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Annual Update 2003 Ophthalmic Drugs

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Abstract

The Annual Update 2003 of Ophthalmic Drugs is comprised of a Compendium of drug R&D in the area of ocular disorders, including 46 drugs for the treatment of glaucoma, diabetic retinopathy, macular degeneration, macular edema, conjunctivitis, keratitis, myopia, cataract, retinitis pigmentosa, retinal detachment, hyphema, uveitis, severe vitreous hemorrhage and dry eye. The section on monographs offers updated information on the following drugs that were published in previous issues of the journal: anecortave acetate, bimatoprost, ciclosporin, diquafosol tetrasodium, epinastine hydrochloride, octreotide, pegaptanib sodium, ruboxistaurin mesilate hydrate and travoprost. A table listing the drugs, their manufacturers, indications and developmental phases is also featured.

Introduction

The Annual Update 2003 of Ophthalmic Drugs is comprised of a Compendium of drug R&D in the area of ocular disorders, including 46 drugs for the treatment of glaucoma, diabetic retinopathy, macular degeneration, macular edema, conjunctivitis, keratitis, myopia, cataract, retinitis pigmentosa, retinal detachment, hyphema, uveitis, severe vitreous hemorrhage and dry eye. The section on monographs offers updated information on the following drugs that were published in previous issues of the journal: anecortave acetate, bimatoprost, ciclosporin, diquafosol tetrasodium, epinastine hydrochloride, octreotide, pegaptanib sodium, ruboxistaurin mesilate hydrate and travoprost. A table listing the drugs, their manufacturers, indications and developmental phases is also featured.

Annual Update 2003: Ophthalmic Drugs

Drug	Source	Condition	Phase
AFP-168/DE-085	Asahi Glass/Santen	Glaucoma	II
AGN-195795	Allergan	Glaucoma	II
AL-6598	Alcon	Glaucoma	II
Bimatoprost[2]	Allergan	Glaucoma	L-2001
DE-092	Santen	Glaucoma	I
ISV-205	InSite Vision	Glaucoma	II
Latanoprost/Timolol Maleate	Pharmacia	Glaucoma	L-2001
Lomerizine Hydrochloride[1,2]	Santen	Glaucoma	II
Memantine Hydrochloride[2]	Allergan	Glaucoma	III
Travoprost[2]	Alcon	Glaucoma	L-2001
AFP-168/DE-085	Asahi Glass/Santen	Hypertension, ocular	II
Lerdelimumab[3]	Cambridge Antibody Technology	Scar, corneal	III
Candesartan Cilexetil[1,2]	Takeda/AstraZeneca	Retinopathy, diabetic	III
Octreotide[1,2]	Novartis	Retinopathy, diabetic	III
Pimagedine[2]	Alteon	Retinopathy, diabetic	III
Ruboxistaurin Mesilate Hydrate[2]	Lilly	Retinopathy, diabetic	III
Vitrase	ISTA Pharmaceuticals	Retinopathy, diabetic	II
AdPEDF	GenVec	Macular degeneration	I
Anecortave Acetate[2]	Alcon	Macular degeneration	III
Celecoxib[1,2]	National Eye Institute (US)	Macular degeneration	II
Fluocinolone Acetonide Implant	Bausch & Lomb/Control Delivery Systems	Macular degeneration	II
Pegaptanib Sodium[2]	EyeTech/Pfizer/Nektar	Macular degeneration	III
Ranibizumab	Genentech	Macular degeneration	III
Rostaporfin	Miravant	Macular degeneration	III
Squalamine	Genaera	Macular degeneration	I/II
Fluocinolone Acetonide Implant	Bausch & Lomb/Control Delivery Systems	Edema, macular	III
Pegaptanib Sodium[2]	EyeTech/Pfizer/Nektar	Edema, macular	II
Posurdex	Oculex	Edema, macular	II
Ruboxistaurin Mesilate Hydrate[2]	Lilly	Edema, macular	III
Veteporfin[1]	Novartis Ophthalmics	Edema, macular	I/II
Apafant	Santen	Conjunctivitis, allergic	II
CAT-213	Cambridge Antibody Technology	Conjunctivitis, allergic	I/II
Ciclosporin[1,2]	Santen	Keratoconjunctivitis, vernal	III
Epinastine Hydrochloride[1]	Allergan	Conjunctivitis, allergic	R-2003
Gatifloxacin[1]	Allergan	Conjunctivitis, infective	L-2003
Gatifloxacin[1]	Senju	Conjunctivitis, infective	III
ISV-401	InSite Vision	Conjunctivitis, infective	II
Moxifloxacin Hydrochloride[1,2]	Alcon	Conjunctivitis, infective	R-2003
Tacrolimus[1,2]	Fujisawa/Sucampo Pharmaceuticals	Conjunctivitis, allergic	II
Tacrolimus[1,2]	Fujisawa/Sucampo Pharmaceuticals	Conjunctivitis, vermnal	II
Tosufloxacin Tosilate[1,2]	Toyama/Nidek	Conjunctivitis, infective	III
DE-094	Santen	Keratitis, bacterial	II
Pirenzepine Hydrochloride[1]	Valley Forge/Novartis Ophthalmics	Myopia	II
Vertporfin[1]	Novartis Ophthalmics	Neovascularization, choroidal	L-2001
N-Acetylcarnosine	Innovative Vision Products	Cataract	II
Epithalone	Russian Academy of Medical Sciences	Retinitis pigmentosa	II
INS-37217	Inspire Pharmaceuticals	Retinal detachment	I/II
Aminocaproic Acid	ISTA Pharmaceuticals/Eastern Virginia Med. School	Hyphema	III
Daclizumab[1]	Protein Design Labs	Uveitis	I/II
Fluocinolone Acetonide Implant	Bausch & Lomb/Control Delivery Systems	Uveitis	III
Vitrase	ISTA Pharmaceuticals/Allergan	Bleeding, vitreous	Prereg
Androgen Tear	Allergan	Dry eyes	III
Ciclosporin[1,2]	Allergan/Inspire	Dry eyes	L-2003
Diquafosol Tetrasodium[2]	Inspire Pharmaceuticals/Allergan/Santen	Dry eyes	III
SmartPlug	Medennium	Dry eyes	L-2001
Tacrolimus[1,2]	Sucampo Pharmaceuticals	Dry eyes	II
Doxycycline Hyclate[1]	CollaGenex	Meibomianitis	II

