Ref 1 : SmPC of Originator

Xalacom eye drops, solution

Summary of Product Characteristics Updated 16-Jul-2015 | Pfizer Limited

1. Name of the medicinal product

Xalacom 50 micrograms/mL + 5 mg/mL, eye drops, solution.

2. Qualitative and quantitative composition

1 mL solution contains latanoprost 50 micrograms and timolol maleate 6.8 mg equivalent to 5 mg timolol.

Excipient with known effect:

Benzalkonium chloride 200 microgram/mL.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Eye drops, solution.

The solution is a clear, colourless liquid.

4. Clinical particulars

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology

Adults (including the elderly)

Recommended therapy is one eye drop in the affected eye(s) once daily. (4.2)

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

Paediatric population

Safety and effectiveness in children and adolescents has not been established.

Method of administration

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. (4.2)

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

Xalacom is contraindicated in patients with:

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker, overt cardiac failure, cardiogenic shock. (4.3)
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Systemic effects (4.4)

Like other topically applied ophthalmic agents, Xalacom is absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic

blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Cardiac reactions, and rarely, death in association with cardiac failures have been reported following administration of timolol.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Xalacom should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

4.4

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions

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

Choroidal detachment

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

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Concomitant therapy

Timolol may interact with other drugs see section 4.5.

The use of two local beta-blockers or two local prostaglandins is not recommended.

Ocular effects

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Similar to

experience with latanoprost eye drops, increased iris pigmentation was seen in16-20% of all patients treated with Xalacom for up to one year (based on photographs). This effect has predominantly been seen in patients with mixed coloured irides, i.e. green-brown, yellow-brown or blue/grey-brown, and is due to increased melanin content in the stromal melanocytes 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 become more brownish. In patients with homogeneously blue, grey, green or brown eyes, the change has only rarely been seen during two years of treatment in clinical trials with latanoprost.

The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes.

No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.

Neither naevi nor freckles of the iris have been affected by the treatment.

Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed but patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia.

There is no documented experience with latanoprost in inflammatory, neovascular, or chronic angle closure glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Latanoprost has no or little effect on the pupil but there is no documented experience in acute attacks of closed angle glaucoma. Therefore it is recommended that Xalacom should be used with caution in these conditions until more experience is obtained.

Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema. Xalacom should be used with caution in these patients.

Use of contact lenses

Xalacom contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctuate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of Xalacom in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying Xalacom but may be reinserted after 15 minutes (see section 4.2).

4.4

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with Xalacom.

There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when Xalacom is given to patients already receiving an oral beta-adrenergic blocking agent, and the use of two or more topical beta-adrenergic blocking agents is not recommended.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic agents. Beta-blockers can mask the signs and

symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Latanoprost

There are no adequate data from the use of latanoprost in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Timolol

There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Xalacom is administered until delivery, the neonate should be carefully monitored during the first days of life.

Consequently Xalacom should not be used during pregnancy (see section 5.3).

Breast-feeding

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Latanoprost and its metabolites may pass into breast milk. Xalacom should therefore not be used in women who are breast-feeding.

Fertility

Neither Latanoprost nor timolol have been found to have any effect on male or female fertility in animal studies.

4.6

4.7 Effects on ability to drive and use machines

Instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

4.7

4.8 Undesirable effects

For latanoprost, the majority of adverse events relate to the ocular system. In data from the extension phase of the Xalacom pivotal trials, 16 - 20% of patients developed increased iris pigmentation, which may be permanent. In an open 5 year latanoprost safety study, 33% of patients developed iris pigmentation (see 4.4). Other ocular adverse events are generally transient and occur on dose administration. For timolol, the most serious adverse events are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospam and allergic reactions.

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Treatment related adverse events seen in clinical trials with Xalacom are listed below.

Adverse events are categorized by frequency as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000).

Nervous system disorders

Uncommon: Headache

Eye disorders

Very common: Increased iris pigmentation.

Common: Eye irritation (including stinging, burning and itching), eye pain

4.8

Uncommon: Eye hyperaemia, conjunctivitis, vision blurred, lacrimation increased, blepharitis, corneal disorders

Skin and subcutaneous tissue disorders

Uncommon: Skin rash, pruritus

Additional adverse events have been reported specific to the use of the individual components of Xalacom in either clinical studies, spontaneous reports or in the available literature.

For latanoprost, these are:

Infections and infestations

Herpetic keratitis

Nervous system disorders

Dizziness

Eye disorders

Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), punctate epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema), dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus

Cardiac disorders

Aggravation of angina in patients with pre-existing disease, palpitations

Respiratory, thoracic and mediastinal disorders

Asthma, asthma aggravation, dyspnoea

Skin and subcutaneous tissue disorders

Darkening of palpebral skin

Musculoskeletal and connective tissue disorders

Joint pain, muscle pain

General disorders and administration site conditions

Chest pain

For timolol, these are:

Immune system disorders

Systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritus, anaphylactic reaction

Metabolism and nutrition disorders

Hypoglycaemia

Psychiatric disorders

Insomnia, depression, nightmares, memory loss

Nervous system disorders

Syncope, cerebrovascular accident, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, dizziness, paresthesia, and headache

Eye disorders

Signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, dry eyes, corneal erosion ptosis, diplopia

Ear and labyrinth disorders

Tinnitus

Cardiac disorders

4.8

Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure

Vascular disorders

Hypotension, Raynaud's phenomenon, cold hands and feet

Respiratory, thoracic and mediastinal disorders

Bronchospasm (predominately in patients with pre-existing bronchospastic disease), dyspnoea, cough

Gastrointestinal disorders

Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting

Skin and subcutaneous tissue disorders

Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash

Musculoskeletal and connective tissue disorders

Myalgia

Reproductive system and breast disorders

Sexual dysfunction, decreased libido

General disorders and administration site conditions

Asthenia/fatigue

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

4.8

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No data are available in humans with regard to overdose with Xalacom.

Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm and cardiac arrest. If such symptoms occur the treatment should be symptomatic and supportive. Studies have shown that timolol does not dialyse readily.

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed.

4.9

If latanoprost is accidentally ingested orally the following information may be useful:

Treatment: Gastric lavage if needed. Symptomatic treatment. Latanoprost is extensively metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. These events were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Ophthalmological-betablocking agents - timolol, combinations

ATC code: S01ED51

Mechanism of action

Xalacom consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.

5.1

Latanoprost, a prostaglandin F_{2alpha} analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by

increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. 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. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short term treatment.

Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Timolol lowers IOP by decreasing the formation of aqueous in the ciliary epithelium.

The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Timolol has not been found to significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

Pharmacodynamic effects

Clinical effects

In dose finding studies, Xalacom produced significantly greater decreases in mean diurnal IOP compared to latanoprost and timolol administered once daily as monotherapy. In two well controlled, double masked six-month clinical studies the IOP reducing effect of Xalacom was compared with latanoprost and timolol monotherapy in patients with an IOP of at least 25 mm Hg or greater. Following a 2-4 week run-in with timolol (mean decrease in IOP from enrollment of 5 mm Hg), additional decreases in mean diurnal IOP of 3.1, 2.0 and 0.6 mm Hg were observed after 6 months of treatment for Xalacom, latanoprost and timolol (twice daily), respectively. The IOP lowering effect of Xalacom was maintained in 6 month open label extension of these studies.

Existing data suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, when considering a recommendation of either morning or evening dosing, sufficient consideration should be given to the lifestyle of the patient and their likely compliance.

It should be kept in mind that in case of insufficient efficacy of the fixed combination, results from studies indicate that the use of unfixed administration of Timolol bid and latanoprost once a day might be still efficient.

Onset of action of Xalacom is within one hour and maximal effect occurs within six to eight hours. Adequate IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

5.2 Pharmacokinetic properties

Latanoprost

Latanoprost is an isopropyl ester prodrug, which per se is inactive but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed during the passage through the cornea. Studies in man indicate that the maximum concentration in the aqueous humour, approximately 15-30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone.After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eye lids.

The acid of latanoprost has a plasma clearance of 0.40 l/h/kg and a small volume of distribution, 0.16 l/kg, resulting in a rapid half life in plasma, 17 minutes. After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45%. The acid of latanoprost has a plasma protein binding of 87%.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Timolol

The maximum concentration of timolol in the aqueous humour is reached about 1 hour after topical administration of eye drops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/mL is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day). The half life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

Xalacom

No pharmacokinetic interactions between latanoprost and timolol were observed, although there was an approximate

2-fold increased concentration of the acid of latanoprost in aqueous humour 1-4 hours after administration of Xalcom compared to monotherapy.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. No adverse ocular or systemic effects were seen in rabbits treated topically with the fixed combination or with concomitantly administered latanoprost and timolol ophthalmic solutions. Safety pharmacology, genotoxicity and carcinogenicity studies with each of the components revealed no special hazards for humans. Latanoprost did not affect corneal wound healing in the rabbit eye, whereas timolol inhibited the process in the rabbit and the monkey eye when administered more frequently than once a day.

For latanoprost, no effects on male and female fertility in rats and no teratogenic potential in rats and rabbits have been established. No embryotoxicity was observed in rats after intravenous doses of up to 250 micrograms/kg/day. However, latanoprost caused embryofetal toxicity, characterised by increased incidence of late resorption and abortion and by reduced foetal weight, in rabbits at intravenous doses of 5 micrograms/kg/day (approximately 100 times the clinical dose) and above. Timolol showed no effects on male and female fertility in rats or teratogenic potential in mice, rats and rabbits.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride

Benzalkonium chloride

Sodium dihydrogen phosphate monohydrate

Disodium phosphate anhydrous

Hydrochloric acid solution (for adjustment to pH 6.0)

Sodium hydroxide solution (for adjustment to pH 6.0)

Water for injections

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with Xalatan. If such drugs are used concomitantly with Xalacom, the eye drops should be administered with an interval of at least five minutes.

6.3 Shelf life

2 years

After opening of container: 4 weeks

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C)

Opened bottle: Do not store above 25°C.

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Dropper container (5 mL) of polyethylene with a screw cap and tamper evident polyethylene overcap.

Each bottle contains 2.5 mL eye drop solution.

Pack sizes: 1 × 2.5 mL

3 × 2.5 mL

6 × 2.5 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The tamper evident overcap should be removed before use.

7. Marketing authorisation holder

Pfizer Limited

Ramsgate Road, Sandwich

Kent

CT 13 9NJ

United Kingdom

8. Marketing authorisation number(s)

PL 00057/1056

9. Date of first authorisation/renewal of the authorisation

16th February 2007

10. Date of revision of the text

05/2015

XM 20_0 UK

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Medical Information Website
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Ref.2 : Drug Information Handbook, 22th Edition.

ion (children 6 months to 5
(children 6 months to 5 years:
ema (9%), facial edema (9%),
or (children 6 months to 5

eadache (9%)
), urticaria (4%), hyperhidrosis
al pain/discomfort (9%), diar-

penia (9%)
)
tion site pain (9%)
Tremor (children 6 months to
(4%), back pain, musculoske-

%)
uration decreased (children 6
%), crepitations (children 6
), respiratory distress (children
≥5%), wheezing (children 6
5%), bronchospasm, cough,

arm/cold (7%), allergic reaction

r life ening): Anaphylaxis,
lure, cardiorespiratory arrest,
avasation, pneumonia, respira-

Effects None known.
e There are no known interac-
nded to avoid concomitant use.
ty There are no known signifi-
g an increase in effect.
are no known significant inter-
ase in effect.
efrigeration at 2°C to 8°C (36°F
rotect from light. Do not shake.
temperature prior to admixture.
determined by body weight. For
or weighing up to 30 kg and with
mpromise), dilute the required
patients weighing >20 kg, dilute
NS. Determine the number of
g the required dose and round-
e vial. From a PVC bag, remove
NS equal to the volume of the
ase. Slowly withdraw from vial(s)
se to the NS; avoid excessive
r needle. Gently rotate infusion
).

on for infusion should be used
ot u mediately, refrigerate.
I be co eted within 36 hours of

Laronidase is a recombinant
L-iduronidase derived from Chi-
duronidase is an enzyme needed
ous glycosaminoglycans (GAGs)
iency of α-L-iduronidase leads to
Gs, causing cellular, tissue, and
n in MPS I. Improved pulmonary
pacity have been demonstrated
laronidase to patients with Hurler,
(with moderate-to-severe symp-

netics
L/kg
3.6 hours
7 to 2.7 mL/minute/kg; during the
apy the clearance of laronidase

increases proportionally to the amount of antibodies a given patient develops against the enzyme. However, with long-term use (≥26 weeks) antibody titers have no effect on laronidase clearance.

Dosage Note: Premedicate with antipyretic and/or antihistamines 1 hour prior to start of infusion.

I.V.: Children ≥6 months and Adults: 0.58 mg/kg once weekly; dose should be rounded up to the nearest whole vial

Dosage adjustment in renal impairment: No dosage adjustment provided in the manufacturer's labeling; has not been studied.

Dosage adjustment in hepatic impairment: No dosage adjustment provided in the manufacturer's labeling; has not been studied.

Administration Administer using PVC container and PVC infusion set with in-line, low protein-binding 0.2 micrometer filter. Antipyretics and/or antihistamines should be administered 60 minutes prior to infusion. Volume and infusion rate are based on body weight; deliver infusion over ~3-4 hours. Vital signs should be monitored every 15 minutes, if stable; rate may be increased as follows:

≤20 kg: Total infusion volume: 100 mL
2 mL/hour for 15 minutes
4 mL/hour for 15 minutes
8 mL/hour for 15 minutes
16 mL/hour for 15 minutes
32 mL/hour for remainder of infusion (~3 hours)
>20 kg: Total infusion volume: 250 mL
5 mL/hour for 15 minutes
10 mL/hour for 15 minutes
20 mL/hour for 15 minutes
40 mL/hour for 15 minutes
80 mL/hour for remainder of infusion (~3 hours)

Note: A total infusion volume of 100 mL NS and slower infusion rate may be considered for patients with cardiac or respiratory compromise who weigh up to 30 kg. In case of infusion-related reaction in any patient, decrease the rate of infusion, temporarily discontinue the infusion, and/or administer additional antipyretics/antihistamines.

Monitoring Parameters Vital signs; injection site reactions, infusion reactions

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:
Aldurazyme®: 2.9 mg/5 mL (5 mL) [contains polysorbate 80; derived from or manufactured using Chinese hamster ovary cells]

- **Lasix®** *see* Furosemide *on page 902*
- **Lasix® Special (Can)** *see* Furosemide *on page 902*
- **L-asparaginase (*E. coli*)** *see* Asparaginase (*E. coli*) *on page 168*
- **L-asparaginase (*Erwinia*)** *see* Asparaginase (*Erwinia*) *on page 170*
- **L-asparaginase with Polyethylene Glycol** *see* Pegaspargase *on page 1516*
- **Lassar's Zinc Paste** *see* Zinc Oxide *on page 2117*

Latanoprost (la TA noe prost)

Brand Names: U.S. Xalatan®
Brand Names: Canada Apo-Latanoprost®; CO Latanoprost; GD-Latanoprost; Xalatan®
Pharmacologic Category Ophthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic
Use Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Pregnancy Risk Factor C

Dosage Adults: Ophthalmic: 1 drop (1.5 mcg) in the affected eye(s) once daily in the evening; do not exceed the once daily dosage because it has been shown that more frequent administration may decrease the IOP lowering effect

Note: A medication delivery device (Xal-Ease™) is available for use with Xalatan®.

Additional Information Complete prescribing information for this medication should be consulted for additional detail.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic [drops]: 0.005% (2.5 mL)
Xalatan®: 0.005% (2.5 mL) [contains benzalkonium chloride]

Latanoprost and Timolol [CAN/INT]

(la TA noe prost & TIM oh lol)

Brand Names: Canada Xalacom™
Index Terms Timolol Maleate and Latanoprost
Pharmacologic Category Beta-Blocker, Nonselective; Ophthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic
Use Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers, prostaglandin analogues, or other IOP-reducing agents and in whom combination therapy is appropriate

4.1

Pregnancy Considerations Reproductive studies have not been conducted with this combination. See individual agents.

Lactation Enters breast milk (timolol)/use caution

Contraindications Hypersensitivity to latanoprost, timolol, benzalkonium chloride, or any component of the formulation; reactive airway disease including severe chronic obstructive pulmonary disease (COPD) and presence or history of bronchial asthma; sinus bradycardia, second-/third-degree atrioventricular block, overt cardiac failure, cardiogenic shock

Warnings/Precautions See individual agents.

Adverse Reactions Percentages as reported with combination product. Also see individual agents.

>10%: Ocular: Eyelash alterations (including darkening, lengthening, thickening) (≤37%), iris pigmentation increased (≤20%), eye irritation (12%)

1% to 10%:
Cardiovascular: Hypertension (≤4%), chest pain (1%)
Central nervous system: Depression (2%), headache (2%)
Dermatologic: Skin disorder (2%), rash (1%)
Endocrine & metabolic: Hypercholesterolemia (2%), diabetes mellitus (1%)
Neuromuscular & skeletal: Arthritis (2%), back pain (1%)
Ocular: Hyperemia (7%), vision abnormal (7%), visual field defect (5%), blepharitis (3%), cataract (3%), conjunctivitis (3%), corneal disorder (3%), eye pain (2%), photophobia (2%), refraction errors (2%), skin disorder (2%), conjunctival disorder (1%), keratitis (1%), meibomianitis (1%)
Respiratory: Upper respiratory infection (6%), sinusitis (2%), bronchitis (1%)
Miscellaneous: Flu-like symptoms (3%), infection (1%)

<1% (Limited to important or life-threatening): Bradycardia, cardiac failure, corneal ulceration, cough, cystitis, cystoid macular edema, dizziness, dyspepsia, dyspnea, epiphora, eyelid edema, glycosuria, hyperglycemia, insomnia, intraocular pressure increased, optic atrophy, pneumonia, retinal disorder, seborrhea, skin discoloration, tachycardia, urinary tract infection, uveitis

Drug Interactions

Metabolism/Transport Effects Refer to individual components.

