released into the waste water system as described above. The effluent waste water is not expected to have any impact on the processes in the municipal sewage plant.

A. (continued)

II. **Pharmaceutical production in the U.S.**

a) Air Emissions

The pharmaceutical production at the ALP plant will not generate any solvent or dust emissions.

Inlet air will be HEPA filtrated. The Pharmacia suite has a designated (separated from the rest of the plant) ventilation system. H_2O_2 will be used, in a closed chamber, for sterilization purposes. The finished product will be stored at about 5°C. A CFC (R 22) will be used as cooling media.

b) Water Discharges

The manufacture of XALATAN will, in principle, not generate any process water. A purge volume (saturation of sterile product filter) of about 30 L/batch (one batch/week; 1.5 g latanoprost/week) will be discharged to wastewater. Only cleaning of equipment and the working rooms will result in discharges to wastewater. Conventional cleaning agents will be used

Discharges of latanoprost and benzalkonium chloride solution NF (50%) are considered insignificant. A closed-loop system will be used for cooling water.

The effluent wastewater is monitored once per year by city officials. Parameters include heavy metals, oils, pH, phenols, etc. The wastewater is treated at the Woodstock Wastewater Works (activated sludge process). The receiving water is the Fox River.

c) Spill Control Procedures

No hazardous solvents or other chemicals will be used in the Pharmacia suite at ALP. The worst case scenario includes release of one batch of finished product to the sewer

It is very unlikely that such a discharge will cause any environmental impact.

d) Hazardous and Non-Hazardous Waste Emissions

There are three categories of waste generated during the manufacturing and cleaning processes: *solid non-hazardous waste, liquid hazardous waste* and *liquid non-hazardous waste*.

A. (continued)

II. d) (continued)

1. Solid Non-Hazardous Waste

Solid non-hazardous waste includes packaging materials and plastic scrap. All cardboard is recycled. The plastic scrap (mainly polyethylene; about 1.5 tons/week) is processed on site and sold for secondary use.

2. Liquid Hazardous Waste

The manufacture of XALATAN at ALP will, in principle, not generate any liquid hazardous waste. However, the laboratory activities and other supporting activities will result in some hazardous waste (discarded chemicals, oils etc). All handling of hazardous waste is in accordance with applicable regulatory requirements. Shipments are properly manifested and reported as required by the regulating agencies (e.g. carrier, container, date, location, and method for destruction is documented).

3. Liquid Non-Hazardous Waste

Water from cleaning of equipment and working rooms will be discharged into the wastewater system. Discarded finished products will be processed on site and the XALATAN solution will be discharged into the wastewater system.

B. Introduction of substances into the environment by the use of the product

Latanoprost is biotransformed in the liver to inactive metabolites. Introduction of its metabolites into waste water will occur via urinary excretion by patients using XALATAN. However, the amounts are very small (<3 μg/day) and are not expected to have any environmental impact.

C. Introduction of substances into the environment by disposal of the product

The used products and its packaging components will be disposed of by the patient, or by personnel at the hospital

materials (cardboard) will be disposed of as household solid waste by the patient or at the hospital. Non-used or expired products will be returned to the prescribing physician, the pharmacy or the manufacturer. The products will be destroyed by incineration.

Products returned to Pharmacia at Clayton will be sent to Advanced Environmental Technical Services, 2176 Will Suit Road, Creedmoor, NC 27522 where they will be incinerated under a permit issued by the state of North Carolina (Department of Environment, Health and Natural Resources). The EPA permit number is NCD 986166338, expiring on June 30, 2000.

C. (continued)

Alternatively products returned to the
incinerated on-site. An on-site approved incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under No. MID 000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions, until final administrative disposition of the owner's and operator's permit application is made.

D. Compliance with emission standards

I. Bulk production

The is in compliance with applicable national, regional and local environmental and occupational health statutes and emission standards. holds licenses for chemical and pharmaceutical production according to Environmental Protection Act (License: The latanoprost production technology is covered by a specific statement (s

Air emissions, wastewater discharges and waste processing is in accordance with the Hungarian legislative framework.