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future. [3]Monograph in preparation.

Compendium of Ophthalmic Drugs

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Glaucoma

Glaucoma is an all-encompassing term for a group of optic neuropathies characterized by the death of retinal ganglion cells, resulting in deformation of the optic nerve ("glaucomatous cupping") and a progressive reduction in the visual field. The disease is often, but not necessarily, associated with elevated intraocular pressure (IOP). The major forms of glaucoma are open-angle (also called primary or chronic), angle-closure (also known as closed-angle), congenital and secondary. Sixty-seven million people worldwide have glaucoma, including four million in the U.S. Open-angle glaucoma is the most common type, affecting about three million Americans, and is one of the leading causes of preventable blindness worldwide. The U.S. National Eye Institute (National Institutes of Health) estimates that as many as 120,000 Americans are blind as a result of glaucoma. According to the National Eye Institute, blindness due to open-angle glaucoma costs the U.S. government more than US $1.5 billion annually in terms of Social Security benefits, lost tax revenues and healthcare expenditures.

Although no cure for glaucoma currently exists, further damage and blindness can almost always be prevented by early detection and treatment. The objective in treating glaucoma is essentially the reduction of IOP in order to prevent additional optic nerve damage and preserve remaining vision. The most frequent treatment for glaucoma is drug therapy, although laser surgery (laser trabeculoplasty) or conventional surgery may be performed if drugs alone are not effective in lowering IOP. The most frequently used drug classes are miotics, β-blockers, α_2-adrenoceptor agonists and carbonic anhydrase inhibitors.

Prostaglandins

Topical administration of prostaglandins was first proven to lower IOP in experimental animals nearly 25 years ago. The prostaglandins decrease intraocular pressure by increasing uveoscleral outflow. Perhaps the most important shortcoming of this class of antiglaucoma drugs is the lack of long-term experience which is available for other drug classes, such as miotics.

Newly marketed prostaglandin compounds and those under active investigation for the treatment of glaucoma are presented in Table I.

Combination products

In October 2001, Pharmacia launched a new combination therapy for glaucoma/ocular hypertension comprising the selective prostaglandin FP receptor agonist latanoprost and the nonselective β_1- and β_2-adrenoceptor-blocking agent timolol maleate. The fixed **latanoprost/timolol maleate** combination is specifically indicated for the reduction in intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to topical β-blockers. It is marketed under the brand name Xalcom™ in Sweden and as Xalacom® in the U.K.