Avoid Concomitant Use

Avoid concomitant use of Latanoprost and Timolol with any of the following: Beta2-Agonists; Floctafenine; Methacholine

Increased Effect/Toxicity

Latanoprost and Timolol may increase the levels/effects of: Alpha-/Beta-Agonists (Direct-Acting); Alpha1-Blockers; Alpha2-Agonists; Amifostine; Antihypertensives; Antipsychotic Agents (Phenothiazines); ARIPiprazole; Bimatoprost; Bupivacaine; Cardiac Glycosides; Cholinergic Agonists; Ergot Derivatives; Fingolimod; Hypotensive Agents; Insulin; Lidocaine (Systemic); Lidocaine (Topical); Mepivacaine; Methacholine; Midodrine; RiTUXimab; Sulfonylureas

The levels/effects of Latanoprost and Timolol may be increased by: Abiraterone Acetate; Acetylcholinesterase Inhibitors; Alpha2-Agonists; Aminoquinolines (Antimalarial); Amiodarone; Anilidopiperidine Opioids; Antipsychotic Agents (Phenothiazines); Calcium Channel Blockers (Dihydropyridine); Calcium Channel Blockers (Nondihydropyridine); CYP2D6 Inhibitors (Moderate); CYP2D6 Inhibitors (Strong); Darunavir; Diazoxide; Dipyridamole; Disopyramide; Dronedarone; Floctafenine; Herbs (Hypotensive Properties); MAO Inhibitors; Pentoxifylline; Phosphodiesterase 5 Inhibitors; Propafenone; Prostacyclin Analogues; QuiNIDine; Reserpine; Selective Serotonin Reuptake Inhibitors

Decreased Effect

Latanoprost and Timolol may decrease the levels/effects of: Beta2-Agonists; Theophylline Derivatives

The levels/effects of Latanoprost and Timolol may be decreased by: Barbiturates; Herbs (Hypertensive Properties); Methylphenidate; Nonsteroidal Anti-Inflammatory Agents; NSAID (Ophthalmic); Rifamycin Derivatives; Yohimbine

Stability Prior to opening, store under refrigeration at 2°C to 8°C (36°F to 46°F). After opening may store at room temperature up to 25°C (77°F) up to 10 weeks. Protect from light.

Mechanism of Action

Latanoprost: A prostaglandin F_2-alpha analog believed to reduce intraocular pressure by increasing the outflow of the aqueous humor

Timolol: Blocks both $beta_1$- and $beta_2$-adrenergic receptors, reduces intraocular pressure by reducing aqueous humor production or possibly outflow; reduces blood pressure by blocking adrenergic receptors and decreasing sympathetic outflow, produces a negative chronotropic and inotropic activity through an unknown mechanism

Pharmacodynamics/Kinetics See individual agents.

Dosage Ophthalmic: Adults: Instill 1 drop into affected eye(s) once daily

Administration Wash hands prior to use. Remove contact lenses prior to administration; wait 15 minutes before reinserting if using products containing benzalkonium chloride. Separate administration of other ophthalmic agents by 5 minutes.

Monitoring Parameters IOP, iris color changes, eyelash changes; systemic effects of beta blockade

Product Availability Not available in U.S.

Dosage Forms: Canada Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Xalacom™: Latanoprost (0.005%) and timolol maleate 0.5% (as base) (2.5 mL) [contains benzalkonium chloride]

- **Latisse®** *see* Bimatoprost *on page 252*
- **Latuda®** *see* Lurasidone *on page 1214*
- **Latuda™ (Can)** *see* Lurasidone *on page 1214*
- **Laxilose (Can)** *see* Lactulose *on page 1124*
- **Lazanda®** *see* FentaNYL *on page 815*
- **l-Bunolol Hydrochloride** *see* Levobunolol *on page 1159*
- **LCM** *see* Lacosamide *on page 1122*
- **L-Deprenyl** *see* Selegiline *on page 1804*
- **LDP-341** *see* Bortezomib *on page 262*
- **LEA29Y** *see* Belatacept *on page 222*
- **Lectopam® (Can)** *see* Bromazepam [CAN/INT] *on page 275*
- **Lederle Leucovorin (Can)** *see* Leucovorin Calcium *on page 1150*
- **Leena®** *see* Ethinyl Estradiol and Norethindrone *on page 769*

Leflunomide (le FLOO noh mide)

Brand Names: U.S. Arava®

Brand Names: Canada Apo-Leflunomide®; Arava®; Mylan-Leflunomide; Novo-Leflunomide; PHL-Leflunomide; PMS-Leflunomide; Sandoz-Leflunomide

Pharmacologic Category Antirheumatic, Disease Modifying

Use Treatment of active rheumatoid arthritis; indicated to reduce signs and symptoms, and to inhibit structural damage and improve physical function

Unlabeled Use Treatment of cytomegalovirus (CMV) disease in transplant recipients resistant to standard antivirals; prevention of acute and chronic rejection in recipients of solid organ transplants

Pregnancy Risk Factor X

Pregnancy Considerations Has been associated with teratogenic and embryolethal effects in animal models at low doses. Leflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be excluded prior to initiating treatment. **[U.S. Boxed Warning]: Women of childbearing potential should not receive therapy until pregnancy has been excluded,** they have been counseled concerning fetal risk, and reliable contraceptive measures have been confirmed. Following treatment, pregnancy should be avoided until undetectable serum concentrations (<0.02 mg/L) are verified. This may be accomplished by the use of an enhanced drug elimination procedure using cholestyramine. Serum concentrations <0.02 mg/L should be verified by two separate tests performed at least 14 days apart. If serum concentrations are >0.02 mg/L, additional cholestyramine treatment should be considered. Pregnant women exposed to leflunomide should be registered with the pregnancy registry (877-311-8972). It is not known if males taking leflunomide may contribute to fetal toxicity. Males taking leflunomide who wish to father a child should consider discontinuing therapy and using the cholestyramine procedure to eliminate the medication.

Lactation Excretion in breast milk unknown/not recommended

Contraindications Hypersensitivity to leflunomide or any component of the formulation; pregnancy

Warnings/Precautions Hazardous agent - use appropriate precautions for handling and disposal (NIOSH, 2012). **[U.S. Boxed Warning]: Use has been associated with rare reports of hepatotoxicity, hepatic failure, and death. Treatment should not be initiated in patients with pre-existing acute or chronic liver disease or ALT >2 x ULN. Use caution in patients with concurrent exposure to potentially hepatotoxic drugs. Monitor**

ALT levels during therapy; discontinue occurs and, if hepatotoxicity is induced, start drug elimination pro tyramine, activated charcoal).

Use has been associated (rarely) disease; discontinue in patients who or worsening of pulmonary symptoms procedures should be considered activated charcoal) if interstitial lung outcomes have been reported. May i to infection, including opportunistic infections, sepsis, and fatalities hav recommended in patients with seve bone marrow dysplasia, or severe, u Caution should be exercised when patients with a history of new/recu conditions that predispose them chronic, latent, or localized infe develop a new infection while underg be monitored closely; consider disc and drug elimination procedures if i

Use may affect defenses against m the development and course of ma defined. As compared to the ge increased risk of lymphoma has trials; however, rheumatoid arthriti associated with an increased rate caution in patients with a prior hist atologic abnormalities; avoid use plasia. Use has been associated agranulocytosis, and thrombocyto given concurrently or recently with immunosuppressive agents. Mon function is required; discontinue if row suppression and begin drug (eg, cholestyramine or activated c dermatologic reactions (including drome and toxic epidermal necroly discontinue if evidence of severe occurs, and begin drug elimination tyramine or activated charcoal). C pathy have been reported; use wit years of age, receiving concomi tions, or patients with diabetes; d peripheral neuropathy occurs an procedures (eg, cholestyramine,

Safety has not been establishe tuberculosis infection. Patients tuberculosis and if necessary, therapy. Use with caution in patie **[U.S. Boxed Warning]: Women tial should not receive therap been excluded,** they have be fetal risk and reliable contracep confirmed. Women of childbear undergo drug elimination proce activated charcoal) following d Patients should be brought up tions before initiating therapy. Li given concurrently; there is no secondary transmission of live ing therapy. Due to variations in to 2 years to reach low levels serum concentrations. A drug e cholestyramine or activated when a more rapid elimination

Adverse Reactions

>10%:

Gastrointestinal: Diarrhea (17

Respiratory: Respiratory trac

APRACLONIDINE HYDROCHLORIDE — OPHTHALMIC

Since apraclonidine is a potent depressor of IOP, closely monitor patients who develop exaggerated reduction in IOP.

Drug Interactions

Apraclonidine Drug Interactions

Precipitant drug	Object drug[a]		Description
Apraclonidine	Cardiovascular agents	↓	Since apraclonidine may reduce pulse and blood pressure, caution in using cardiovascular drugs is advised. Patients using cardiovascular drugs concurrently with apraclonidine 0.5% should have pulse and blood pressures frequently monitored.
Apraclonidine	MAO inhibitors	↑	Apraclonidine should not be used in patients receiving MAO inhibitors (see Contraindications).

[a] ↑ = Object drug increased. ↓ = Object drug decreased.

Do not use apraclonidine in patients receiving MAO inhibitors. Although no specific drug interactions with topical glaucoma drugs or systemic medications were identified in clinical studies of apraclonidine 0.5% ophthalmic solution, consider the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, anesthetics). Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with apraclonidine can lead to a reduction in IOP-lowering effect. No data on the level of circulating catecholamines after apraclonidine withdrawal are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. Exercise caution with simultaneous use of clonidine and other similar pharmacologic agents.

An additive hypotensive effect has been reported with the combination of systemic clonidine and neuroleptic therapy. Systemic clonidine may inhibit the production of catecholamines in response to insulin-induced hypoglycemia and mask the signs and symptoms of hypoglycemia.

Adverse Reactions

➤*0.5% solution:* In clinical studies the overall discontinuation rate related to apraclonidine 0.5% ophthalmic solution was 15%. The most commonly reported events leading to discontinuation included (in decreasing order of frequency) hyperemia, pruritus, tearing, discomfort, lid edema, dry mouth, and foreign body sensation.

The following adverse reactions (incidences) were reported in clinical studies of apraclonidine 0.5% ophthalmic solution as being possibly, probably, or definitely related to therapy:

Ophthalmic –

The following adverse reactions were reported in 5% to 15% of patients: Discomfort, hyperemia, and pruritus.

The following adverse reactions were reported in 1% to 5% of patients: Blanching, blurred vision, conjunctivitis, discharge, dry eye, foreign body sensation, lid edema, and tearing.

The following adverse reactions were reported in less than 1% of patients: Abnormal vision, blepharitis, blepharoconjunctivitis, conjunctival edema, conjunctival follicles, corneal erosion, corneal infiltrate, corneal staining, edema, irritation, keratitis, keratopathy, lid disorder, lid erythema, lid margin crusting, lid retraction, lid scales, pain, photophobia.

Miscellaneous – Dry mouth occurred in approximately 10% of the patients.

The following adverse reactions were reported in less than 3% of patients: Abnormal coordination, asthenia, arrhythmia, asthma, chest pain, constipation, contact dermatitis, depression, dermatitis, dizziness, dry nose, dyspnea, facial edema, headache, insomnia, malaise, myalgia, nausea, nervousness, paresthesia, parosmia, peripheral edema, pharyngitis, rhinitis, somnolence, and taste perversion.

Postmarketing – The following events have been identified during postmarketing use of apraclonidine 0.5% ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to apraclonidine 0.5% ophthalmic solution, or a combination of these factors, include bradycardia.

➤*1% solution:* The following adverse events, occurring in less than 2% of patients, were reported in association with the use of apraclonidine ophthalmic solution in laser surgery: conjunctival blanching, irregular heart rate, mydriasis, nasal decongestion, ocular inflammation, ocular injection, and upper lid elevation.

The following adverse events were observed in investigational studies dosing apraclonidine ophthalmic solution once or twice daily for up to 28 days in nonlaser studies:

CNS – Decreased libido, dream disturbances, insomnia, irritability.

GI – Abdominal pain, diarrhea, emesis, stomach discomfort.

Ophthalmic – Allergic response, blurred or dimmed vision, burning, conjunctival blanching, conjunctival microhemorrhage, discomfort, dryness, foreign body sensation, hypotony, itching, mydriasis, upper lid elevation.

Miscellaneous – Body heat sensation, chest heaviness or burning, clammy or sweaty palms, dry mouth, extremity pain or numbness, fatigue, head cold sensation, headache, increased pharyngeal secretion, nasal burning or dryness, paresthesia, pruritus not associated with rash, shortness of breath, taste abnormalities.

Overdosage

➤*Symptoms:* Ingestion of apraclonidine 0.5% ophthalmic solution has been reported to cause bradycardia, drowsiness, and hypothermia.

Accidental or intentional ingestion of oral clonidine has been reported to cause apnea, arrhythmias, asthenia, bradycardia, conduction defects, diminished or absent reflexes, dryness of the mouth, hypotension, hypothermia, hypoventilation, irritability, lethargy, miosis, pallor, respiratory depression, sedation or coma, seizure, somnolence, transient hypertension, and vomiting.

➤*Treatment:* Treatment of an oral overdose includes supportive and symptomatic therapy; maintain a patent airway. Hemodialysis is of limited value, since a maximum of 5% of circulating drug is removed.

Patient Information

Do not touch dropper tip to any surface as this may contaminate the contents.

Apraclonidine can cause dizziness and somnolence. Warn patients who engage in hazardous activities requiring mental alertness of the potential for a decrease in mental alertness, physical dexterity, or coordination while using apraclonidine.

Ophthalmic Beta-Adrenergic Blocking Agents (Beta Blockers)

Refer to the general discussion of these products in the Topical Ophthalmic Introduction for more complete and comparative information.

Indications

➤*Glaucoma:* Lowering intraocular pressure (IOP) in patients with chronic open-angle glaucoma.

For specific approved indications, refer to individual drug monographs.

Administration and Dosage

➤*Concomitant therapy:* If IOP is not controlled with these agents, institute concomitant pilocarpine, other miotics, dipivefrin or systemic carbonic anhydrase inhibitors.

Use of epinephrine with topical β-blockers is controversial. Some reports indicate initial effectiveness of the combination decreases over time (see Drug Interactions).

➤*Monitoring:* The IOP-lowering response to betaxolol and timolol may require a few weeks to stabilize.

Because of diurnal IOP variations in individual patients, satisfactory response to once-a-day therapy is best determined by measuring IOP at different times during the day.

Actions

➤*Pharmacology:* Timolol, levobunolol, carteolol and metipranolol are nonselective (β$_1$ and β$_2$) β-blockers; betaxolol is a cardioselective (β$_1$) β-blocker. Topical β-blockers do not have significant membrane-stabilizing (local anesthetic) actions or intrinsic sympathomimetic activity. They reduce elevated and normal IOP, with or without glaucoma.

The exact mechanism of ocular antihypertensive action is not established, but it appears to be a reduction of aqueous production. However, some studies show a slight increase in outflow facility with timolol and metipranolol.

These agents reduce IOP with little or no effect on pupil size or accommodation. Blurred vision and night blindness often associated with miotics are not associated with these agents. The inability to see around lenticular opacities when the pupil is constricted is avoided. These agents may be absorbed systemically (see Warnings).

➤*Pharmacokinetics:*

Pharmacokinetics of Ophthalmic Beta-Adrenergic Blocking Agents

Drug	β-receptor selectivity	Onset (min)	Maximum effect (hr)	Duration (hr)
Carteolol	β$_1$ and β$_2$	nd[a]	2	12
Betaxolol	β$_1$	≤ 30	2	12
Levobunolol	β$_1$ and β$_2$	less than 60	2 to 6	≤ 24
Metipranolol	β$_1$ and β$_2$	≤ 30	≈ 2	24
Timolol	β$_1$ and β$_2$	≤ 30	1 to 2	≤ 24

[a] nd = No data

Contraindications

Bronchial asthma, a history of bronchial asthma or severe chronic obstructive pulmonary disease; sinus bradycardia; second-degree and third-degree AV block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the products.

Warnings/Precautions

➤*Systemic absorption:* These agents may be absorbed systemically. The same adverse reactions found with systemic β-blockers (see group monograph in Cardiovascular section) may occur with topical use. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in asthmatics, and rarely, death associated with cardiac failure, have been reported with topical β-blockers.

➤*Cardiovascular:* Timolol may decrease resting and maximal exercise heart rate even in healthy subjects.

Cardiac failure – Sympathetic stimulation may be essential for circulation support in diminished myocardial contractility; its inhibition by β-receptor blockade may precipitate more severe failure.

In patients without history of cardiac failure, continued depression of myocardium with β-blockers may lead to cardiac failure. Discontinue at the first sign or symptom of cardiac failure.

➤*Non-allergic bronchospasm:* Patients with a history of chronic bronchitis, emphysema, etc, should receive β-blockers with caution; they may block bronchodilation produced by catecholamine stimulation of β_2-receptors.

