

Trial Shows Anecortave Acetate Lowers IOP

During the Annual American Glaucoma Society Meeting in Washington, DC, Alcon Laboratories, Inc. (Fort Worth, TX), released the results of a second controlled proof-of-concept study evaluating the efficacy of anecortave acetate for lowering IOP.¹

The investigators randomized 89 patients with open-angle glaucoma to receive anecortave acetate or the vehicle via a single anterior juxtascular depot. At baseline, all of the patients' IOPs (without hypotensive agents) measured between 24 and 36 mm Hg. The difference between the treatment and vehicle groups was statistically significant.

According to a news release from Alcon, approximately 55% of the patients who received 7.5- and 15-mg doses

of anecortave acetate satisfied the study's primary endpoint of maintaining an IOP of 21 mm Hg or lower at 3 months. Only two patients in the vehicle group (6.4%) achieved similar results.

"These results, together with our recently conducted phase 1 safety evaluation of larger doses and injection volumes, allows us to proceed in 2008 with studies that evaluate higher doses and injection volumes in our phase 2/3 clinical development program," stated Scott Krueger, PhD, Alcon's vice president of R&D, pharmaceutical development.

1. Alcon Laboratories, Inc., Web site. Alcon presents clinical trial data on anecortave acetate for glaucoma. Available at: <http://invest.alconinc.com/phoenix.zhtml?c=130946&p=irol-pressReleasesArticle&ID=1116349&highlight=>. Accessed March 11, 2008.

Experimental Test Uses Motion to Detect Early Glaucomatous Vision Loss

Investigators from Moorfields Eye Hospital in London observed the first annual World Glaucoma Day on March 6, 2008, by presenting a new technology for evaluating visual loss to Members of Parliament.¹

Unlike many perimetric tests, which are proprietary to specific devices, the Moorfields Motion Displacement Test (MDT) can be used on any personal computer. In addition, as its name suggests, the MDT uses motion versus light-based stimuli to detect defects in the visual fields of glaucoma patients.

To take the MDT, patients focus on a white spot in the center of a gray background on the computer's screen. The spot is surrounded by 32 white lines, each of which corresponds to a location on the Humphrey 24-2 program (Carl Zeiss Meditec, Inc., Dublin, CA). Patients are asked to press the mouse every time they see one of the lines move.² Clinicians identify visual field defects by analyzing the patients' responses.

A news release from the BBC stated that starting next month, clinics in Toronto, Rome, and Singapore will participate in a clinical trial designed to evaluate the MDT's utility for detecting early glaucomatous visual field loss.¹ In the meantime, investigators at Moorfields Eye Hospital

and City University London are developing a normative database and strategies for reducing testing time and intertest variability.²

1. BBC Web site. Test to spot early glaucoma signs. Available at <http://news.bbc.co.uk/1/hi/health/7276822.stm>. Accessed March 11, 2008.

2. Moorfields Eye Hospital Web site. Moorfields Motion Displacement Test (MDT) background for clinicians. Available at: <http://www.moorfieldsmdt.co.uk/clinicians.html>. Accessed March 11, 2008.

Interim Results for Canaloplasty

Interim results from a multicenter prospective trial of combined cataract surgery and canaloplasty show that this surgical approach safely and effectively reduced IOP in patients with open-angle glaucoma.¹

The investigators evaluated 54 eyes that underwent circumferential viscodilation of Schlemm's canal during clear corneal cataract surgery. The researchers successfully catheterized all 360° of the canal in 44 eyes (81%) and placed tensioning sutures in 40 eyes (74%). The placement of a suture is thought to facilitate the flow of aqueous fluid from the anterior chamber by placing pressure on and distending the trabecular meshwork.

By 1 month postoperatively, the treated eyes' mean IOP decreased from 24.4 ± 6.1 mm Hg to 13.6 ± 3.8 mm Hg. At 6 and 12 months, the eyes maintained low IOPs (13.0 ± 2.9 mm Hg and 13.7 ± 4.4 mm Hg, respectively). The number

of IOP-lowering medications used by patients also decreased, dropping from 1.5 ± 1.0 at baseline to 0.2 ± 0.4 per patient at 12 months.

Although the investigators observed lower mean IOPs at 6 and 12 months in patients who received tensioning sutures, the difference was not statistically significant compared with the IOPs of patients who underwent circumferential viscodilation only.

Based on these results, the investigators concluded that combined canaloplasty and phacoemulsification "effectively lowers IOP with few complications and with continued control of IOP in patients followed up to 12 months."¹

1. Shingleton B, Tetz M, Korber N. Circumferential viscodilation and tensioning of Schlemm's canal (canaloplasty) with temporal clear corneal phacoemulsification cataract surgery for open-angle glaucoma and visually significant cataract. One-year results. *J Cataract Refract Surg.* 2008;34:433-440.