Vasodilators

The angiotensin AT_1 antagonist **DE-092** (CS-088), discovered at Sankyo, is being developed by Santen for the treatment of glaucoma. A once-daily ophthalmic solution of DE-092 is in phase I testing in Japan.

Nippon Organon has licensed worldwide development and marketing rights for **lomerizine hydrochloride** to

Table I: Prostaglandin compounds recently marketed and under development for glaucoma.

Drug Name	Source	Status
Bimatoprost	Allergan	L-2001
Travoprost	Alcon	L-2001
AL-6598	Alcon	Phase II
AFP-168/DE-085	Asahi Glass/Santen	Phase II

Santen for ophthalmological indications. Lomerizine is marketed in Japan as Terranas® for the treatment of migraine, but its ability to produce vasodilatation via a calcium antagonist effect also suggests potential as a therapeutic agent for glaucoma. Santen is conducting phase II trials for this indication.

Neuroprotective strategies

One of the newer strategies being investigated for the treatment of glaucoma is centered on neuroprotection. This ever more widely studied approach is based on the premise that glaucoma is a neurodegenerative disorder. Retinal ganglion cell death is the final common event in nearly all diseases affecting the optic nerve, including glaucoma. Studies in recent years have demonstrated that the process of apoptosis is initiated following axonal injury, eventually culminating in retinal ganglion cell death. Various approaches have been taken to prevent this process from happening, including the use of growth factors and other trophic agents to improve the metabolism of the optic nerve and enable it to better withstand damage secondary to glaucoma, and axonal rescue, or the use of antiischemic agents to prevent the specific negative effects of ischemia on the optic nerve. Neuroprotective agents will probably be used in combination with conventional IOP-lowering drugs.

In spite of the high level of enthusiasm among scientists about neuroprotective strategies for glaucoma, it is important to bear in mind the extremely high failure rate of these drugs in clinical trials for stroke, the indication for which they have been most widely studied. The potential for efficacy that has been observed in preclinical models has yet to be substantiated in clinical trials.

The NMDA antagonist **memantine hydrochloride**, which is marketed for the treatment of Alzheimer's disease, is in phase III testing at Allergan for the indication of glaucoma. Specifically, Allergan is evaluating the ability of oral memantine to protect the eye from damage caused by glaucoma.

Gene-targeted drugs and gene therapies

Glaucoma is caused by the buildup of a sticky protein in the drainage system of the eye, which hampers the eye's natural ability to equalize pressure through the influx and efflux of fluid. It has been determined that the *TIGR* gene codes for this sticky protein. InSite Vision's **ISV-205**, a DuraSite formulation of diclofenac, has been shown to inhibit the production of the TIGR protein. This novel approach treats the cause of glaucoma rather than the symptoms. ISV-205 is in phase II clinical trials for the prevention of steroid-induced IOP elevation and treatment of ocular hypertension.

In October 2000, Allergan filed an Investigational New Drug (IND) application with the FDA for **AGN-195795** (AC-170472), a gene-specific adrenergic agonist for the treatment of glaucoma. This drug candidate was discovered through the functional genomics collaboration formed by Acadia and Allergan in September 1997. Using Acadia's functional genomics platform as the foundation for discovery efforts and Allergan's disease models and medicinal chemistry, the companies successfully identified and validated the specific α-adrenoceptor gene product that affects IOP and developed AGN-195795, a gene product-specific small-molecule drug that selectively activates this gene target. In preclinical animal studies, AGN-195795 demonstrated a profile superior to that of existing adrenergic agents, suggesting that it may offer potential advantages to glaucoma patients.

Corneal scar

Cambridge Antibody Technology's **lerdelimumab** (CAT-152) is a human IgG_4 monoclonal antibody that neutralizes transforming growth factor β_2 ($TGF\beta_2$), a protein produced in response to injury in the eye, for example following surgery for glaucoma. $TGF\beta_2$ is believed to be responsible for the formation of excessive scar tissue at the wound, which is the main reason for failure of glaucoma surgery. Results from early clinical trials indicate lower pressure in the eye and a trend for reduced postoperative intervention in patients who received lerdelimumab, which may translate into reduced failure of surgery. It is estimated that there are about 250,000 operations per year in North America and Europe that could benefit from this product. If lerdelimumab proves to be successful at preventing the need for reoperation or long-term drug therapy, surgeons may be encouraged to operate more, thus expanding the market. There are currently no approved drugs to prevent scarring in the eye following surgery.