➤*Major surgery:* Withdrawing β-blockers before major surgery is controversial. Beta-receptor blockade impairs the heart's ability to respond to β-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia. Some patients on β-blockers have had protracted severe hypotension during anesthesia. Difficulty restarting and maintaining heartbeat has been reported. In elective surgery, gradual withdrawal of β-blockers may be appropriate.

The effects of β-blocking agents may be reversed by β-agonists such as isoproterenol, dopamine, dobutamine, or levarterenol.

➤*Diabetes mellitus:* Administer with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially labile diabetics). Beta-blocking agents may mask signs and symptoms of acute hypoglycemia.

➤*Thyroid:* Beta-adrenergic blocking agents may mask clinical signs of hyperthyroidism (eg, tachycardia). Manage patients suspected of developing thyrotoxicosis carefully to avoid abrupt withdrawal of β-blockers, which might precipitate thyroid storm.

➤*Cerebrovascular insufficiency:* Because of potential effects of β-blockers on blood pressure and pulse, use with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop, consider alternative therapy.

➤*Angle-closure glaucoma:* The immediate objective is to reopen the angle, requiring constriction of the pupil with a miotic. These agents have little or no effect on the pupil. When they are used to reduce elevated IOP in angle-closure glaucoma, use with a miotic.

➤*Muscle weakness:* Beta-blockade may potentiate muscle weakness consistent with certain myasthenic symptoms (eg, diplopia, ptosis, generalized weakness). Timolol has increased muscle weakness in some patients with myasthenic symptoms or myasthenia gravis.

➤*Long-term therapy:* In long-term studies (2 and 3 years), no significant differences in mean IOP were observed after initial stabilization.

➤*Sulfite sensitivity:* Some of these products contain sulfites which may cause allergic-type reactions (eg, hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or atopic nonasthmatics.

➤*Pregnancy: Category C.* There have been no adequate and well controlled studies in pregnant women. Use during pregnancy only if the potential benefits outweigh potential hazards to the fetus.

Carteolol – Increased resorptions and decreased fetal weights occurred in rabbits and rats at maternal doses approximately 1052 and 5264 times the maximum human dose, respectively. A dose-related increase in wavy ribs was noted in the developing rat fetus when pregnant rats received doses approximately 212 times the maximum human dose.

Betaxolol – In oral studies with rats and rabbits, evidence of postimplantation loss was seen at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol was not teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels.

Levobunolol – Fetotoxicity was observed in rabbits at doses 200 and 700 times the glaucoma dose.

Metipranolol – Increased fetal resorption, fetal death and delayed development occurred in rabbits receiving 50 mg/kg orally during organogenesis.

Timolol – Doses of 1000 mg/kg/day (142,000 times the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in increased fetal resorptions. Increased fetal resorptions were also seen in rabbits at 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

➤*Lactation:* It is not known whether betaxolol, levobunolol or metipranolol are excreted in breast milk. Systemic β-blockers and topical and ophthalmic timolol maleate are excreted in milk. Carteolol is excreted in breast milk of animals. Exercise caution when administering to a nursing mother.

Because of the potential for serious adverse reactions from timolol in nursing infants, decide whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

➤*Children:* Safety and efficacy for use in children have not been established.

Drug Interactions

Ophthalmic Beta Blocker Drug Interactions

Precipitant drug	Object drug[a]		Description
Beta blockers, ophthalmic	Beta blockers, oral	↑	Use topical beta blockers with caution because of the potential for additive effects on systemic and ophthalmic beta-blockade.
Beta blockers, ophthalmic	Calcium antagonists	↑	Possible cases of hypotension, left ventricular failure, and atrioventricular conduction disturbances may occur from coadministration of timolol maleate and calcium antagonists. Avoid use in patients with impaired cardiac function.
Beta blockers, ophthalmic	Catecholamine-depleting drugs (eg, reserpine)	↑	Use of reserpine with ophthalmic beta blockers can cause additive effects and the production of hypotension or marked bradycardia, which may result in syncope, vertigo, or postural hypotension. Close observation is recommended.
Catecholamine-depleting drugs (eg, reserpine)	Beta blockers, ophthalmic		
Beta blockers, ophthalmic	Digitalis	↑	Coadministration of ophthalmic beta blockers with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.
Digitalis	Beta blockers, ophthalmic		
Quinidine	Beta blockers, ophthalmic	↑	Decreased heart rate has been reported during combined treatment with timolol maleate and quinidine, possibly because quinidine inhibits the metabolism of timolol maleate via the P450 enzyme, CYP2D6.
Beta blockers	Phenothiazine compounds	↑	Potential additive hypotensive effects due to mutual inhibition of metabolism.

[a] ↑ = Object drug increased.

Other drugs that may interact with systemic β-adrenergic blocking agents may also interact with ophthalmic agents. For further information, refer to the β-blocker group monograph in the Cardiovasculars chapter.

Adverse Reactions

➤*The following have occurred with ophthalmic β_1 and β_2 (nonselective) blockers:*

Cardiovascular – Arrhythmia; syncope; heart block; cerebral vascular accident; cerebral ischemia; congestive heart failure; palpitation.

CNS – Headache; depression.

Dermatologic – Hypersensitivity, including localized and generalized rash.

Endocrine – Masked symptoms of hypoglycemia in insulin-dependent diabetics (see Warnings).

GI – Nausea.

Ophthalmic – Keratitis; blepharoptosis; visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases); diplopia; ptosis.

Respiratory – Bronchospasm (predominantly in patients with preexisting bronchospastic disease); respiratory failure.

➤*Carteolol:*

Ophthalmic – Transient irritation, burning, tearing, conjunctival hyperemia, edema (approximately 25%); blurred/cloudy vision; photophobia; decreased night vision; ptosis; blepharoconjunctivitis; abnormal corneal staining; corneal sensitivity.

Systemic – Bradycardia; decreased blood pressure; arrhythmia; heart palpitation; dyspnea; asthenia; headache; dizziness; insomnia; sinusitis; taste perversion.

➤*Betaxolol:*

Cardiovascular – Bradycardia; heart block; CHF.

CNS – Dizziness; vertigo; headaches; depression; lethargy; increased signs and symptoms of myasthenia gravis.

Ophthalmic – Brief discomfort (25%); occasional tearing (5%); Decreased corneal sensitivity; erythema; itching; corneal punctate staining keratitis, anisocoria; photophobia; edema.

Pulmonary – Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma, and respiratory failure.

Miscellaneous – Taste and smell perversions; hives; toxic epidermal necrolysis; hair loss; glossitis; insomnia.

➤*Metipranolol:*

Ophthalmic – Transient local discomfort; conjunctivitis; eyelid dermatitis; blepharitis; blurred vision; tearing; browache; abnormal vision; photophobia; edema; uveitis.

Systemic – Allergic reaction; headache; asthenia; hypertension; MI; atrial fibrillation; angina; palpitation; bradycardia; nausea; rhinitis; dyspnea; epistaxis; bronchitis; coughing; dizziness; anxiety; depression; somnolence; nervousness; arthritis; myalgia; rash.

➤*Levobunolol:*

Cardiovascular – Effects may resemble timolol.

CNS – Ataxia, dizziness, headache, lethargy (rare).

Dermatologic – Urticaria, pruritus (rare).

Ophthalmic – Transient burning/stinging(up to 33%); blepharoconjunctivitis (up to 5%); iridocyclitis (rare); decreased corneal sensitivity.

➤*Timolol:*

Cardiovascular – Bradycardia; arrhythmia; hypotension; syncope; heart block; cerebral vascular accident; cerebral ischemia; heart failure; palpitation; cardiac arrest.

CNS – Dizziness; depression; fatigue; lethargy; hallucinations; confusion.

Ophthalmic – Ocular irritation including conjunctivitis; blepharitis; keratitis; blepharoptosis; decreased corneal sensitivity; visual disturbances including refractive changes; diplopia; ptosis.

Respiratory – Bronchospasm (mainly in patients with preexisting bronchospastic disease); respiratory failure; dyspnea.

Miscellaneous – Aggravation of myasthenia gravis; alopecia; nausea; localized and generalized rash; urticaria; impotence, decreased libido; masked symptoms of hypoglycemia in diabetics; diarrhea.

➤*Systemic β-adrenergic blocker-associated reactions:* Consider potential effects with ophthalmic use (see Warnings).

Overdosage

4.9

If ocular overdosage occurs, flush eye(s) with water or normal saline. If accidentally ingested, efforts to decrease further absorption may be appropriate (gastric lavage).

The most common signs and symptoms of overdosage from systemic β-blockers are bradycardia, hypotension, bronchospasm and acute cardiac failure. If these occur, discontinue therapy and initiate appropriate supportive therapy.

Patient Information

Transient stinging/discomfort is relatively common; notify physician if severe.

Do not touch dropper tip to any surface; do not use with contact lenses in eyes.

LEVOBUNOLOL HYDROCHLORIDE

Rx	**Levobunolol** (Various, eg, Bausch & Lomb)	**Solution:** 0.25%	In 5 and 10 mL.
Rx	**Betagan Liquifilm** (Allergan)		In 5 and 10 mL dropper bottles with B.I.D. *C Cap.*[a]
Rx	**Levobunolol** (Various, eg, Bausch & Lomb, Falcon)	**Solution:** 0.5%	In 5, 10, and 15 mL.
Rx	**Betagan Liquifilm** (Allergan)		In 2 mL bottles with standard cap and 5, 10, and 15 mL with B.I.D. and Q.D. *C Cap.*[a]

[a] With 1.4% polyvinyl alcohol; 0.004% benzalkonium chloride; sodium metabisulfite; EDTA; sodium phosphate, dibasic; potassium phosphate, monobasic; NaCl; hydrochloric acid; sodium hydroxide.

LEVOBUNOLOL HYDROCHLORIDE — OPHTHALMIC

For complete and comparative prescribing information, refer to the Ophthalmic Beta-Adrenergic Blocking Agents group monograph.

Indications

➤*Elevated IOP:* Lowering IOP in chronic open-angle glaucoma or ocular hypertension.

Administration and Dosage

➤*Adults:*

Elevated intraocular pressure –

0.25% solution: 1 to 2 drops in the affected eye(s) twice daily.

0.5% solution: 1 to 2 drops in the affected eye(s) once a day. In patients with more severe or uncontrolled glaucoma, the 0.5% solution can be administered twice a day.

Dosages greater than 1 drop of 0.5% levobunolol twice daily are not generally more effective. If IOP is not at a satisfactory level on this regimen, concomitant therapy can be instituted.

➤*Concomitant therapy:* Do not administer 2 or more ophthalmic beta-adrenergic blocking agents simultaneously.

➤*Storage / Stability:* Store at 15° to 30°C (59° to 86°F). Protect from light.

BETAXOLOL HYDROCHLORIDE

Rx	**Betaxolol HCl** (Various, Akorn, Falcon)	**Solution:** 5.6 mg (equiv. to 5 mg base) per mL (0.5%)	In 2.5, 5, 10, and 15 mL.
Rx	**Betoptic S** (Alcon)	**Suspension:** 2.8 mg (equiv. to 2.5 mg base) per mL (0.25%)	In 2.5, 5, 10, and 15 mL *Drop-Tainer* dispensers.[b]

[a] With 0.01% benzalkonium chloride, NaCl, hydrochloric acid and/or sodium hydroxide, EDTA.

[b] With 0.01% benzalkonium chloride, mannitol, poly sulfonic acid, hydrochloric acid or sodium hydroxide, EDTA.

BETAXOLOL HYDROCHLORIDE — OPHTHALMIC

For complete and comparative prescribing information, refer to the Ophthalmic Beta-Adrenergic Blocking Agents group monograph.

Indications

➤*Elevated intraocular pressure:* Treatment of ocular hypertension and chronic open-angle glaucoma. May be used alone or in combination with other antiglaucoma drugs.

Administration and Dosage

➤*General dosing considerations:* In some patients, the intraocular pressure-lowering responses to betaxolol may require a few weeks to stabilize.

➤*Adults:*

Elevated intraocular pressure –

Usual dosage: 1 to 2 drops in the affected eye(s) twice daily.

Concomitant therapy: If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with pilocarpine and other miotics, or epinephrine or carbonic anhydrase inhibitors can be instituted.

➤*Administration:* Shake suspension well before using. Do not touch dropper tip to any surface as this may contaminate the solution.

➤*Storage / Stability:* Store at room temperature.

METIPRANOLOL

Rx	**Metipranolol** (Falcon)	**Solution:** 0.3%	In 5 and 10 mL.[a]
Rx	**OptiPranolol** (Bausch & Lomb)		In 5 and 10 mL dropper bottles.[b]

[a] With 0.004% benzalkonium chloride, povidone, hydrochloric acid, NaCl, EDTA.

[b] With 0.004% benzalkonium chloride, glycerin, povidone, hydrochloric acid, NaCl, sodium hydroxide and/or hydrochloric acid, EDTA.

METIPRANOLOL — OPHTHALMIC

For complete and comparative prescribing information, refer to the Ophthalmic Beta-Adrenergic Blocking Agents group monograph.

Indications

➤*Elevated intraocular pressure:* Treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

Administration and Dosage

➤*Adults:*

Elevated intraocular pressure –

Usual dosage: 1 drop in the affected eye(s) twice daily.

Concomitant therapy: Concomitant therapy to lower IOP can be instituted.

➤*Storage / Stability:* Store between 15° to 30°C (59° to 86°F). Replace cap immediately after use.

LATANOPROST — OPHTHALMIC

melanocytes or deposition of pigment granules to other areas of the eye are 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.

Eyelid skin darkening has also been reported in association with the use of latanoprost.

Latanoprost may gradually change eyelashes and vellus hair; these changes include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

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

➤*Other forms of glaucoma:* There is limited experience with latanoprost in the treatment of angle closure, inflammatory or neovascular glaucoma.

➤*Infections:* 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.

➤*Contact lenses:* Contact lenses should be removed prior to the administration of latanoprost, and may be reinserted 15 minutes after administration.

➤*Renal/Hepatic function impairment:* Latanoprost has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients. (4.2)

➤*Special risk:*

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

Macular edema, including cystoid macular edema – Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Latanoprost should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

➤*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. Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (4.6)

➤*Lactation:* 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 latanoprost is administered to a nursing woman.

➤*Children:* Safety and effectiveness in pediatric patients have not been established.

➤*Monitoring:* Latanoprost is hydrolyzed in the cornea. The effect of continued administration of latanoprost sterile ophthalmic solution on the corneal endothelium has not been fully evaluated. Latanoprost sterile ophthalmic solution may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with latanoprost can be continued in patients who develop noticeably increased iris pigmentation, these 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.

Drug Interactions

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost. If such drugs are used they should be administered with an interval of at least 5 minutes between applications.

Adverse Reactions

➤*Adverse reactions referred to in other sections:* Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and macular edema, including cystoid macular edema.

➤*Adverse reactions in controlled clinical trials:* Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with latanoprost required discontinuation of therapy because of intolerance to conjunctival hyperemia.

Ophthalmic – The ocular adverse reactions and ocular signs and symptoms reported in 5% to 15% of the patients on latanoprost sterile ophthalmic solution in the 6-month, multicenter, 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.

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

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

➤*Postmarketing:* The following reactions have been identified during postmarketing use of latanoprost in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to latanoprost, or a combination of these factors, include the following: Asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash changes (increased length, thickness, pigmentation, and number); vellus hair changes (increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; and toxic epidermal necrolysis.

Overdosage

➤*Symptoms:* 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 mcg/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 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

➤*Treatment:* If overdosage with latanoprost sterile ophthalmic solution occurs, treatment should be symptomatic.

Patient Information

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of latanoprost.

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with latanoprost. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

The increased pigmentation to the iris and eyelid, as well as the changes to the eyelashes, may be permanent.

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 (eg, trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

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 latanoprost 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 administration of latanoprost. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

Ophthalmic Carbonic Anhydrase Inhibitors

DORZOLAMIDE

Rx	**Dorzolamide** (Prasco Labs)	**Solution; ophthalmic:** 2%	As dorzolamide hydrochloride. In 10 mL *Ocumeter Plus.*[a]
Rx	**Trusopt** (Merck)		As dorzolamide hydrochloride. In 5 and 10 mL *Ocumeters.*[a]

[a] With benzalkonium chloride 0.0075%, hydroxyethyl cellulose, sodium hydroxide, and sodium citrate.

DORZOLAMIDE HYDROCHLORIDE — OPHTHALMIC

For complete and comparative prescribing information, refer to the Ophthalmic Carbonic Anhydrase Inhibitors group monograph.

Indications

➤*Elevated intraocular pressure (IOP):* For the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma.

Administration and Dosage

➤*Adults:*

Elevated intraocular pressure –

Usual dosage: One drop in the affected eye(s) 3 times daily.

Concomitant therapy: May be used concomitantly with other topical ophthalmic drug products to lower IOP.

➤*Children:*

Elevated intraocular pressure – See Adults for dosing.

➤*Renal function impairment:* Not recommended in patients with severe renal function impairment (creatinine clearance less than 30 mL/min).

➤*Administration:* If more than 1 ophthalmic drug is being used, administer the drugs at least 10 minutes apart.

➤*Storage / Stability:* Store at 15° to 30°C (59° to 86°F). Protect from light.

BRINZOLAMIDE

Rx	**Azopt** (Alcon)	**Suspension:** 1%	In 2.5, 5, 10, and 15 mL *Drop-Tainers.*[a]

[a] With 0.01% benzalkonium chloride, mannitol, carbomer 974P, tyloxapol, sodium chloride, hydrochloric acid and/or sodium hydroxide, and EDTA.