II. Pharmaceutical production in the United States

The ALP plant in the United States is in compliance with applicable national, regional and local environmental and occupational health statutes and emission standards.

The wastewater discharges are in accordance with the "Ordinance Enacting A General Pretreatment Program, Regulating Use of Sewers and Providing Penalties for Violations Thereof in the City of Woodstock" (Ordinance No. 2299; approved 06-18-91). Hazardous waste is handled in accordance with the Unifer Hazardous Waste Manifest (20-FS-C6), hazardous waste ILD 984778613, State of Illinois Environmental Protection Agency.

E. Expected Introduction Concentrations

Information concerning estimates of annual production and the calculation of the Estimated Introduction Concentrations (EIC) is provided in Confidential Appendix 2. The EIC is calculated to be much less than 1 ppb.

7 - 11 and 15.

In accordance with 21 CFR 25.31a(b)(3), information for items 7-11 and 15 are not normally required for abbreviated assessments.

12. LIST OF PREPARERS

Torbjörn Brorson

Environmental Manager; Pharmacia, Sweden

Education: B.Sc., Chemistry and Biology; M.Sc., Occupational Hygiene; Dr. Med. Sc., Occupational and Environmental Medicine, Lund University, Sweden.

Experience: 16 years experience in occupational and environmental issues, 6 years in the pharmaceutical industry.

Eskil Hansson

President, Prosafe International AB, Göteborg, Sweden

Education: Degree of Veterinary Medicine at the Royal Veterinary College, Stockholm; Vet. Med. Dr. at the Royal Veterinary College, Stockholm (Ph.D. in Pharmacology)

Experience: about 40 years of experience in pharmaceutical research and development (e.g., Director of the Toxicological Laboratory, AB Astra, Sweden; Research Director, AB Draco, Sweden; Head of Toxicology, AB Hässle, Sweden)

Frank Leo

Vice President New Products/R&D, Automatic Liquid Packaging, Inc., U.S.A.

Education: Loyola University of Chicago, Biology and Chemistry.

Experience: 17 years in industry; 10 years at Automatic Liquid Packaging, Inc. (1984 - 1987 as Head of Research and Development; 1987 - present as Vice President New Products/R&D).

oma

Edward L. Samp

Facility Engineer, Automatic Liquid Packaging Inc., U.S.A.

Experience: 26 years in industry; 14 years at Automatic Liquid Packaging, Inc. (1988 - present as Plant Manager; 1981 - 1988 as Plant Engineer).

Birgitta Sjöquist

Head of Pharmacokinetics, Glaucoma Research, Pharmacia Pharmaceuticals, Uppsala, Sweden.

Education: Ph.D. in Organic Chemistry; Ph.D. in Pharmacology; Associate Professor in Chemical Pharmacology. Karolinska Institutet, Stockholm, Sweden.

Experience: 30 years in research positions; 1985 - present at Pharmacia.

13. CERTIFICATION

The undersigned official certifies that the information presented in the Environmental Assessment is true, accurate, and complete to the best knowledge of the firm.

Torbjörn Brorson, Dr.
Environmental Manager
Pharmacia Environment & Risk Management

14. REFERENCES

Hansson, E. Sjöquist, B. and Selén, G. (1994). Latanoprost. Non clinical pharmacology and toxicology summary. Pharmacia AB.

Harvey, D., Basu, S., Betteridge, K., Goft, A. K. and Kindahl, H. (1984). The influence of pregnancy on $PGF_{2\alpha}$ secretion in Cattle. II: Urinary levels of 11-ketotetranor-PGF-metabolites and plasma progesterone concentrations during oestrous cycle and early pregnancy. Animal Reprod. Science, 7:217-234.

Hoskins Jr, H. D. and Kass, M. (1989). Becker-Shaffer's Diagnosis and Therapy of the Glaucomas, 6th edition. The C. V. Mossby Company.

Sjöquist, B., Bergh, K. and Byding, P. (1994). The metabolism of tritium labelled latanoprost in healthy male volunteers after a single intravenous or topical administration on the eyes. Pharmacia AB.