Recruitment of patients in a phase II/III European clinical trial of lerdelimumab continues. This has progressed at a slower rate than previously expected, which means that completion of enrollment is expected in the first half of 2003. Internationally the product is in phase III testing, and in the U.S. the FDA has approved an IND application that was made in November 2002 to begin clinical trials in the U.S.

Diabetic retinopathy

The most common and most serious eye complication of diabetes is diabetic retinopathy, which may result in poor vision or even blindness. Retinopathy is the medical term for damage to the capillaries that nourish the retina, the area at the back of your eye that captures light and relays information to your brain. These blood vessels are often affected by the high blood sugar levels associated with diabetes. There are two types of diabetic retinopathy: nonproliferative diabetic retinopathy, which is more common and usually mild, and proliferative diabetic retinopathy, the more advanced form of the disease. The longer a

person has diabetes, the more likely it is that diabetic retinopathy will develop. After having type 1 diabetes for 20 years, almost everyone with this condition has some degree of retinopathy. After the same number of years, more than 60% of people with type 2 diabetes have some degree of retinopathy. In the U.S., diabetes is responsible for 8% of the cases of legal blindness, making it the leading cause of new cases of blindness in adults 20-74 years of age. Each year, from 12,000-24,000 people lose their sight because of diabetes. Diabetic retinopathy is the leading cause of legal blindness among adults in the U.S.

With early detection and treatment, the risk of severe vision loss from diabetic retinopathy is less than 5%. There is no cure for this condition. The two main treatments for diabetic retinopathy are panretinal laser photocoagulation and vitrectomy.

A.G.E. formation inhibitors

Alteon has completed a phase II/III clinical trial with **pimagedine**, its lead A.G.E. (Advanced Glycosylation Endproducts) formation inhibitor. In diabetic patients with overt nephropathy, pimagedine therapy was shown to result in a statistically significant and clinically meaningful reduction of urinary protein excretion, an effect which was over and above the effect of angiotensin-converting enzyme inhibition as standard medical care in the trials. Pimagedine also reduced, to a statistically significant extent, triglycerides levels as well as the progression of retinopathy. Pimagedine may function as a broadly active agent against the key complications of diabetes, as demonstrated by its clinical activity in slowing the progression of nephropathy and retinopathy and its effect on lowering lipid levels. Although primarily targeted to the treatment of diabetic nephropathy, Alteon is also evaluating pimagedine in phase III trials for the diabetic retinopathy indication.

Angiotensin AT_1 antagonists

Candesartan cilexetil, an angiotensin AT_1 antagonist marketed since 1997 for the treatment of essential hypertension, is now being studied by AstraZeneca and Takeda for diabetic retinopathy. The ongoing DIabetic REtinopathy Candesartan Trial (DIRECT) trial is evaluating the drug for both the prevention and the slowing of progression of diabetic retinopathy. The 4-year, multicenter trial, enrolling 4,500 patients from approximately 20 countries, will involve the once-daily administration of candesartan cilexetil or placebo. The DIRECT trial consists of three arms: the first arm is examining the effects of candesartan cilexetil in the prevention of diabetic retinopathy in insulin-dependent diabetic subjects; the second arm is observing the effects of the drug in slowing the progression of diabetic retinopathy in insulin-dependent diabetic subjects; and the third arm is evaluating the effects of the drug in slowing the progression of diabetic retinopathy in non-insulin-dependent diabetic patients. DIRECT will run through 2004.

Protein kinase C inhibitors

Lilly announced in late 2002 that the company has decided to delay the European submission of its protein kinase C (PKCβ) inhibitor **ruboxistaurin mesilate hydrate** (LY-333531) for diabetic retinopathy, which was planned for 2003, after results from a trial in this indication failed to meet their primary endpoints. In the trial, the overall rate of disease progression was much lower than expected in the placebo group and this was reflected in the results. In the trial however, use of ruboxistaurin was associated with a decrease in the number of patients with sustained visual loss as measured by visual acuity assessment. Given these results, Lilly will begin additional registration trials in 2003 to investigate ruboxistaurin for diabetic retinopathy.

Hyaluronidase-based treatments

Hyaluronidase is a naturally occurring enzyme that digests certain forms of carbohydrate molecules called proteoglycans. ISTA Pharmaceuticals' lead investigational product candidate, **Vitrase®**, is a proprietary formulation of highly purified hyaluronidase. Vitrase® is in phase II testing in the U.S. as a potential treatment for diabetic retinopathy.