BRINZOLAMIDE — OPHTHALMIC

For complete and comparative prescribing information, refer to the Ophthalmic Carbonic Anhydrase Inhibitors group monograph.

Indications

➤*Elevated intraocular pressure (IOP):* Treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma.

Administration and Dosage

➤*Adults:*

Increased intraocular pressure –

Usual dosage: One drop in the affected eye(s) 3 times daily.

Concomitant therapy: May be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

➤*Renal function impairment:* Not recommended in patients with severe renal impairment.

➤*Administration:* Shake well before use. If more than one topical ophthalmic drug is being used, administer the drugs at least 10 minutes apart.

➤*Storage / Stability:* Store at 4° to 30°C (39° to 86°F).

Prostaglandin Agonists

LATANOPROST

Rx	**Latanoprost** (Various, eg, Apotex, Bausch & Lomb, Greenstone, Mylan)	**Solution; ophthalmic:** 0.005%	May contain benzalkonium chloride 0.02%, sodium chloride. In 2.5 mL.
Rx	**Xalatan** (Pfizer)		Benzalkonium chloride 0.02%, sodium chloride. In 2.5 mL fill dropper bottles.

LATANOPROST — OPHTHALMIC

Refer to the Topical Ophthalmic Drugs introduction for more complete and comparative information.

Indications

➤*Elevated intraocular pressure:* 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.

Administration and Dosage

➤*Adults:*

Elevated intraocular pressure –

Usual dosage: 1 drop in the affected eye(s) once daily in the evening.

Maximum dose: 1 drop once daily.

Concomitant therapy: May be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

➤*Administration:* If more than 1 ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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

Actions

➤*Pharmacology:* 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. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. (5.1)

➤*Pharmacokinetics:*

Absorption – Latanoprost is absorbed through the cornea where the isopropyl ester prodrug 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 2 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 minutes) 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.

Contraindications

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

Warnings/Precautions

➤*Ocular pigment changes:* Latanoprost has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent. Pigmentation is expected to increase as long as latanoprost is administered. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known.

Latanoprost sterile ophthalmic solution 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

 Ref. 4: AHFS Information, 2013

Pharmacokinetics

In all studies described in the pharmacokinetics section, betaxolol was administered as the hydrochloride salt; dosages and concentrations of the drug are expressed in terms of betaxolol. Data from animal studies demonstrate that topically (i.e., to the eye) administered betaxolol 0.25% resin-formulated suspension and the 0.5% solution are bioequivalent.

■ **Absorption** The extent of ocular and systemic absorption of betaxolol hydrochloride following topical application to the eye has not been elucidated.

Following topical application to the eye of a 0.5% solution or a 0.25% resin-formulated suspension of betaxolol, reduction in IOP is usually evident within 0.5–1 hour, reaches a maximum within about 2 hours, and persists for about 12 hours or longer. The effect of a single dose of betaxolol on IOP usually dissipates within 24 hours after instillation; however, as with other ophthalmic β-blocking agents, some reduction in IOP may persist for as long as 1 week after discontinuance of betaxolol. In patients with open-angle glaucoma, the maximal lowering of IOP occurs after approximately 1–2 weeks of twice-daily application of the drug.

Betaxolol is well absorbed following oral administration. Following oral administration of a single 20-mg dose of betaxolol in healthy adults, peak blood concentrations of about 46 ng/mL occur within approximately 3–4 hours. Following oral administration of betaxolol, β-adrenergic blocking activity (e.g., as measured by a decrease in exercise-induced heart rate) and/or reduction in systolic blood pressure begins within 3–6 hours and generally persists for 24 hours or longer.

■ **Distribution** Distribution of betaxolol into human ocular tissues and fluids has not been characterized to date.

Following IV administration in animals, betaxolol hydrochloride is widely distributed, with highest concentrations attained in liver, kidneys, heart, and lungs; the drug is also rapidly distributed into the CNS. The apparent volume of distribution of betaxolol is reportedly about 4.9–9.8 L/kg in healthy adults.

In vitro, betaxolol is approximately 45–60% bound to plasma proteins, mainly to albumin and, to a lesser extent, to α_1-acid glycoprotein (α_1-AGP). Betaxolol crosses the placenta. In one study in several pregnant women, the median ratio of fetal cord to maternal plasma drug concentrations was 0.7. No accumulation of betaxolol was observed in the fetus or in amniotic fluid. Betaxolol is distributed into milk in humans.

■ **Elimination** The metabolic fate and elimination characteristics of betaxolol hydrochloride following topical application to the eye have not been described to date.

Following oral or IV administration, the elimination half-life of betaxolol is about 15 hours (range: 11–21 hours) in healthy adults and about 20 hours (range: 10.5–29) in hypertensive patients. The half-life of betaxolol is prolonged in patients with renal or hepatic insufficiency, and in geriatric patients.

Systemically absorbed betaxolol is extensively metabolized to at least 5 metabolites. The principal metabolite is the carboxylic acid derivative formed by oxidative deamination. The drug also undergoes *O*-dealkylation, yielding an alcohol derivative, and subsequent oxidation to form another carboxylic acid derivative. Small amounts of hydroxybetaxolol are formed by hydroxylation at the α carbon of the benzene ring. Small amounts of a dihydroxy metabolite are also formed from hydroxybetaxolol and from the *O*-dealkylated derivative. Only hydroxybetaxolol has β-adrenergic blocking activity (approximately 50% that of betaxolol).

Following oral administration of a single dose of betaxolol in healthy adults, about 80–90% of the dose is excreted in urine and 1–3% in feces within 7 days; approximately 16% of the dose is excreted in urine unchanged, 35% as the deaminated carboxylic acid derivative, 24% as the carboxylic acid derivative formed by *O*-dealkylation and subsequent oxidation, 1% as hydroxybetaxolol, and less than 1% each as the alcohol and dihydroxy derivatives. It is not known whether the drug and metabolites excreted in feces represent unabsorbed drug or were excreted via biliary elimination. In animals, small amounts of the drug and/or its metabolites are excreted in feces via biliary elimination.

Renal clearance of betaxolol is reduced in patients with renal insufficiency; however, total body clearance of the drug in patients with renal or hepatic insufficiency is similar to that in healthy individuals.

Betaxolol is not appreciably removed by hemodialysis or peritoneal dialysis.

Chemistry and Stability

■ **Chemistry** Betaxolol hydrochloride is a β_1-selective adrenergic blocking agent. Betaxolol occurs as a racemic mixture of the *R*- and *S*-enantiomers. Betaxolol is structurally related to metoprolol, differing only by the addition of a cyclopropyl group at the terminal carbon of the methoxyethyl side chain of metoprolol. The presence of large substituents in the *para* position is believed to account for the selective β_1-adrenergic blocking effect of betaxolol.

Betaxolol hydrochloride occurs as a white, crystalline powder and has solubilities of 350 mg/mL in water and greater than 100 mg/mL in alcohol at room temperature. The drug is lipophilic and has a pK_a of 9.38.

USP currently states that potency of betaxolol hydrochloride preparations should be expressed both in terms of the salt and the base ("active moiety"). Previously, potency was expressed only in terms of betaxolol base. Dosage currently continues to be expressed in terms of the base. Therefore, care should be taken to avoid confusion between labeled potencies as the salt and base and dosage of betaxolol hydrochloride. Each 2.8 or 5.6 mg of betaxolol hydrochloride is equivalent to about 2.5 or 5 mg of betaxolol, respectively.

Betaxolol hydrochloride ophthalmic solution is a sterile, isotonic solution of the drug in purified water; hydrochloric acid and/or sodium hydroxide may be added to adjust pH to 5.5–8. Betaxolol hydrochloride ophthalmic suspension is a sterile, isotonic, resin-formulated suspension of the drug in purified water; hydrochloric acid and/or sodium hydroxide may be added to adjust pH. The commercially available ophthalmic solution and suspension also contain benzalkonium chloride as a preservative and edetate disodium; sodium chloride is added to the solution to adjust tonicity.

■ **Stability** Betaxolol hydrochloride ophthalmic solution and resin-formulated suspension should be stored in tight containers at room temperature.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Betaxolol Hydrochloride

Ophthalmic		
Solution	0.5% (of betaxolol)*	**Betaxolol Hydrochloride Ophthalmic Solution**
Suspension	0.25% (of betaxolol)	**Betoptic® S,** Alcon

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Timolol

■ Timolol is a nonselective β-adrenergic blocking agent.

Uses

■ **Ocular Hypertension and Glaucoma** In ophthalmology, topical timolol is used to reduce elevated IOP in patients with open-angle glaucoma or ocular hypertension. Dorzolamide hydrochloride and timolol maleate in a fixed-combination ophthalmic solution is used topically to reduce elevated IOP in patients with open-angle glaucoma or ocular hypertension who have not responded adequately (i.e., failed to achieve target IOP as determined after multiple measurements over time) to a topical β-adrenergic blocking agent. Topical timolol also has been used to reduce elevated IOP in patients with aphakic glaucoma† and some secondary glaucomas†. Elevated IOP presents a major risk factor in glaucomatous visual field loss; the higher the level of IOP, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. Current data from a limited number of controlled studies suggest similar clinical efficacy for ophthalmic timolol maleate and ophthalmic timolol as the hemihydrate.

Timolol may be used alone or in conjunction with a topical miotic (e.g., pilocarpine), latanoprost and/or a topical or systemic carbonic anhydrase inhibitor. When used in conjunction with these agents, timolol may have an additive IOP-lowering effect. While therapy with timolol in fixed combination with dorzolamide twice daily is associated with greater decreases in IOP than monotherapy with timolol 0.5% twice daily or dorzolamide 2% three times daily, therapy with timolol 0.5% twice daily in combination with dorzolamide 2% three times daily is associated with a slightly greater decrease in IOP (1 mm Hg) than the twice-daily regimen of timolol in fixed combination with dorzolamide. If timolol is used to reduce IOP in patients with angle-closure glaucoma, the drug should not be used alone but rather in combination with a topical miotic since timolol has little or no effect on pupil size.

Like levobunolol, timolol reduces elevated IOP in patients with chronic open-angle glaucoma without producing the miosis and/or ciliary spasm that are associated with miotic agents. In double-blind studies in patients with open-angle glaucoma, usual doses of timolol have been found to be at least as effective as therapeutic doses of pilocarpine in reducing elevated IOP without the miosis, ocular irritation, and blurred vision associated with pilocarpine therapy. Timolol maleate also has been found in multiclinic studies to be at least as effective as epinephrine in reducing IOP in patients with open-angle glaucoma. Like other ophthalmic nonselective β-blocking agents (e.g., levobunolol), ophthalmic timolol has been associated with adverse systemic pulmonary and cardiovascular effects. The drug should be used with caution in patients with diminished pulmonary function, and is contraindicated in patients with asthma or a history of asthma and in patients with severe chronic obstructive pulmonary disease. Following prolonged therapy with topical timolol, the effect in reducing IOP is generally well maintained, but tolerance has been reported in some patients. In one long-term study in patients receiving timolol for at least 3 years, the reduction in mean IOP was maintained following initial stabilization with the drug.

For systemic uses of timolol maleate, see 24:24.

Dosage and Administration

■ **Administration** Timolol is applied topically to the eye as an ophthalmic solution. Care should be taken to avoid contamination of the solution container. (See Cautions: Precautions and Contraindications.)

The fixed-combination ophthalmic solution of dorzolamide hydrochloride and timolol maleate should not be administered while wearing soft contact lenses. Contact lenses may be reinserted 15 minutes after a dose of the fixed-combination ophthalmic solution.

If the patient is receiving more than one ophthalmic drug, the drugs should be administered at least 10 minutes apart. Containers of timolol maleate ophthalmic gel-forming solution should be inverted and shaken once just prior to administration of each dose. Patients receiving ophthalmic gel-forming solutions of the drug who also are receiving other ophthalmic preparations should be instructed that other topical preparations be administered at least 10 minutes before a dose of the gel-forming solution.

■ **Dosage** *Ocular Hypertension and Glaucoma* Dosage of timolol maleate or timolol (as the hemihydrate) is expressed in terms of timolol.

When used alone or when added to existing glaucoma therapy, the usual initial dosage of timolol is 1 drop of a 0.25% solution in the affected eye(s) twice daily. If necessary for adequate reduction of IOP, dosage may be increased to 1 drop of a 0.5% solution in the affected eye(s) twice daily. The dose may then be reduced to 1 drop of the effective strength in the affected eye(s) once daily if satisfactory IOP is maintained. When timolol maleate ophthalmic gel-forming solution is used, the usual dosage of timolol is 1 drop of a 0.25 or 0.5% solution in the affected eye(s) once daily. Because of diurnal variations in IOP, IOP should be measured at different times during the day to determine if an adequate effect is maintained in patients receiving single daily dose therapy. Since IOP may not stabilize for a few weeks after initiating timolol therapy in some patients, IOP should also be determined after about 4 weeks of therapy with the drug. Dosages exceeding 1 drop of a 0.5% solution twice daily generally have not produced a further reduction in IOP. Dosages exceeding 1 drop of a 0.5% gel-forming solution once daily or 1 drop of a 0.5% solution containing timolol as the hemihydrate administered twice daily have not been studied.

If further reduction of IOP is required in patients receiving 1 drop of a timolol 0.5% solution twice daily, pilocarpine or other miotics, latanoprost, and/or topical or systemically administered carbonic anhydrase inhibitors (e.g., acetazolamide) may be added to the timolol regimen. For the treatment of glaucoma or ocular hypertension, the usual dosage of timolol maleate in fixed combination with dorzolamide hydrochloride is 1 drop in the affected eye(s) twice daily. If further reduction in IOP is needed in patients receiving 1 drop of a timolol 0.5% gel-forming solution once daily, concomitant therapy should be considered. When once-daily dosing of timolol gel-forming ophthalmic solution has been substituted for twice-daily dosing of timolol maleate conventional ophthalmic solution, the IOP-lowering effect has remained consistent.

Cautions

Timolol ophthalmic solutions generally are well tolerated following topical application to the eye; however, adverse effects may occasionally be severe enough to require discontinuance of the drug.

■ **Ocular Effects** In clinical studies, blurred vision (lasting 0.5–5 minutes) upon instillation has been reported in about 33% of patients receiving timolol maleate gel-forming ophthalmic solution. Blurred vision requiring discontinuance of the gel-forming solution reportedly occurred in less than 1% of patients. The most common adverse effects of ophthalmic timolol solutions, occurring in about 13% of patients, are burning or stinging upon instillation.

Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), itching and tearing, foreign body sensation, dry eyes, eyelid erythema, and blepharoptosis have been reported occasionally in patients receiving topical timolol therapy. Visual disturbances including refractive changes (resulting from withdrawal of miotic therapy in some patients) have been infrequently associated with timolol therapy. Decreased corneal sensitivity, diplopia, cystoid macular edema, pseudopemphigoid, choroidal detachment following filtration surgery, epiphora, photophobia, blurred vision, conjunctival injection, corneal fluorescein staining, cataract, retinal vascular disorder, and ptosis also have occurred.

■ **Systemic Effects** *Cardiovascular Effects* Aggravation or precipitation of certain cardiovascular disorders, presumably related to effects of systemic β-adrenergic blockade, may occur during therapy with topical timolol and may include bradycardia, arrhythmia, congestive heart failure, hypotension, hypertension, syncope, heart block, cerebrovascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, cardiac arrest, pulmonary edema, palpitation, chest pain, peripheral edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet. Slight reduction of resting heart rate also may occur, and slightly decreased blood pressure has been reported in some patients receiving high doses of the drug (i.e., 1 drop of a 1% solution to each eye). Rarely, death associated with cardiac failure has been reported in patients receiving systemic or topical (ocular) timolol.

Nervous System Effects Headache and dizziness occurred in 1–5% of patients receiving timolol maleate gel-forming ophthalmic solution in clinical studies. Other adverse nervous system effects reported with ocular administration of topical timolol therapy include exacerbation of myasthenia gravis (e.g., increased muscle weakness), paresthesia, asthenia and/or fatigue, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances (e.g., depression, confusion, hallucinations, anxiety, disorientation, nervousness, memory loss).

Respiratory Effects Aggravation or precipitation of certain respiratory disorders, presumably related to effects of systemic β-adrenergic blockade, may occur during therapy with topical timolol and may include dyspnea, nasal congestion, cough, upper respiratory infections, sinusitis, and respiratory failure. Severe respiratory reactions, including death resulting from bronchospasm (mainly in patients with preexisting bronchospastic disease [e.g., asthma]) have been reported in patients receiving topical timolol therapy.

Dermatologic and Sensitivity Reactions Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and localized or generalized rash have occurred rarely during topical timolol therapy. Alopecia, psoriasiform rash, exacerbation of psoriasis, and systemic lupus erythematosus also have been reported.

GI Effects Diarrhea, nausea, dyspepsia, anorexia, and dry mouth have been reported in patients receiving topical timolol therapy.

Genitourinary Effects Retroperitoneal fibrosis, impotence, decreased libido, and Peyronie's disease have been reported in some patients receiving topical timolol therapy.

Endocrine Effects Because β-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia, these agents should be administered with caution in patients subject to spontaneous hypoglycemia and in diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. However, masked symptoms of hypoglycemia in insulin-dependent diabetics, have been reported rarely with topical timolol.