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Pharmacia
Pharmaceuticals Uppsala

SAFETY DATA SHEET

1. PRODUCT AND COMPANY IDENTIFICATION

LATANOPROST (GENERIC NAME)

Pharmacia AB
S-751 82 UPPSALA, SWEDEN
Telephone: +46 18 16 30 00
Telefax: +46 18 12 60 77

2. COMPOSITION/INFORMATION ON INGREDIENTS

Chemical name:

Isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-hydroxy-5 -phenyl-1-pentyl]cyclopentyl]-5-heptenoate.

CAS NO.: 130209-82-4

3. HAZARD IDENTIFICATION

Inhalation:	Not applicable
Skin contact:	Irritating to skin. Absorbed through intact skin.
Eye contact:	Irritating to skin. Absorbed through mucous membranes.
Ingestion:	May cause nausea and diarrhoea.

Large quantities (> 10 g) should not be handled by pregnant women (Directive 92/85 EEC) or persons with bronchial asthma.

4. FIRST-AID MEASURES

Inhalation:	Fresh air.
Skin contact:	Remove contaminated clothing. Wash thoroughly with soap and water. Seek medical advise.
Eye contact:	Immediately rinse with large quantities of water (Keep eyelids apart) Seek medical advise.
Ingestion:	Give water to drink and induce vomiting. Seek medical attention.

5. FIRE-FIGHTING MEASURES

Carbon dioxide, dry chemical powder, appropriate foam or water spray.

Pharmacia
Pharmaceuticals Uppsala

6. ACCIDENTAL RELEASE MEASURES

Use personal protective equipment stated below.
Sweep up and remove. Flush spillage area with water.
Place waste in an appropriate container.
Local laws and regulations shall be observed.

7. HANDLING AND STORAGE

Avoid exposion; special instructions should be available. Should only be handled by trained personal.

Store in airtight glass bottles at 2 - 8 °C, protected from light.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Wear suitable gloves (resistant against fat soluble materials). Safety goggles.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	A colourless to slightly yellow, highly viscous odourless oil.
Boiling point:	Above 280 °C
Flash point:	-
Ignition temperature:	-
Flammability:	-
Auto flammability:	-
Vapour pressure:	At 30 °C: $2,6 \times 10^{-7}$ Pa Estimated at 20 °C: $\leq 1,26 \times 10^{-7}$ Pa
Solubility:	
in water:	Slightly 40 - 50 µg/ml
in solvent:	Soluble in ethanol, methanol and ethyl acetate
Log Octanol/Water Partition Coefficient:	4,35 (pH 7,4)

10. STABILITY AND REACTIVITY

Stable at room temperature.

11. TOXICOLOGICAL INFORMATION

LD_{50} (orl -rat):	approx. 2000 mg/kg
LD_{50} (ivn - rat):	> 2 mg/kg
Rat and mouse:	No carcinogenic effect observed in tests.

Pharmacia
Pharmaceuticals Uppsala

12. ECOTOXICOLOGICAL INFORMATION

Latanoprost is expected to be biodegradable. It is not expected to bioaccumulate. Detailed information about the environmental fate of latanoprost is available from Pharmacia AB, Uppsala, Sweden.

13. DISPOSAL CONSIDERATIONS

Local laws and regulations shall be observed.

14. TRANSPORT INFORMATION

Latanoprost is not classified as dangerous goods.

15. REGULATORY INFORMATION

According to Directive 67/548 EEC:	Symbol:	T
	R-phrase:	R 61
	S-phrase:	S 53

16. OTHER INFORMATION

R 61 = May cause harm to the unborn child.

S 53 = Avoid exposure - obtain special instructions before use.

Attachment 3

Automatic Liquid Packaging, Inc.

6 February 1996

Martin J. Williamson, Ph.D.
PHARMACIA INC.
P.O. Box 16529
Columbus, Ohio 43216-6529

RE: Environmental Assessment for Latanoprost in the Xalatan NDA.

Dear Dr. Williamson:

As per your letter of February 2, 1996 the following is the signed statement you requested indicating the status for the Environmental Assessment for Latanoprost at Automatic Liquid Packaging, Inc.