Novel Glaucoma Drug Completes Exploratory Trial

The preliminary results of an exploratory, phase 2 clinical trial indicated that the novel glaucoma drug BVT.28949 (Biovitrum, Stockholm, Sweden) reduces IOP in patients with glaucoma and ocular hypertension in a dose-dependent manner. BVT.28949 is a serotonin receptor 2A-agonist that reportedly lowers IOP by stimulating aqueous outflow through the trabecular meshwork. Other glaucoma drugs, including the prostaglandin analogs, lower IOP by increasing uveoscleral outflow and bypassing the trabecular meshwork.

The patients who received the highest dose of BVT.28949 (7 mg/mL) experienced a 10% reduction in IOP from baseline after 4 weeks of treatment. Although the difference between the drug and placebo was statistically significant at 2 weeks of treatment

ISTALOL® (timolol maleate ophthalmic solution) 0.5%

Brief Summary of Prescribing Information

Sterile

INDICATIONS AND USAGE

ISTALOL ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

ISTALOL is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, ISTALOL should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma) or a history of bronchial asthma, in which ISTALOL is contraindicated (see CONTRAINDICATIONS) should, in general, not receive beta-blockers, including ISTALOL.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents, if necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

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

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with ISTALOL, alternative therapy should be considered. There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see PRECAUTIONS, Information for Patients).

Information for Patients

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g., timolol). Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. ISTALOL should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

(see PRECAUTIONS, General)

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

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product (see CONTRAINDICATIONS).

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

Drug Interactions

Although ISTALOL used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with ISTALOL and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and ISTALOL should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as ISTALOL, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided. Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in producing atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (see PRECAUTIONS, General, Anaphylaxis)

Pregnancy

Teratogenic Effects — Pregnancy Category C. Teratogenicity studies with timolol in

mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose. In this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. ISTALOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from ISTALOL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon installation in 38% of patients treated with ISTALOL. Additional events reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE

Asthenia/fatigue and chest pain.

CARDIOVASCULAR

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE

Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC

Systemic lupus erythematosus.

NERVOUS SYSTEM/PsYCHIATRIC

Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN

Alpecia and psoriasisiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY

Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash.

RESPIRATORY

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease); respiratory failure; dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE

Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES

Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudophthalmia; choroidal detachment following filtration surgery (see PRECAUTIONS, General, and Intraocular Surgery).

UROGENITAL

Retroprostatic fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocker agents and may be considered potential effects of ophthalmic timolol maleate: ALLERGIC: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress. BODY AS A WHOLE: Extremity pain, decreased exercise tolerance, weight loss. CARDIOVASCULAR: Worsening of arterial insufficiency; vasodilatation; DIGESTIVE: Gastrointestinal pain, hiccups, vomiting, mesenteric arterial thrombosis, ischemic colitis; HEMATOLOGIC: Northumbrocytopenic purpura; thrombocytopenic purpura, agranulocytosis; ENDOCRINE: Hyperglycemia, hypoglycemia; SKIN: Pruritus, skin irritation, increased pigmentation, sweating; MUSCULOSKELETAL: Arthralgia; NERVOUS SYSTEM/PSYCHIATRIC: Verigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; RESPIRATORY: Rales, bronchial obstruction; UROGENITAL: Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with ISTALOL ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

An in vitro hemodialysis study, using 10 ml timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSE AND ADMINISTRATION

ISTALOL ophthalmic solution is available in a concentration of 0.5 percent. The starting dose is one drop of 0.5 percent ISTALOL in the affected eye(s) once a day in the AM. If the patient's intraocular pressure is not at a satisfactory level on this regimen, concomitant therapy with other agents for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended (see PRECAUTIONS, Drug Interactions, Beta-adrenergic blocking agents).

HOW SUPPLIED

Sterile Ophthalmic Solution ISTALOL is a clear, colorless to light yellow solution. ISTALOL Ophthalmic Solution, 0.5% supplied in white LDPE bottle with 15 mm LDPE yellow cap and 15mm LDPE white dropper tip as follows:

NDC 67425-003-50 5 mL in 10 mL container

NDC 67425-003-12 2.5 mL in 7.5 mL container

Storage

Store at 15-25°C (59-77°F)

Rx Only

Manufactured for: ISTA Pharmaceuticals®, Inc. Irvine, CA 92618

By: Bausch & Lomb Incorporated, Tampa, FL 33637

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