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

Other Systemic Effects Common cold and pain in the extremities have been reported in some patients receiving topical timolol therapy. The possibility that other adverse systemic effects associated with systemic timolol or other β-adrenergic blocking agents may occur during topical timolol therapy should be considered.

■ **Precautions and Contraindications** Timolol ophthalmic solution shares the toxic potentials of systemically administered timolol, and the usual precautions of systemic timolol therapy should be observed with the topical preparation. (See Cautions: Precautions and Contraindications, in Timolol Maleate 24:24.) Severe respiratory and cardiac reactions, including death resulting from bronchospasm in patients with asthma and, rarely, death associated with cardiac failure, have been reported in patients receiving systemic or topical (ocular) timolol. Patients receiving topical timolol and a systemic β-adrenergic blocking agent concomitantly should be observed carefully for potential additive effects on IOP and/or systemic effects of β-adrenergic blockade.

Patients who have a history of atopy or of a severe anaphylactic reaction to a variety of allergens reportedly may be more reactive to repeated accidental, diagnostic, or therapeutic challenges with such allergens while taking β-adrenergic blocking agents and may be unresponsive to usual doses of epinephrine used to treat anaphylactic reactions.

Bacterial keratitis has been reported with the use of multidose containers of topical ophthalmic preparations. These containers had been contaminated inadvertently by patients who, in most cases, had a concurrent corneal disease or disruption of the ocular epithelial surface. Patients should be informed that improper handling of ocular solutions can result in contamination of the solution by common bacteria known to cause ocular infections and should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic solutions. Patients also should be advised to seek their physician's advice immediately regarding the continued use of the present multidose container if an intercurrent ocular condition (e.g., trauma, ocular surgery or infection) occurs. Because benzalkonium chloride may be absorbed by soft contact lenses, patients receiving timolol ophthalmic solutions that contain this preservative should be advised to wait at least 15 minutes after instillation of the ophthalmic solution before they insert their soft contact lenses.

Because timolol has little or no effect on pupil size, the drug should not be used alone in patients with angle-closure glaucoma, but only in combination with a miotic. Timolol ophthalmic solutions usually should not be used concomitantly with another ophthalmic β-adrenergic blocking agent concomitantly; in patients being transferred from another β-blocker to timolol, the other β-blocker should be discontinued before initiating timolol.

Patients with mild or moderately severe chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema), bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma in which condition timolol ophthalmic solution is contraindicated) generally should not receive β-adrenergic blocking agents. Timolol ophthalmic solution is contraindicated in patients with bronchial asthma or a history of bronchial asthma and in patients with severe chronic obstructive pulmonary disease, sinus bradycardia, atrioventricular block greater than first degree, overt cardiac failure, or cardiogenic shock. Timolol ophthalmic solution also is con-

traindicated in patients with known hypersensitivity to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of timolol ophthalmic solutions in children have not been established.

■ **Geriatric Precautions** Safety and efficacy of timolol ophthalmic solutions were similar in patients 65 years of age or older compared with younger patients; however, the possibility that some older patients may exhibit increased sensitivity to the preparation cannot be ruled out.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in mice, rats, and rabbits using oral timolol dosages up to 50 mg/kg daily (7000 times the systemic exposure following the maximum recommended human ophthalmic dosage) have not revealed evidence of harm to the fetus. Although delayed fetal ossification was observed at this dosage in rats, no adverse effects on postnatal development occurred in this species. Oral timolol dosages of 1 g/kg daily (142,000 times the systemic exposure following the maximum recommended human ophthalmic dosage) were maternotoxic and resulted in an increased number of fetal resorptions in mice. Increased fetal resorptions were also observed in rabbits receiving oral timolol dosages 14,000 times the systemic exposure following the maximum recommended human ophthalmic dosage. There are no adequate and controlled studies to date using timolol ophthalmic solution in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Reproduction studies in male and female rats using oral timolol dosages up to 125 times the maximum human oral dosage (based on patient weight of 50 kg) have not revealed evidence of impaired fertility.

Timolol is distributed into milk following oral or ophthalmic administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

■ **Ocular Hypotensive Agents** When used in conjunction with topical miotics, latanoprost, and/or topical or systemically administered carbonic anhydrase inhibitors, the effect of timolol in lowering IOP may be additive. This effect may be used to therapeutic advantage in the treatment of glaucoma. While therapy with timolol in fixed combination with dorzolamide twice daily is associated with greater decreases in IOP than monotherapy with timolol 0.5% twice daily or dorzolamide 2% three times daily, therapy with timolol 0.5% twice daily in combination with dorzolamide 2% three times daily is associated with a slightly greater decrease in IOP (1 mm Hg) than the twice-daily regimen of timolol in fixed combination with dorzolamide.

■ **Systemic β-Adrenergic Blocking Agents** The possibility of an additive effect on IOP and/or systemic β-adrenergic blockade should be considered in patients who are receiving a systemic β-adrenergic blocking agent and topical timolol concomitantly.

■ **Catecholamine-depleting Drugs** When topical timolol is administered concomitantly with a catecholamine-depleting drug (e.g., reserpine), the patient should be observed closely for possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, and/or postural hypotension.

4.5

■ **Other Cardiovascular Drugs** Concomitant administration of β-adrenergic blocking agent and a calcium-channel blocking agent and a cardiac glycoside may have additive effects on prolonging AV conduction. Because AV conduction disturbances, left ventricular failure, and/or hypotension may occur, caution should be exercised if timolol and a calcium-channel blocking agent are used concomitantly, and such concomitant use should be avoided in patients with impaired cardiac function. Severe bradycardia (e.g., 36 bpm), which was associated with a wandering pacemaker in one patient, and transient asystole have been reported when ophthalmic timolol and oral verapamil were used concomitantly. A single IV dose of atropine was effective in managing serious bradycardia in at least one patient. Verapamil should be used with extreme caution in patients receiving ophthalmic timolol; when therapy with a calcium-channel blocking agent is indicated (e.g., for angina) in such patients, an agent with minimal effects on SA node and cardiac conduction (e.g., nifedipine) should be used if possible.

Sinus bradycardia, which recurred upon rechallenge, has been reported when ophthalmic timolol and oral quinidine were used concomitantly. This interaction has been attributed to inhibition of timolol metabolism (via the cytochrome P-450 [CYP] 2D6 isoenzyme) by quinidine. Although oral β-adrenergic blocking agents may exacerbate rebound hypertension that may occur following discontinuance of clonidine, such an effect has not been reported in patients receiving ophthalmic timolol.

Pharmacology

Timolol is a nonselective β-adrenergic blocking agent. Timolol does not have substantial intrinsic sympathomimetic, parasympathomimetic, or local anesthetic activity.

■ **Ocular Effects** Following topical application to the eye, timolol reduces both elevated and normal intraocular pressure (IOP) in patients with or without open-angle (chronic simple, noncongestive) glaucoma or ocular hypertension. Timolol reduces IOP with little or no effect on accommodation or pupillary size. In patients with elevated IOP, timolol reduces mean IOP by about 25–33%. The drug appears to be equally effective in light- and dark-colored eyes.

4.4

The exact mechanism by which β-blockers, including timolol, reduce IOP has not been clearly defined. Fluorophotometric studies suggest that reduced aqueous humor formation is the predominant effect. β-Adrenergic blocking agents may block endogenous catecholamine-stimulated increases in cyclic adenosine monophosphate (AMP) concentrations within the ciliary processes and subsequent formation of aqueous humor. Timolol appears to cause little or no change in aqueous humor outflow facility.

In some studies, timolol applied topically to one eye reduced IOP in both eyes; the mechanism of this effect has not been elucidated.

A slight decrease in the intraocular hypotensive effect may occur during the first 3 weeks of timolol therapy, and tolerance may develop with prolonged use; however, the IOP-lowering effect has been maintained for at least 3 years with continuous use of the drug in some patients.

■ **Systemic Effects** Like levobunolol, which is also a nonselective β-adrenergic blocking agent, timolol can produce systemic pulmonary and cardiovascular effects following topical application to the eye. Adverse pulmonary effects (e.g., bronchoconstriction, increased airway resistance) have been reported following ophthalmic application of timolol. Following topical application to the eye, timolol can substantially affect blood pressure and heart rate in some patients.

Pharmacokinetics

The degree of systemic absorption of timolol after topical application to the eye has not been fully elucidated; however, some absorption can apparently occur, since adverse systemic effects have occurred following ophthalmic instillation of the drug. Following topical administration of timolol 0.5% solution twice daily to the eye in a limited number of individuals, mean peak plasma concentrations were 0.46 or 0.35 ng/mL following the morning or afternoon dose, respectively. In individuals receiving topical timolol 0.5% as the gel-forming ophthalmic solution once daily in the morning, mean peak plasma concentrations following the dose were 0.28 ng/mL. Following topical application to the eye of a 0.25 or 0.5% solution of the drug, reduction in IOP usually occurs within 15–30 minutes, reaches a maximum within 1–5 hours, and persists about 24 hours.

Chemistry and Stability

■ **Chemistry** Timolol is a nonselective β-adrenergic blocking agent. The drug, which occurs as the *l*-isomer, is commercially available as the maleate salt and as the hemihydrate. Timolol maleate and the hemihydrate occur as white, odorless, crystalline powders; timolol maleate is soluble in water and alcohol, and timolol hemihydrate is slightly soluble in water and freely soluble in alcohol. Each 2.56 mg of timolol as the hemihydrate provides about 2.5 mg of timolol. Timolol maleate has a pK_a of approximately 9 in water at 25°C. Each 3.4 mg of timolol maleate provides about 2.5 mg of timolol. For ophthalmic use, timolol is commercially available as an ophthalmic solution of timolol, timolol maleate, or timolol maleate in fixed combination with dorzolamide hydrochloride. The commercially available timolol, timolol maleate, and timolol maleate in fixed combination with dorzolamide ophthalmic preparations are sterile, isotonic solutions of the drugs in water for injection. Timolol is a clear colorless solution, whereas timolol maleate is a clear and colorless to light yellow solution. The fixed-combination ophthalmic solution of dorzolamide hydrochloride and timolol maleate is a clear, colorless to nearly colorless, slightly viscous solution. The timolol and timolol maleate ophthalmic solutions are buffered to a pH of 6.5–7.5 with monobasic and dibasic sodium phosphate; timolol maleate ophthalmic solution also contains sodium hydroxide as a buffer. The fixed-combination ophthalmic solution of dorzolamide hydrochloride and timolol maleate contains hydroxyethyl cellulose, mannitol, and sodium citrate; sodium hydroxide is added to adjust the pH to approximately 5.65. The commercially available ophthalmic solutions also may contain benzalkonium chloride as a preservative.

Timolol maleate also is available as a gel-forming ophthalmic solution. The commercially available gel-forming ophthalmic solution is a colorless or nearly colorless, slightly opalescent, and slightly viscous sterile, isotonic solution of the drug in water for injection and contains benzododecinium bromide as a preservative, Gelrite® gellan gum, tromethamine, and mannitol. Gelrite® is a purified anionic heteropolysaccharide derived from gellan gum; in the presence of a cation, an aqueous solution of this polysaccharide has the ability to gel. Upon contact with the precorneal tear film, the gel-forming solution forms a gel that subsequently is removed by the flow of tears.

■ **Stability** Solutions of timolol maleate are stable up to a pH of 12. In general, timolol ophthalmic solutions should be protected from light and stored in tight containers at 15–30°C and protected from freezing. The fixed-combination ophthalmic solution of dorzolamide hydrochloride and timolol maleate should be stored in light-resistant containers at 15–25°C. Timolol gel-forming ophthalmic solution should be stored at 15–25°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Timolol (Hemihydrate)

Ophthalmic		
Solution	0.25% (of anhydrous timolol)	**Betimol®**, Vistakon
	0.5% (of anhydrous timolol)	**Betimol®**, Vistakon

Timolol Maleate

Ophthalmic		
Solution	0.25% (of timolol)*	**Timolol Maleate Ophthalmic Solution**
		Timoptic® Ocumeter® Plus, Merck
		Timoptic® Ocudose®, Merck
	0.5% (of timolol)*	**Timolol Maleate Ophthalmic Solution**
		Timoptic® Ocumeter® Plus, Merck
		Timoptic® Ocudose®, Merck
Solution, gel-forming	0.25% (of timolol)*	**Timolol Gel-forming Solution**
		Timolol GFS®, Falcon
		Timoptic-XE® Ocumeter®, Merck
	0.5% (of timolol)*	**Timolol Gel-forming Solution**
		Timolol GFS®, Falcon
		Timoptic-XE® Ocumeter®, Merck

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Timolol Maleate Combinations

Ophthalmic		
Solution	0.5% (of timolol) with Dorzolamide Hydrochloride 2% (of dorzolamide)	**Cosopt® Ocumeter® Plus**, Merck

†Use is not currently included in the labeling approved by the US Food and Drug Administration

CARBONIC ANHYDRASE INHIBITORS 52:40.12

Carbonic Anhydrase Inhibitors General Statement

■ Carbonic anhydrase inhibitors decrease the formation of aqueous humor and also may exhibit diuretic activity.

Uses

■ **Glaucoma** Oral carbonic anhydrase inhibitors (i.e., acetazolamide, dichlorphenamide, methazolamide) are used principally as adjuncts for prolonged therapy in patients with open-angle (noncongestive, chronic simple) glaucoma not controlled by miotics alone. Oral carbonic anhydrase inhibitors should be used in conjunction with topical miotics or epinephrine derivatives which, unlike the carbonic anhydrase inhibitors, increase the facility of aqueous outflow. Orally or parenterally administered carbonic anhydrase inhibitors may also be used for short-term administration with miotics and/or osmotic agents such as glycerin, mannitol, or urea to lower intraocular pressure prior to surgery for the correction of acute angle-closure (obstructive, narrow-angle), infantile glaucoma, or glaucoma secondary to intumescent cataract or phacolysis. The drugs should not be used for long-term administration in patients with chronic noncongestive angle-closure glaucoma, because further closure of the angle may occur while worsening of the glaucoma is masked by lowered intraocular pressure.

Oral carbonic anhydrase inhibitors are also used as adjuncts in the short-term treatment of self-limiting secondary glaucomas which may result from anterior uveitis, trauma, iritis, herpes zoster infections, or the glaucomatocyclitic crisis syndrome. Prolonged therapy with oral carbonic anhydrase inhibitors may be of value in the treatment of some chronic secondary glaucomas. In the rare hypersecretion form of glaucoma, these drugs may be effective when used alone.

Carbonic anhydrase inhibitors are of doubtful value in the treatment of severe glaucoma caused by peripheral anterior synechiae and hemorrhagic glaucoma, and one manufacturer of dichlorphenamide indicates that it is contraindicated in these conditions. The manufacturer of methazolamide states that the drug is contraindicated in the treatment of severe or absolute glaucoma.

Topical carbonic anhydrase inhibitors (e.g., brinzolamide ophthalmic suspension, dorzolamide ophthalmic solution) are used topically to reduce elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Topical carbonic anhydrase inhibitors are useful as a first-line agent, especially when a topical β-adrenergic blocking agent cannot be used because of intolerance or a contraindication. In addition, the drugs are useful as a first-line "add-on" agent when more than one drug is needed.

Tolerance may develop in patients receiving therapy with a carbonic anhydrase inhibitor for glaucoma; in such cases one of the other drugs in this group may be effective.

■ **Edema** Acetazolamide may be used in the management of edema secondary to congestive heart failure or drug therapy. However, carbonic anhydrase inhibitors are much less potent diuretics than are the thiazide diuretics and metabolic acidosis resulting in loss of diuretic effect occurs after 2–4 days of continuous therapy with carbonic anhydrase inhibitors. For these reasons, carbonic anhydrase inhibitors have largely been supplanted by the thiazides.

■ **Seizure Disorders** Acetazolamide is used as an adjunct to other anticonvulsants in the management of centrencephalic epilepsies (e.g., petit mal, unlocalized seizures). Tolerance to the anticonvulsant effects of carbonic anhydrase inhibitors develops quickly, and they may be ineffective for prolonged therapy. Although acetazolamide may be useful in partial, myoclonic, absence, and primary generalized seizures that have not responded adequately to other anticonvulsants, acetazolamide has not been evaluated in controlled clinical studies in specific seizure types and guidelines for appropriate use of the drug are not available.

■ **Acute High- Altitude Sickness** Acetazolamide is used to increase altitude tolerance in the prevention or amelioration of symptoms associated with acute high-altitude sickness (mountain sickness) in climbers attempting rapid ascent and in those who are very susceptible to the condition despite gradual ascent. Acetazolamide has been designated an orphan drug by the US Food and Drug Administration for this use. It should be remembered, however, that whenever possible, gradual ascent and adequate acclimatization (e.g., spending 24 hours at an intermediate altitude, minimizing exertion during the initial 24–48 hours at high altitude) are desirable to prevent acute high-altitude sickness. In controlled studies, prophylactic administration of 250 mg of acetazolamide every 8–12 hours as conventional tablets or 500 mg once daily as extended-release capsules before and during rapid ascent to high altitudes decreased the frequency and/or ameliorated the severity of symptoms of acute high-altitude sickness, including headache, nausea, shortness of breath, dizziness, drowsiness, and fatigue. Pulmonary function (e.g., minute ventilation, expired vital capacity, peak flow) was better in acetazolamide-treated patients, including symptomatic and asymptomatic patients, than in those receiving placebo. Climbers treated with acetazolamide also had less difficulty sleeping. The drug decreases periodic breathing and apnea during sleep and diminishes sleep hypoxemia.