The manufacture of Xalatan at Automatic Liquid Packaging, Inc. will have no effect on our ability to comply with current emission requirements.

Please contact me if you require any additional information.

Signature: John Brda Date: 2/6/96
John Brda
Regulatory Affairs/Compliance Mgr.

Sincerely,

AUTOMATIC LIQUID PACKAGING, INC.

John Brda

John Brda
Regulatory Affairs/Compliance Mgr.

ckr

2200 W. Lake Shore Drive, Woodstock, Illinois 60098-7498
Fax: 815/338-5504 Phone: 815/338-9500

MAY 9 1996 ~~MAY 10 1996~~

Holmes
550

REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 20-597
9 May 1996

A. 1. NDA 20-597
APPLICANT: Pharmacia/Upjohn Inc.
P.O. Box 16529
Columbus, OH 43216-6529

2. PRODUCT NAMES: Xalantan® (Latanoprost) Sterile Ophthalmic Solution 0.005% (50 μg/mL)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile solution for installation into the eye (eye drop).

4. METHODS OF STERILIZATION:
The drug product is aseptically filled and preserved with 0.02% benzalkonium chloride.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product, a prostaglandin $F_2\alpha$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humor. It is used in treatment of elevated intraocular pressure associated with glaucoma and ocular hypertension.

B. 1. DATE OF INITIAL SUBMISSION: 14 June 1995

2. DATE OF AMENDMENT: 24 April 1996

3. RELATED DOCUMENTS:
Table 1: Documents referenced in NDA 20-597.

DMF/IND #	Subject	Holder

4. ASSIGNED FOR REVIEW: 29 April 1996

C. REMARKS: The Application provides for manufacture, filling, labeling, and packaging of the drug product at:

Automatic Liquid Packaging, Inc.
2200 West Lake Shore Drive
Woodstock, IL 60098-7498

Each container has a nominal fill volume of 2.5 mL and delivers a drop size of approximately 30 μL.

D. CONCLUSIONS: The application is approvable upon the resolution of microbiology concerns.

"Microbiologist's Draft of Letter to Applicant".

9 May 1996
Paul Stinavage, Ph.D.

cc: Original NDA 20-597
HFD-550/J. Holmes
HFD-805/Consult File/Stinavage

5/9/96

Drafted by: P. Stinavage, 9 May 1996
R/D initialed by P. Cooney, 9 May 1996

Shrawagi LTB

OCT 23 1995

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF

Microbiologist's Review #1 of NDA 20-597
19 October 1995

A. 1. NDA 20-597
APPLICANT: Pharmacia/Upjohn Inc.
P.O. Box 16529
Columbus, OH 43216-6529

2. PRODUCT NAMES: Xalantan® (Latanoprost) Sterile Ophthalmic Solution 0.005% (50 μg/mL)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile solution for installation into the eye (eye drop).

4. METHODS OF STERILIZATION:
The drug product is aseptically filled and preserved with 0.02% benzalkonium chloride.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product, a prostaglandin $F_2\alpha$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humor. It is used in treatment of elevated intraocular pressure associated with glaucoma and ocular hypertension.

B. 1. DATE OF INITIAL SUBMISSION: 14 June 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:
Table 1: Documents referenced in NDA 20-597.

DMF/IND #	Subject	Holder

4. ASSIGNED FOR REVIEW: 25 September 1995

C. REMARKS: The Application provides for manufacture, filling, labeling, and packaging of the drug product at:

Automatic Liquid Packaging, Inc.
2200 West Lake Shore Drive
Woodstock, IL 60098-7498

Each container has a nominal fill volume of 2.5 mL and delivers a drop size of approximately 30 μL.

D. CONCLUSIONS: The application is approvable upon the resolution of microbiology concerns.

"Microbiologist's Draft of Letter to Applicant".

19 October 1995
Paul Stinavage, Ph.D.
10/23/95

cc: Original NDA 20-597
HFD-520/K. Chapman
HFD-805/Consult File/Stinavage
Drafted by: P. Stinavage, 19 October 1995
R/D initialed by P. Cooney, 19 October 1995

END

MD

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011