About 50% of untreated, nonacclimatized individuals who rapidly ascend to an altitude of 10,000 feet or higher develop symptoms of acute high-altitude sickness within 6–8 hours. Some individuals develop severe symptoms even with gradual ascent. The syndrome usually responds to rest and supplemental oxygen at night and subsides after 3–4 days, but severe forms of acute altitude sickness (e.g., high-altitude pulmonary and/or cerebral edema) requiring prompt descent and appropriate therapy occasionally occur. The number of individuals at risk of developing acute altitude sickness is increasing as rapid ascents and air travel to areas of high altitude by tourists, without periods of adequate acclimatization, increase. Acetazolamide therapy can hasten acclimatization and may prevent or ameliorate the symptoms of acute altitude sickness in these individuals. Use of acetazolamide does not obviate prompt descent in patients with severe forms of acute altitude sickness. The drug does not prevent acute altitude sickness, but rather shortens the time of acclimatization and has little, if any, effect after symptoms of altitude sickness occur.

■ **Other Uses** Acetazolamide has been used in the treatment of both hyperkalemic and hypokalemic forms of periodic paralysis†, and it may be the drug of choice in the hypokalemic form of this condition.

Acetazolamide has been used with good results in the prevention or treatment of alkalosis following open-heart surgery†. Correction of the blood pH and diminished respiratory and cardiac distress were reported to occur within 30 minutes after the drug was administered.

Acetazolamide has been used to increase excretion of phenobarbital, lithium carbonate, or salicylates in acute intoxication caused by these drugs†. However, because metabolic acidosis results both from salicylate intoxication and acetazolamide administration, use of acetazolamide in the treatment of salicylate intoxication is dangerous and can lead to severe complications; if it is used at all, acetazolamide should probably be used only in adults with respiratory alkalosis and only under the supervision of clinicians experienced in the use of the drug in salicylate overdosage.

Although intracranial pressure may be lowered in some hydrocephalic patients† receiving oral acetazolamide or methazolamide, the drugs have not been consistently effective in the treatment of this condition.

In one controlled randomized study in preterm infants with posthemorrhagic ventricular dilatation, infants who received acetazolamide (100 mg/kg daily) and furosemide (1 mg/kg daily) in addition to standard therapy (intermittent removal of CSF) experienced a higher rate of shunt placement and increased neurologic morbidity compared with infants who received standard therapy alone.

Because acetazolamide may inhibit the formation of gastric and pancreatic

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Bimatoprost is distributed in milk in animals. Caution if used in nursing women.

Pediatric Use. Safety and efficacy not established in children.

Geriatric Use. No substantial differences in safety and efficacy relative to younger adults.

Renal and Hepatic Impairment. No studies have been performed in these patients; use with caution.

■ **Common Adverse Effects** Conjunctival hyperemia, growth of eyelashes, and ocular pruritus occurred in approximately 15–45% of patients who received bimatoprost ophthalmic solution in clinical trials. Approximately 3% of patients discontinued therapy because of conjunctival hyperemia. Ocular dryness, visual disturbance, ocular burning, foreign body sensation, ocular pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening have been reported in approximately 3–10% of patients who received bimatoprost ophthalmic solution in clinical trials. Adverse ocular effects reported in approximately 1–3% of patients include ocular discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema.

Adverse systemic events reported in approximately 1–10% of patients include infection (primarily colds and upper respiratory tract infections), headache, abnormal liver function test results, asthenia, and hirsutism.

Drug Interactions

No formal drug interaction studies have been performed. The manufacturer states that pharmacokinetic interactions are unlikely.

Pharmacokinetics

Absorption *Bioavailability* Following once-daily topical ocular administration for 2 weeks, peak blood concentrations were attained within 10 minutes and were below the lower limit of detection within 1.5 hours. Steady-state blood levels were achieved during the first week of dosing.

Onset Reduction in IOP generally occurs within 4 hours after topical application and peaks within 8–12 hours.

■ **Distribution** *Extent* Moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma.

Bimatoprost is distributed into milk in animals; it is not known whether the drug distributes into milk in humans.

Plasma Protein Binding 88%.

■ **Elimination** *Metabolism* Undergoes oxidation, *N*-deethylation, and glucuronidation to form various metabolites.

Elimination Route Approximately 67% excreted in urine and 25% excreted in feces after IV administration.

Half-life 45 minutes after IV administration.

Description

Bimatoprost, a prostamide, is a synthetic prostaglandin analog that is an ocular hypotensive agent. The drug appears to mimic the effects of endogenous prostamides and exhibits little or no pharmacologic activity at prostanoid receptors. Bimatoprost appears to reduce intraocular pressure (IOP) by facilitating outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.

A reduction in IOP generally occurs within 4 hours after topical application of bimatoprost and peaks within 8–12 hours.

Advice to Patients

Risk of changes in eyelashes and permanent darkening of iris, eyelashes, or skin around the eyes associated with therapy.

Importance of learning and adhering to proper administration techniques to avoid contamination of the solution with common bacteria that can cause ocular infections (e.g., bacterial keratitis). Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic solutions.

Importance of patients informing clinicians if they develop an intercurrent ocular condition (e.g., trauma, infection) or will undergo ocular surgery. Importance of immediately reporting ocular reactions, particularly conjunctivitis and eyelid reactions. Importance of administering different topical ophthalmic preparations at least 5 minutes apart.

Importance of delaying insertion of contact lenses for at least 15 minutes after bimatoprost instillation, since benzalkonium chloride preservative may be absorbed by soft lenses.

Importance of women informing clinicians if they are or intend to become pregnant or to breast-feed.

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. Is is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Bimatoprost

Ophthalmic		
Solution	0.03%	Lumigan®, Allergan

Latanoprost

■ Latanoprost, a synthetic analog of naturally occurring prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is an ocular hypotensive agent.

Uses

Latanoprost ophthalmic solution is used topically to reduce elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Elevated IOP presents a major risk factor in glaucomatous field loss; the higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. The manufacturer states that there is limited experience with latanoprost in the management of angle-closure glaucoma†, inflammatory glaucoma†, or neovascular glaucoma† is limited.

Prostaglandin analogs (including latanoprost) are considered one of several first-line agents to reduce elevated IOP. Like topical β-adrenergic blocking agents, latanoprost reduces elevated IOP in patients with open-angle glaucoma without producing miosis and/or ciliary spasm that are associated with miotic agents. In addition, use of latanoprost in patients with central lenticular opacities can avoid visual impairment caused by a constricted pupil. Although use of some topical β-adrenergic blocking agents (e.g., levobunolol, timolol) may be associated with adverse pulmonary and cardiovascular effects, these adverse systemic effects also have been reported with latanoprost.

Latanoprost is highly effective in reducing IOP when used alone or in conjunction with other ocular hypotensive agents. In phase III studies in patients with open-angle glaucoma or ocular hypertension, less than 1% of patients receiving latanoprost alone dropped out of the studies because of inadequate IOP response to the drug. Latanoprost also can be used in conjunction with a topical β-adrenergic blocking agent (e.g., betaxolol, carteolol, levobunolol, metipranolol, timolol), topical dipivefrin, topical epinephrine, an oral carbonic anhydrase inhibitor (e.g., acetazolamide), or a topical carbonic anhydrase inhibitor (e.g., dorzolamide). When latanoprost is used in conjunction with these agents, the IOP-lowering effects of the drugs may be additive. (See Drug Interactions: Ocular Hypotensive Agents.)

Safety and efficacy of latanoprost have been evaluated in several multicenter, randomized, double-blind, active-controlled studies that involved several hundred patients with open-angle glaucoma or ocular hypertension. In these studies, which included patients with mean baseline IOP values of 23–25 mm Hg, topical application of latanoprost 0.005% once daily for up to 12 months reduced IOP by 6.3–8.6 mm Hg which corresponds to a 27–35% reduction in IOP from baseline values.

Latanoprost appears to be more effective than unoprostone, as effective as travoprost, and slightly less effective than bimatoprost in reducing IOP in patients with open-angle glaucoma or ocular hypertension. In several randomized, comparative studies, once-daily administration of latanoprost 0.005% was associated with greater reductions in IOP than twice-daily administration of unoprostone 0.12–0.15%. Latanoprost appears to be slightly less effective than bimatoprost in reducing IOP or achieving target IOP. In several multicenter, randomized, comparative studies, once-daily administration of latanoprost 0.005% was associated with slightly smaller reductions in IOP than once-daily administration of bimatoprost 0.03% but the differences were not always statistically significant; however, in one study, reductions in IOP following latanoprost were significantly smaller than those achieved with bimatoprost. In addition, data from most comparative studies indicate that latanoprost generally is less effective than bimatoprost in achieving target IOP (particularly lower target IOP); in these studies, target IOP was achieved in fewer patients receiving latanoprost compared with those receiving bimatoprost. Although slightly less effective than bimatoprost, treatment with latanoprost was associated with a lower incidence of conjunctival hyperemia than treatment with bimatoprost.

Once-daily administration of latanoprost 0.005% appears to be more effective or at least as effective as twice daily administration of timolol 0.5% in reducing IOP in patients with open-angle glaucoma or ocular hypertension. In one comparative study in patients with mean baseline IOP of 24.6–25.5 mm Hg who received latanoprost 0.005% once daily or timolol 0.5% twice daily, 69% of those who received latanoprost had a diurnal IOP (defined as the average of IOPs determined at 8 am, 12 noon, and 4 pm) of 17 mm Hg or lower at the end of the 6-month study compared with 34% of those who received timolol during the same period. Once-daily administration of latanoprost 0.005% appears to be more effective than thrice-daily administration of dorzolamide 2%.

Studies to date indicate that tolerance to latanoprost does not occur and that

the reduction in mean IOP is maintained for up to at least 24 months of therapy after initial stabilization.

Pigmentation changes in the iris that may be induced by latanoprost do not appear to decrease the drug's efficacy. Data from a 3-year open-label study with a 2-year extension phase indicate that clinical response to latanoprost (i.e., reduction in IOP) in patients with an increase in brown pigmentation in the iris as a result of latanoprost therapy is similar to the response in other patients. (See Ocular Effects: Increased Iris Pigmentation, in Cautions.)

Dosage and Administration

■ **Administration** Latanoprost is applied topically to the eye as an ophthalmic solution. Care should be taken to avoid contamination of the solution container. (See Cautions: Precautions and Contraindications.)

Latanoprost ophthalmic solution contains benzalkonium chloride, which may be absorbed by some contact lenses. The manufacturer states that contact lenses should be removed prior to administration of each dose of latanoprost ophthalmic solution but may be reinserted 15 minutes after the dose.

If the patient is receiving more than one topical ophthalmic drug, the drugs should be administered at least 5 minutes apart.

■ **Dosage** For the treatment of open-angle glaucoma or ocular hypertension, the usual dosage of latanoprost is 1 drop of a 0.005% solution (1.5 mcg) in the affected eye(s) once daily in the evening. Patients should be instructed that latanoprost ophthalmic solution should be applied no more frequently than once daily since more frequent dosing may paradoxically reduce the IOP-lowering effect of the drug. If the patient misses a dose of latanoprost, the dose should be omitted and the next dose applied the following evening.

If a further reduction in IOP is required in patients receiving the usual dosage of latanoprost once daily in the evening, a topical β-adrenergic blocking agent (e.g., betaxolol, carteolol, levobunolol, metipranolol, timolol), a topical miotic (e.g., pilocarpine), topical dipivefrin, topical epinephrine, an oral carbonic anhydrase inhibitor (e.g., acetazolamide), or a topical carbonic anhydrase inhibitor (e.g., dorzolamide) may be used in conjunction with latanoprost. (See Drug Interactions: Ocular Hypotensive Agents.)

Cautions

Information on the safety and efficacy of latanoprost has been obtained principally in patients with glaucoma or ocular hypertension who received the drug for 6 months or longer in phase III clinical studies; selection criteria for these studies excluded patients with known contraindications to the active control drug (i.e., timolol).

Latanoprost ophthalmic solution generally is well tolerated following topical application to the eye. Discontinuance of latanoprost therapy was required in about 5.1% of patients in clinical studies, principally because of increased iris pigmentation. Less than 1% of patients required discontinuation of latanoprost therapy because of conjunctival hyperemia.

In phase III clinical studies, the incidence of most adverse ocular effects (e.g., punctate keratopathy, dry eye, blurred vision, excessive tearing, ocular or eyelid discomfort, burning, stinging, itching, foreign body sensation) in patients receiving once daily topical latanoprost generally was similar to that in patients receiving twice daily topical timolol. While the percentage of patients who experienced increases in conjunctival hyperemia from baseline was slightly higher with latanoprost than with timolol and mean conjunctival hyperemia was graded slightly higher with latanoprost, all cases of hyperemia were graded as mild in severity. In one study, mild punctate epithelial keratopathy occurred more frequently in patients receiving latanoprost than those receiving timolol but this was attributed to the higher concentration of benzalkonium chloride (0.02%) in latanoprost ophthalmic solution and vehicle compared with the concentration in timolol ophthalmic solution (0.01%).

■ **Ocular Effects** *Increased Iris Pigmentation* Use of latanoprost ophthalmic solution has been associated with an increase in brown pigmentation of the iris in some patients. The increased pigmentation develops slowly, and may not be evident until after several months to years of latanoprost therapy. In most affected eyes, brown pigmentation around the pupil gradually spreads concentrically toward the periphery; however, the entire iris or parts of the iris also may become brownish in color. Data from a 3-year open-label study with a 2-year extension phase indicate that increased pigmentation in the iris does not affect the incidence, type, or severity of other adverse effects associated with latanoprost therapy or clinical response to the drug. Experience in patients receiving latanoprost for up to 5 years indicates that noticeable increased pigmentation generally occurred within the first year of therapy and that pigmentation increases as long as latanoprost ophthalmic solution is administered. While latanoprost therapy can be continued in patients who experience increased pigmentation in the iris, these patients should be examined regularly. While the increase in brown pigment generally does not progress further if latanoprost is discontinued, the change in iris color is likely to be permanent. The effects of increased pigmentation beyond 5 years remain to be determined.

In phase III clinical studies, increased pigmentation of the iris occurred in approximately 6.8 or 15.5% of patients receiving the drug for 6 or 12 months, respectively. Incidence of pigmentation changes varied among clinical study sites, with a 12-month incidence of 22.9% reported in the United Kingdom, 10.9% in Scandinavia, or 8.8% in the US. The higher incidence of this effect in the UK study population has been attributed to the greater frequency of irides predisposed to increased pigmentation. Increased pigmentation during latanoprost therapy generally occurs in individuals with mixed colored irides (i.e., blue-brown, grey-brown, green-brown, yellow-brown). Increased brown pigmentation was not reported in patients with uniform blue, grey, or brown color irides who received latanoprost therapy for 1 year in clinical studies.

Examination in monkeys and patients experiencing increased pigmentation indicate that this effect is most likely the result of a direct melanogenic effect (i.e., stimulation of melanin production in the melanocytes of the iris) without structural alterations or signs of pathology. Iris melanocytes appear to be continent (i.e., do not release pigment to neighboring cells) and pigmentation changes have not been observed in other tissues of the eye, specifically in the trabecular meshwork or choroid. Preexisting iris freckles or nevi do not appear to be affected by latanoprost therapy.

Other Ocular Effects Blurred vision, burning and stinging, foreign body sensation, itching, and punctate epithelial keratopathy have been reported in 5–15% of patients receiving latanoprost ophthalmic solution in phase III clinical studies. While conjunctival hyperemia occurred in 5–15% of patients in phase III clinical studies, less than 1% of patients required discontinuation of the drug because of this adverse effect. Conjunctival hyperemia generally is transient, occurring in the first 1–2 days of latanoprost therapy and diminishing after 2–4 weeks of therapy. In one study evaluating the long-term safety and efficacy of latanoprost in patients with increased baseline IOP, mean conjunctival hyperemia was considered slight at baseline and did not change appreciably throughout 1 year of therapy.

Dry eye, excessive tearing, eye pain, lid crusting, lid edema, lid erythema, lid discomfort/pain, or photophobia occurred in 1–4% of patients receiving latanoprost ophthalmic solution in phase III clinical studies. Adverse ocular effects reported in less than 1% of these patients include conjunctivitis, diplopia, or discharge from the eye. There have been rare reports of retinal artery embolus, retinal detachment, allergic reaction, keratitis, herpes simplex keratitis, and vitreous hemorrhage from diabetic retinopathy in patients receiving latanoprost. Intraocular inflammation (i.e., iritis/uveitis), ocular hypotony,corneal edema and erosions, and choroidal effusions also have been reported in patients receiving topical latanoprost. Macular edema, including cystoid macular edema, has occurred in patients receiving latanoprost. Most reports of macular edema occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

In phase III studies, latanoprost therapy was not associated with infiltration of cells into the anterior chamber or changes in aqueous flare intensity. In one study evaluating the long-term safety and efficacy of latanoprost in patients who received the drug for 1 year, slight aqueous flare was observed at least once in a few patients and a few cells in the anterior chamber were observed in some patients. Compared with baseline, latanoprost therapy has not been associated with substantial changes in visual acuity, refraction, or slit-lamp biomicroscopic examination.

Hypertrichosis and increased pigmentation in lashes and periorbital tissue (eyelid) have occurred following topical application of latanoprost. While pigmentation increases as long as latanoprost ophthalmic solution is administered, these changes have been reversible following discontinuance of the drug in some patients. In patients receiving latanoprost, hypertrichosis involving terminal lashes, regional intermediate hairs, and vellus hairs was observed in patients receiving the drug for an average of 19 weeks (range: 17–36 weeks). Eyelash or vellus hair changes associated with latanoprost therapy include longer, thicker, more numerous, darker lashes or hairs, and misdirected growth of eyelashes. Eyelash changes usually are reversible upon discontinuance of latanoprost.

■ **Systemic Effects** Latanoprost appears to have a low potential for causing adverse systemic effects when applied topically to the eye. Upper respiratory tract infection/cold/flu has occurred in 4% of patients receiving latanoprost ophthalmic solution in phase III clinical studies. Adverse systemic effects reported in 1–2% of patients receiving latanoprost in these studies include muscle/joint/back pain, chest pain/angina pectoris, or rash/allergic skin reactions. Toxic epidermal necrolysis, edema (peripheral and facial), dyspnea, asthma, exacerbation of asthma, migraine headache, tachycardia, myocardial infarction, cerebral vascular accident, and hypertension have occurred in patients receiving latanoprost. While IV administration of high-doses of latanoprost in monkeys (i.e., 50–150 times the usual human dose) has been associated with transient increases in airway resistance and blood pressure, latanoprost ophthalmic solution has been used in individuals with bronchial asthma without inducing bronchoconstriction.

Laboratory analysis of blood and urine before and during latanoprost therapy have not revealed any substantial change in hematologic, urinary, or clinical chemistry values in patients receiving the drug.

■ **Precautions and Contraindications** Because topical latanoprost therapy can cause irreversible changes in iris pigmentation (i.e., increased brown pigmentation) in some patients, especially those with mixed colored irides, patients should be informed of the possibility of iris color change. The increase in brown pigmentation presumably is due to an increase in the number of melanosomes (pigment granules) within melanocytes and not due to a proliferation of melanocytes. While latanoprost therapy can be continued in patients who experience increased pigmentation in the iris, these patients should be examined regularly.

Latanoprost therapy also can cause increases in pigmentation of the peri-

orbital tissue (i.e., eyelid) and changes in eyelashes and vellus hair. Patients expected to receive latanoprost therapy in only one eye should be informed of the potential for increased brown pigmentation in the iris, periorbital tissue, eyelashes, and vellus hairs in the treated eye and that heterochromia between the eyes could occur. Patients also should be advised of the potential for a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Increased pigmentation of the periorbital tissue may be reversible in some patients following discontinuance of latanoprost; eyelash changes usually are reversible upon discontinuance of the drug.

The effect of long-term topical prostaglandin therapy, including the effect of a long-term increase in uveoscleral outflow, effect on chorioretinal circulation or episcleral venous pressure, and effect on the glaucomatous process have not been determined to date.

Latanoprost should be used with caution in patients with a history of ocular inflammation (i.e., iritis/uveitis); the drug generally should not be used in patients with active intraocular inflammation. Because macular edema, including cystoid macular edema, has been reported mainly in aphakic patients, pseudophakic patients, and patients with risk factors for macular edema receiving latanoprost, the drug should be used with caution in patients who do not have an intact posterior capsule or who have risk factors for macular edema.

Bacterial keratitis has been reported with the use of multidose containers of topical ophthalmic preparations. These containers were contaminated inadvertently by patients who, in most cases, had concurrent corneal disease or disruption of the ocular epithelial surface. Patients should be informed that improper handling of ocular solutions can result in contamination of the solution by common bacteria known to cause ocular infections and that they should avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic solutions. Patients receiving latanoprost ophthalmic solution should be advised to contact their clinician at the first sign of conjunctivitis, lid reactions, or any other ocular reaction and immediately seek advice regarding the continued use of the present multidose container if an intercurrent ocular condition (e.g., trauma, ocular surgery or infection) occurs.

Patients who wear contact lenses should be warned to remove their lenses prior to receiving a dose of latanoprost ophthalmic solution since the solution contains benzalkonium chloride which may be absorbed by some lenses. (See Dosage and Administration: Administration.)

Latanoprost ophthalmic solution is contraindicated in patients with known hypersensitivity to latanoprost, benzalkonium chloride, or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of latanoprost ophthalmic solution in pediatric patients have not been established.

■ **Geriatric Precautions** No overall differences in safety or efficacy have been observed between geriatric and younger patients. Results from phase III clinical studies indicate that age does not appear to affect IOP response to latanoprost.

■ **Mutagenicity and Carcinogenicity** Latanoprost was not mutagenic in microbial (Ames), mouse lymphoma, or in mouse micronucleus tests; however, chromosome aberrations were observed in vitro with human lymphocytes.

No evidence of carcinogenic potential was observed in mice or rats given latanoprost by oral gavage in dosages up to 170 mcg/kg daily (approximately 2800 times the recommended maximum human dose) for 20 or 24 months, respectively. In vitro and in vivo studies evaluating unscheduled DNA synthesis in rats receiving latanoprost were negative.

■ **Pregnancy, Fertility, and Lactation** Latanoprost has been embryocidal in rabbits when given in dosages greater than 15 times the maximum human dose. In rabbits given latanoprost dosages 80 times the maximum human dose, approximately 25% of dams had no viable fetuses. There are no adequate and controlled studies to date evaluating latanoprost in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Reproductive studies in male and female rats receiving latanoprost have not revealed evidence of impaired fertility.

It is not known whether latanoprost or its metabolites are distributed into milk following topical application to the eye. Latanoprost should be used with caution in nursing women.

Drug Interactions

■ **Ocular Hypotensive Agents** When latanoprost is used in conjunction with a topical β-adrenergic blocking agent (e.g., betaxolol, carteolol, levobunolol, metipranolol, timolol), topical dipivefrin, topical epinephrine, an oral carbonic anhydrase inhibitor (e.g., acetazolamide), or a topical carbonic anhydrase inhibitor (e.g., dorzolamide), the IOP-lowering effects of these agents may be additive. This additive effect may be used to therapeutic advantage in the management of glaucoma or ocular hypertension. However, when more than one topical ophthalmic drug is used in a patient receiving latanoprost ophthalmic solution, the drugs should be administered at least 5 minutes apart.

Combined therapy with latanoprost and a topical miotic (e.g., pilocarpine) appears to be additive; order and timing of administration of pilocarpine relative to latanoprost appear to alter ocular hypotensive activity.

In one study in patients with open-angle glaucoma or capsular glaucoma receiving timolol 0.5% twice daily in whom IOP was not adequately controlled (i.e., IOP values remained at 22 mm Hg or higher), concomitant use of latanoprost 0.006% once daily resulted in a further decrease in IOP of 32 or 37% at 4 or 12 weeks, respectively. While specific data are limited, use of latanoprost in conjunction with dipivefrin or acetazolamide also appears to be more effective in lowering IOP than use of these agents alone.

■ **Thimerosal** In vitro studies indicate that precipitation occurs when ophthalmic products containing thimerosal are admixed with latanoprost ophthalmic solution. If latanoprost ophthalmic solution is administered to a patient who is receiving an ophthalmic product that contains thimerosal, an interval of at least 5 minutes should elapse between administration of latanoprost ophthalmic solution and the other ophthalmic product.

Acute Toxicity

Limited information is available on the acute toxicity of latanoprost in humans. Other than ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of high doses of latanoprost ophthalmic solution are unknown. In ocular toxicity studies in cynomolgus monkeys, topical administration of 6 mcg of latanoprost daily in each eye (4 times the human daily dose) resulted in increased palpebral fissure; this effect was reversible.

While no adverse effects were reported following IV infusion of latanoprost doses up to 3 mcg/kg in healthy individuals, IV infusion of latanoprost doses of 5.5–10 mcg/kg has resulted in abdominal pain, dizziness, fatigue, hot flashes, nausea, and sweating. Because one of the systemic effects of naturally occurring $PGF_{2\alpha}$ is bronchoconstriction, it has been suggested that a similar effect possibly could occur with high-dose systemic administration of latanoprost. IV infusion of latanoprost doses of 2–6 mcg/kg in monkeys (50–150 times the usual human dose) has been associated with transient bronchoconstriction. However, bronchoconstriction has not been reported to date in humans receiving topical or systemic latanoprost. Latanoprost ophthalmic solution has been used in at least 11 patients with bronchial asthma and did not induce bronchoconstriction in these patients.

■ **Treatment** If topical overdosage of latanoprost ophthalmic solution occurs, treatment should be symptomatic. Overdosage following oral ingestion of the commercially available ophthalmic solution is unlikely given the limited amount of latanoprost present in the solution.

Pharmacology

Latanoprost, a synthetic isopropyl ester analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is a selective prostanoid agonist. Latanoprost is a prodrug of latanoprost acid and has little, if any, pharmacologic activity until hydrolyzed in vivo to latanoprost acid. Naturally occurring $PGF_{2\alpha}$ is a potent FP subtype receptor agonist that also has appreciable agonist activity at some other prostanoid receptors including EP and TP subtypes. Latanoprost acid is highly specific for and has high affinity for the FP subtype prostanoid receptor and, to a lesser extent, the EP_1 subtype prostanoid receptor.

■ **Ocular Effects** Latanoprost is a potent ocular hypotensive agent. Following topical application to the eye and in vivo conversion to latanoprost acid, the drug reduces both elevated and normal intraocular pressure (IOP) in patients with or without glaucoma. In patients with elevated IOP, topical latanoprost can produce mean IOP reductions of about 23–35% from baseline. In healthy individuals with normal IOP or patients with normal-pressure (low-tension) glaucoma, the drug can produce IOP reductions averaging 19–25% from baseline. In dose-ranging studies evaluating commercially available latanoprost ophthalmic solution, maximum reduction in IOP occurred with a topical latanoprost dosage of 1.5 mcg daily (i.e., 1 drop [30 μL] of latanoprost ophthalmic solution 0.005% once daily). Administration of topical latanoprost twice daily does not result in a greater reduction in IOP than administration of the drug once daily and may paradoxically reduce the IOP-lowering effect of the drug. In adults with open-angle glaucoma or ocular hypertension, once daily topical administration of latanoprost effectively lowers IOP during the night and day. While results from one study indicated that once daily topical administration of latanoprost in the evening reduces mean diurnal IOP to a greater extent than administration in the morning, results of other studies have not shown such a difference. Any difference in efficacy between morning and evening administration may reflect the time interval between the latanoprost dose and IOP measurement rather than a difference in effectiveness between morning and evening administration. The IOP response to latanoprost does not appear to be affected by age, gender, ethnicity, baseline IOP, diagnosis, or previous treatment with β-adrenergic receptor blocking agents (e.g., timolol). Results of one study suggested that the response to latanoprost was better in patients with hazel eyes than in those with blue-green-grey eyes; however, iris color did not affect IOP response to the drug in two other studies.

The exact mechanism by which latanoprost reduces IOP has not been fully elucidated. Pharmacodynamic studies suggest that increased outflow of aqueous humor, specifically increased uveoscleral outflow, is the principal effect. In one study, uveoscleral outflow increased from a baseline rate of 0.39 μL/minute to 0.87 μL/minute following topical application of latanoprost 0.006% twice daily for 8 days. In the normal eye, outflow of aqueous humor occurs principally through the trabecular meshwork to the canal of Schlemm and, to a lesser extent, by uveoscleral outflow through the ciliary muscle, suprachoroidal space, and the sclera. While aqueous humor leaving the eye through the

trabecular meshwork and Schlemm's canal is opposed by a pressure gradient of about 10 mm Hg (the episcleral venous pressure), uveoscleral outflow drains against an intraorbital pressure of essentially 0 mm Hg. The more favorable pressure gradient associated with uveoscleral outflow may account for the substantial ocular hypotensive effect associated with topical $PGF_{2\alpha}$ and its analogs. Because uveoscleral outflow is independent of the postural effects of episcleral venous pressure, $PGF_{2\alpha}$ and its analogs lower IOP in patients who are supine to a similar extent as in patients who are sitting. Although the biochemical or cellular mechanism by which $PGF_{2\alpha}$ and its analogs increase uveoscleral outflow has not been studied in humans, studies in nonhuman primates suggest that outflow is increased by relaxation of the ciliary muscle or alterations in its interstitial matrix, resulting in greater pressure-dependent flow through the uvea. In vitro studies in human ciliary muscle cells indicate that $PGF_{2\alpha}$ and its analogs increase prometalloproteinases and metalloproteinases, resulting in degradation or remodeling of the ciliary muscle extracellular matrix. However, prostaglandins modulate and modify many cellular functions and other mechanisms of action may contribute to IOP-lowering activity. Latanoprost acid is highly specific for and has a high affinity for the FP subtype prostanoid receptor, and it has been suggested that uveoscleral outflow may be mediated by the FP receptor. Latanoprost reduces IOP without affecting pupillary size or accommodation.

Glaucoma generally results from impaired outflow of aqueous humor rather than excessive formation. Unlike some other topical ocular hypotensive agents, including β-adrenergic blocking agents (e.g., betaxolol, carteolol, levobunolol, metipranolol, timolol) and carbonic anhydrase inhibitors (dorzolamide), latanoprost does not reduce aqueous humor formation. Because avascular ocular structures depend on aqueous humor flow for metabolic exchanges, long-term reduction in aqueous humor formation may have deleterious effects. Because latanoprost lowers IOP by increasing outflow, effects associated with long-term reduction in aqueous humor formation are avoided; however, the long-term effect of diverting flow through the ciliary muscle and alteration of the ciliary muscle extracellular matrix have not been determined.

While studies in animals indicate that naturally occurring $PGF_{2\alpha}$ can affect the permeability of the blood-aqueous barrier and cause vascular effects and changes in blood flow in the eye, studies using latanoprost in patients with open-angle glaucoma or ocular hypertension indicate that this analog has no effect on capillary permeability in ocular tissues or permeability of the blood-aqueous barrier, has no adverse effects on ocular blood flow, and generally does not cause ocular irritation.

■ **Systemic Effects** Although experience is limited, topical administration of latanoprost has been associated with minimal systemic effects to date. Naturally occurring $PGF_{2\alpha}$ stimulates the contraction of uterine and bronchial smooth muscle and produces vasoconstriction in some vessels. Because naturally occurring $PGF_{2\alpha}$ can cause bronchoconstriction, it has been suggested that a similar effect possibly could occur with high-dose systemic administration of latanoprost. However, studies evaluating the systemic effects of latanoprost in various animals indicate that systemically administered latanoprost has little, if any, effect on cardiovascular and pulmonary systems. Results of a study in patients with asthma (no previous exposure to inhaled corticosteroids) indicate that latanoprost administration is not associated with changes in morning and evening peak expiratory flow, daytime or nocturnal asthma symptoms, or use of asthma medications. In anesthetized cynomolgus monkeys, administration of latanoprost 0.6 mcg/kg IV had no clinically important effect on arterial blood pressure, cardiac output, heart rate, stroke volume, cardiac work, or coronary blood flow. In addition, IV latanoprost was not associated with clinically important effects on respiration rate in monkeys breathing normally or on the intrathoracic inspiratory-expiratory pressure difference and had no effect on blood flow to the eye, brain, stomach, small intestine, colon, liver, kidneys, urogenital organs, or bronchial arteries.

Pharmacokinetics

Latanoprost is a prodrug of latanoprost acid and has little, if any, pharmacologic activity until hydrolyzed in vivo to latanoprost acid.

■ **Absorption** The extent of ocular and systemic absorption of latanoprost following topical application to the eye has not been fully elucidated. Studies using radiolabeled latanoprost indicate that about 1% of a topical dose of the drug penetrates the human eye. The remaining portion is absorbed into systemic circulation through blood vessels in the conjunctiva and mucous membranes of the nose, pharynx, esophagus, and GI tract. Drug absorbed through the cornea is rapidly and completely hydrolyzed to latanoprost acid by esterases present in the cornea, and peak aqueous humor concentrations of biologically active latanoprost acid are reached within 2 hours following a topical dose. Following topical application to the eye of 1 drop (30 μL) of a 0.005% solution (1.5 mcg) of latanoprost 0.5–24 hours prior to surgery in a limited number of patients undergoing cataract extraction, aqueous humor concentrations of latanoprost acid averaged 5.7 ng/mL at 30 minutes, 18.7 ng/mL at 1 hour, 32.6 ng/mL at 2 hours, 29 ng/mL at 4 hours, and less than 0.2 ng/mL at 24 hours after the dose.

A reduction in intraocular pressure (IOP) generally occurs within 3–4 hours after topical application of latanoprost, peaks within 8–12 hours, and persists for up to 24 hours or longer. In patients who have received long-term therapy with latanoprost ophthalmic solution (i.e., 6 months), pharmacologic effects may persist for at least 14 days after the drug is discontinued.

Although some systemic absorption of latanoprost occurs following topical application of the drug to the eyes, latanoprost ophthalmic solution appears to have a low potential for causing systemic effects. Systemically absorbed latanoprost is almost completely hydrolyzed to latanoprost acid by esterases present in the plasma. In patients receiving a single 3-mcg dose of latanoprost ophthalmic solution in phase II studies, approximately 45% of the dose was present in systemic circulation as biologically active latanoprost acid. In healthy males who received 1 drop (30 μL) of a 0.005% solution (1.5 mcg) of radiolabeled latanoprost in each eye, peak plasma concentrations of latanoprost acid occurred within 5–15 minutes and were 53 pg/mL. In a limited number of patients receiving long-term therapy (i.e., minimum of 1 year) with usual doses of latanoprost ophthalmic solution (1.5 mcg of latanoprost in each eye once daily), peak plasma concentrations of latanoprost acid were 32–67 pg/mL in 40% of these patients but were less than 30 pg/mL (the minimum level of detection) in 60% of patients; plasma concentrations of latanoprost were below the level of detection (30 pg/mL) in all patients.

■ **Distribution** Distribution of latanoprost acid into human ocular tissues and fluids has not been fully characterized to date. The volume of distribution of latanoprost acid in humans following topical or IV administration is 0.36 or 0.16 L/kg, respectively. Latanoprost is about 90% protein bound immediately after IV administration; protein binding reportedly decreases to about 60% within 2 hours.

It is not known whether latanoprost or latanoprost acid is distributed into human milk.

■ **Elimination** Latanoprost is rapidly hydrolyzed to latanoprost acid by esterases in the cornea and plasma. The elimination half-life of latanoprost acid from aqueous humor has been estimated to be 3 hours. Following IV or topical administration of latanoprost, plasma concentrations of latanoprost acid decline rapidly with a plasma elimination half-life of 17 minutes. Systemic clearance following topical or IV administration averages 13 or 7 mL/minute per kg, respectively.

Although naturally occurring prostaglandins are metabolized in the lungs by 15-prostaglandin dehydrogenase (15-PGDH), latanoprost acid is a poor substrate for 15-PGDH and its metabolism does not occur via this enzyme. The double bond between carbon 13 and 14 and the phenyl ring on the omega chain of latanoprost may account for the poor binding between latanoprost acid and 15-PGDH. Following topical application to the eye, latanoprost absorbed through the cornea is hydrolyzed to latanoprost acid and does not appear to undergo additional metabolism in ocular tissues. Systemically absorbed latanoprost acid is metabolized in the liver by fatty acid β-oxidation to the 1,2-dinor and 1,2,3,4-tetranor metabolites. These metabolites are excreted principally in the urine; however, biliary excretion may also occur since radioactivity has been detected in feces following IV administration of radiolabeled latanoprost. Unchanged latanoprost or latanoprost acid generally are not recovered in urine or feces. Following IV or topical administration of radiolabeled latanoprost, 98 or 88% of the dose was eliminated in urine. In these studies, IV and topical administration was associated with quantitative recovery of total radioactivity, indicating that no drug or drug related compounds remained in the body.

Chemistry and Stability

■ **Chemistry** Latanoprost, a synthetic analog of naturally occurring prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is an ocular hypotensive agent. The drug differs structurally from $PGF_{2\alpha}$ by the presence of an isopropyl group at the carboxylic acid terminal, the presence of a saturated double-bond between carbon 13 and 14, and substitution of a phenyl ring for part of the omega chain. Esterification of the carboxylic acid terminal of $PGF_{2\alpha}$ increases lipophilicity resulting in better corneal penetration following topical administration, and the phenyl group improves ocular tolerability. Latanoprost is a prodrug and has little, if any, pharmacologic activity until hydrolyzed in vivo to latanoprost acid. Latanoprost, also known as PhXA41, is one of several 17-phenyl substituted isopropyl ester analogs of $PGF_{2\alpha}$ that have been investigated for use as ocular hypotensive agents. While initial studies focused on PhXA34, an equimolar mixture of 15*R* and 15*S* epimers of a 17-phenyl substituted $PGF_{2\alpha}$ analog, subsequent studies focused on latanoprost which is the 15*R* epimer of PhXA34. Because the 15*S* epimer has about 10% of the activity of the 15*R* epimer, latanoprost is about twice as potent as PhXA34.

Latanoprost occurs as a colorless to slightly yellow oil. Latanoprost is freely soluble in alcohol and practically insoluble in water, having a solubility of 200 mg/mL in alcohol and 50 mcg/mL in water at 25°C. The estimated pK_a of the drug is 4.88.

Commercially available latanoprost ophthalmic solution is a clear, colorless, isotonic solution of the drug in sterile water for injection; benzalkonium chloride is added as a preservative. The ophthalmic solution is buffered with monobasic sodium phosphate and dibasic sodium phosphate, and sodium chloride is added to adjust tonicity. Commercially available latanoprost ophthalmic solution has a pH of approximately 6.7 and an osmolality of 275 mOsm/kg.

■ **Stability** Unopened bottles of latanoprost ophthalmic solution should be refrigerated at 2–8°C and protected from light. When stored as directed, the ophthalmic solution has an expiration date of 18 months following the date of manufacture. The bottle in use may be stored at room temperature for up to 6 weeks but should not be exposed to temperatures exceeding 25°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Latanoprost

Ophthalmic		
Solution	0.005%	Xalatan®, Pfizer

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Tafluprost

■ Tafluprost, a fluorinated analog of naturally occurring prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is an ocular hypotensive agent.

Uses

■ **Ocular Hypertension and Glaucoma** Tafluprost ophthalmic solution is used topically to reduce elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Safety and efficacy of preservative-containing and preservative-free tafluprost have been evaluated in several multicenter, randomized, double-blind studies in patients with open-angle glaucoma or ocular hypertension. In these studies, which included patients with a baseline IOP of 23–26 mm Hg, ocular instillation of tafluprost 0.0015% once daily in the evening reduced IOP at 3 and 6 months by 6–8 and 5–8 mm Hg, respectively.

Tafluprost is commercially available in the US as a preservative-free preparation; the drug is available in other countries as preservative-containing and/or preservative-free preparations. Data from a 4-week randomized, crossover phase 3 study in a limited number of patients 18 years of age and older with open-angle glaucoma or ocular hypertension indicate that preservative-containing and preservative-free tafluprost produce similar reductions in IOP (4.56–6.18 and 4.8–6.17 mm Hg, respectively, at 4 weeks). It is not known whether preservative-free tafluprost provides any advantages (e.g., improved adherence or safety) over preservative-containing preparations; however, some clinicians suggest that preservative-free tafluprost may be useful in patients who are allergic or have adverse events related to preservative-containing ocular hypotensives, have sensitive or dry eyes, or do not adequately respond to or cannot tolerate other therapies (e.g., topical prostaglandin analogs).

Tafluprost is noninferior to timolol in reducing IOP in patients with open-angle glaucoma or ocular hypertension. In a 12-month randomized, double-blind, phase 3 study in 458 patients 18 years of age and older with open-angle glaucoma or ocular hypertension, treatment with preservative-containing tafluprost 0.0015% once daily or preservative-containing timolol 0.5% twice daily reduced IOP by 4.84–6.53 or 4.21–6.57 mm Hg, respectively, at 12 months. In a 12-week randomized, double-blind, phase 3 study in 643 patients 18 years of age and older with primary open-angle glaucoma, pigmentary glaucoma, capsular glaucoma/pseudoexfoliation, or ocular hypertension, treatment with preservative-free tafluprost 0.0015% once daily or preservative-free timolol 0.5% twice daily reduced IOP by 6.2–7.4 or 5.7–7.5 mm Hg, respectively, at 12 weeks. In this study, substantial IOP-lowering was apparent after 2 weeks of treatment with tafluprost or timolol and was sustained throughout the 12-week assessment period; the IOP-lowering effect of tafluprost was noninferior to timolol at all visits and time points over 12 weeks. Results of these studies demonstrated that preservative-containing and preservative-free tafluprost are noninferior to preservative-containing and preservative-free timolol, respectively.

Noninferiority of tafluprost to latanoprost has not been established, and tafluprost may be inferior to travoprost in reducing IOP in patients with open-angle glaucoma or ocular hypertension. In a 24-month randomized, double-blind, phase 3 study in 533 patients 18 years of age and older with open-angle glaucoma, capsular glaucoma, pigmentary glaucoma, or ocular hypertension, treatment with preservative-containing tafluprost 0.0015% once daily or preservative-containing latanoprost 0.005% once daily reduced IOP by 7.1 or 7.7 mm Hg, respectively, at 24 months. Although the difference in IOP-lowering effects was clinically small, this study failed to demonstrate noninferiority of tafluprost compared with latanoprost. In another study designed to compare efficacy and safety of tafluprost with travoprost, patients receiving tafluprost 0.0015% had slightly (but statistically significantly) higher 12-hour mean IOP compared with those receiving travoprost 0.004% (17.5 versus 16.9 mm Hg) following 6 weeks of therapy. Because of study limitations (e.g., small sample size [51 patients], short duration), the clinical significance of this difference in IOP-lowering effect is unclear, and whether such difference exists following *long-term* therapy remains to be established.

The addition of tafluprost to existing timolol therapy further reduces IOP in patients with open-angle glaucoma or ocular hypertension. In a 12-week double-blind, phase 3 study, 185 patients 18 years of age and older with a mean baseline IOP of 22–30 mm Hg following timolol therapy were randomized to receive either timolol 0.5% twice daily and preservative-free tafluprost 0.0015% once daily *or* timolol 0.5% twice daily with vehicle once daily for 6 weeks, after which, all patients received open-label timolol with tafluprost for an additional 6 weeks. At 6 weeks, greater reductions in diurnal IOP were achieved in patients receiving timolol and tafluprost (5.49–5.82 mm Hg) compared with patients receiving timolol and vehicle (3.99–4.15 mm Hg). During the extension period (weeks 6–12), patients previously randomized to receive timolol with tafluprost achieved further reduction in IOP; IOP was reduced by 6.22–6.79 mm Hg at week 12. These results indicate that tafluprost may be used in patients with glaucoma or ocular hypertension that is not controlled with timolol alone.

Dosage and Administration

■ **Administration** Tafluprost is applied topically to the eye(s) as an ophthalmic solution.

If the patient is receiving more than one topical ophthalmic drug, the drugs should be administered at least 5 minutes apart.

Tafluprost is available as a preservative-free 0.015 mg/mL (0.0015%) solution packaged in single-use containers; each single-use container has 0.3 mL of solution, corresponding to 0.0045 mg of tafluprost. Because tafluprost ophthalmic solution contains no preservatives, the drug should be used immediately after opening the single-use container; any unused portion should be discarded immediately after administration since sterility cannot be maintained after the container is opened.

■ **Dosage** The recommended dosage of tafluprost for the treatment of open-angle glaucoma or ocular hypertension is 1 drop of a 0.0015% solution in the conjunctival sac of the affected eye(s) once daily in the evening. Tafluprost should not be administered more frequently than once daily since more frequent dosing may diminish the intraocular pressure (IOP)-lowering effect of the drug.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** The manufacturer states there are no known contraindications to the use of tafluprost.

■ **Warnings/Precautions** ***Pigmentation*** Changes in pigmented tissues, including increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes, have been reported with tafluprost ophthalmic solution. Changes in pigmentation result from increased melanin content in the melanocytes rather than from an increase in the number of melanocytes. Pigmentation is expected to increase as long as tafluprost is administered. Following discontinuance of therapy, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Long-term effects of increased pigmentation are unknown.

Increased pigmentation of the iris develops slowly and may not be evident until after several months to years of tafluprost therapy. Typically, the brown pigmentation around the pupil spreads concentrically toward the periphery of the iris, and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. Tafluprost may be continued in patients who develop noticeably increased iris pigmentation; however, these patients should be examined regularly.

Eyelash Changes Tafluprost may gradually change eyelashes and vellus hair in the treated eye, including increased length, color, thickness, shape, and number of eyelashes. These changes usually are reversible upon discontinuance of therapy.

Intraocular Inflammation Tafluprost should be used with caution in patients with active intraocular inflammation (e.g., iritis/uveitis) because the inflammation may be exacerbated.

Macular Edema Macular edema, including cystoid macular edema, has been reported during therapy with prostaglandin $F_{2\alpha}$ analogs. Tafluprost should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Teratogenicity, embryolethality, and decreased fetal weight have been demonstrated in animals receiving IV tafluprost. There are no adequate and well-controlled studies using tafluprost in pregnant women. Tafluprost should not be used during pregnancy unless the potential benefits justify the potential risk to the fetus. Women of childbearing potential should use effective contraceptive methods during tafluprost therapy.

Lactation. Tafluprost and/or its metabolites are distributed into milk in rats; it is not known whether tafluprost and/or its metabolites are distributed into human milk. Because many drugs are distributed into human milk, caution should be exercised when tafluprost ophthalmic solution is administered to a nursing woman.

Pediatric Use. Use in pediatric patients is not recommended because of potential safety concerns related to increased pigmentation following long-term use.

Geriatric Use. No overall clinical differences in safety or efficacy have been observed between geriatric patients and younger adults.

■ **Common Adverse Effects** Adverse ocular effects reported in 2% or more of patients receiving tafluprost ophthalmic solution include conjunctival hyperemia, ocular stinging/irritation, ocular pruritus (including allergic con-

Ref. 5 : ตัวอย่างแก้ไข Storage Condition.

แบบ ย. ๕
FORM MA-5

เลขรับที่ 6527/60
วันที่ 12 ต.ค. 2560
ลงชื่อ.....ผู้รับคำขอ

คำขอแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยา

ข้าพเจ้า นางจันทนา ขนบธรรมชัย ผู้รับอนุญาต/ผู้ดำเนินกิจการ ตามใบอนุญาต

[ ] ผลิตยา [√] นำหรือสั่งยาเข้ามาในราชอาณาจักร
[√] แผนปัจจุบัน [ ] แผนโบราณ

ใบอนุญาตเลขที่ 31/2553 ในนามของ (บริษัท/~~ห้าง/ร้าน~~) อัลโวเจน (ประเทศไทย) จำกัด
ขอแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยา ชื่อ LATAMOLOL เลขทะเบียนที่ 2C 8/59(NG)
รายการที่ขอแก้ไขเปลี่ยนแปลง(ระบุ) สภาวะการเก็บรักษาของผลิตภัณฑ์ยา (Storage Condition)

ข้าพเจ้าได้แนบเอกสารหรือหลักฐานตามที่สำนักงานคณะกรรมการอาหารและยาประกาศกำหนดมาพร้อมนี้ และขอรับรองว่าข้อความอื่นใดที่ไม่ได้ระบุไว้ในคำขอฉบับนี้เหมือนเดิมทุกประการและขอยกเลิกรายการเดิมในทะเบียนตำรับยา ตั้งแต่วันที่ได้รับอนุญาตให้แก้ไขเปลี่ยนแปลงรายการดังกล่าวในทะเบียนตำรับยา เว้นแต่พนักงานเจ้าหน้าที่จะมีคำสั่งเป็นอย่างอื่น

(ลายมือชื่อ) ..... ผู้รับอนุญาต
(นางจันทนา ขนบธรรมชัย)

(ลายมือชื่อ) ..... ผู้มีหน้าที่ปฏิบัติการ
(นางสาวมาริสา โพธิกุล)

(ยื่นแบบคำขอพร้อมสำเนาคู่ฉบับ)

(ส่วนนี้สำหรับเจ้าหน้าที่)

คำสั่งพนักงานเจ้าหน้าที่
[✓] อนุญาต
[ ] ไม่อนุญาต เนื่องจาก .....
[ ] คำสั่งอื่น.....

เอกสารแนบใหม่
Outta
28 ก.ย. 2560

รับรองสำเนาถูกต้อง
Outta

(ลายมือชื่อ) .....
ตำแหน่ง นักวิชาการสาธารณสุข
ชำนาญการปฏิบัติการ
พนักงานเจ้าหน้าที่
๑๙ ก.ค. ๒๕๖๐

รายละเอียดการแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยา

- การแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยาตามแบบ ย.๕ เลขรับที่ _____

ชื่อยา LATAMOLOL เลขทะเบียนที่ 2C 8/59(NG)

รายการขอแก้ไขเปลี่ยนแปลง

[ ] ฉลาก
[ ] เอกสารกำกับยา
[ ] ขนาดบรรจุ
[ ] ชื่อยา
[ ] ลักษณะยา
[ ] สูตรยา (แสดงรายละเอียดการแก้ไขเปลี่ยนแปลงสูตรตำรับยา)
[ ] วิธีวิเคราะห์และข้อกำหนดมาตรฐาน
(แสดงรายละเอียดการแก้ไขเปลี่ยนแปลงวิธีวิเคราะห์และข้อกำหนดมาตรฐาน)
[√] อื่นๆ เกี่ยวกับผลิตภัณฑ์ยา (Storage Condition)

- ขอแก้ไขเปลี่ยนแปลง จาก Store below 5°C in refrigerator

ที่เคยได้รับอนุมัติไว้

เป็น Store at 2-8°C in refrigerator

เป็นการขอแก้ไขเปลี่ยนแปลง

[√] ยาแผนปัจจุบัน
[✓] ตาม ASEAN Variation Guideline (AVG) [✓] MaV.16 [ ] MiV-PA..... [ ] MiV-N.....
[ ] นอกเหนือจากที่กำหนดไว้ใน ASEAN Variation Guideline (AVG)
[ ] ยาแผนโบราณ

- เอกสารหลักฐาน
[√] สำเนาใบสำคัญการขึ้นทะเบียนตำรับยาหรือใบแทน
[√] สำเนาใบอนุญาต
[√] เอกสารสนับสนุนการขอแก้ไขเปลี่ยนแปลง
[✓] เอกสารตาม AVG
[ ] กรณีที่นอกเหนือ AVG
[ ] ยาแผนโบราณ
[ ] รายละเอียดการแก้ไขเปลี่ยนแปลงสูตรตำรับยา
[ ] รายละเอียดการแก้ไขเปลี่ยนแปลงวิธีวิเคราะห์และข้อกำหนดมาตรฐาน
[ ] อื่นๆ _____

เอกสารแนบใหม่
Outta
28 ก.ย. 2560

รับรองสำเนาถูกต้อง
Outta.