Somatostatin analogues

Novartis is developing an intramuscular formulation of the somatostatin analogue **octreotide** (Sandostatin® LAR) for the treatment of diabetic retinopathy. The company plans to file for marketing approval of this new indication in 2004.

Macular degeneration

Macular degeneration is an all-encompassing term for a number of different disorders that have a common end result: the light-sensing cells of the central region of the retina (the macula) malfunction and eventually die, with gradual decline and loss of central vision, while peripheral vision is retained.

There are two basic types of macular degeneration: "dry" and "wet". Approximately 85-90% of the cases of macular degeneration are the dry (atrophic) type, in which the deterioration of the retina is associated with the formation of small yellow deposits, known as drusen, under the macula, leading to a thinning and drying out of the macula. The amount of central vision loss is directly related to the location and amount of retinal thinning caused by the drusen. Approximately 10% of the cases of

macular degeneration are the wet (exudative) type, in which abnormal blood vessels (known as subretinal neovascularization) grow under the retina and macula. These new blood vessels may then bleed and leak fluid, thereby causing the macula to bulge or lift up, thus distorting or destroying central vision. Under these circumstances, vision loss may be rapid and severe.

Macular degeneration is the leading cause of blindness among people aged 55 and older in the U.S., affecting more than 10 million Americans. When it affects older individuals, the condition is called age-related macular degeneration (AMD). Rarely, younger people, including infants and young children, develop macular degeneration due to mutated genes. These types of macular degeneration are collectively called juvenile macular degeneration.

There is no known treatment or cure for the dry type of macular degeneration. Many doctors recommend immediate laser surgery in the early stages of wet macular degeneration if vision is to be saved. However, laser surgery does not guarantee that vision will be saved. Other treatment options include photocoagulation, macular translocation surgery and photodynamic therapy.

Angiogenesis inhibitors

Angiogenesis inhibitors target the abnormal neovascularization characteristic of wet AMD. A pharmacological treatment that would prevent the development of choroidal neovascularization or that would cause it to regress before photoreceptors are irreversibly affected could represent a major step in the prevention of blindness related to this disease. Several compounds with this mechanism of action are known to be in active development at this time.

Ranibizumab (rhuFab V2) is an anti-VEGF monoclonal antibody fragment that binds to vascular endothelial growth factor (VEGF), blocking its ability to induce choroidal neovascularization and blood vessel leakiness. Based on positive data from a phase Ib/II randomized, single-agent study in patients with wet AMD, Genentech plans to advance the product into phase III testing.

Pfizer and EyeTech Pharmaceuticals have entered into an agreement to jointly develop and commercialize Eyetech's **pegaptanib sodium** (Macugen™, EYE-001), a product in development for the treatment of AMD and diabetic macular edema. Pegaptanib sodium holds fast track status for the wet form of AMD, as well as for diabetic macular edema. The product is an aptamer that selectively binds to and neutralizes VEGF. In early clinical studies, pegaptanib sodium inhibited abnormal blood vessel growth and stabilized and/or reversed blood vessel leakage in the back of the eye, resulting in improved vision by three lines or more on standard eye charts in 26% of patients treated. Pegaptanib sodium is being developed as monotherapy and in combination with photodynamic therapy. An ongoing phase III program in wet AMD involves nearly 1,200 patients at 117 sites in the U.S., Canada, South America, Europe, Israel and Australia. EyeTech acquired the rights to the product from Gilead in 2000.

Another angiogenesis inhibitor in advanced clinical testing for the treatment of wet AMD is Alcon's **anecortave acetate**. This compound has been shown in long-term phase III trials to be safe, well tolerated and effective in maintaining vision and preventing vision loss. Alcon recently began enrolling patients in a new phase III trial that will compare the efficacy of anecortave acetate to Visudyne® photodynamic therapy, the current standard of treatment.

Squalamine, a novel antiagiogenic molecule from Genaera, directly blocks endothelial cell activation, migration and proliferation by multiple growth factors. This intracellular blockade of multiple growth factors contrasts with other angiogenesis inhibitor programs. Squalamine is in phase I/II testing for wet AMD.

In November 2002, GenVec's **AdPEDF** entered phase I testing in patients with AMD. AdPEDF is a modified adenovirus that carries the transgene encoding for the PEDF (pigment epithelium-derived factor) protein. The PEDF gene is carried into various eye cells where it stimulates the cells to produce PEDF, thereby increasing PEDF levels and potentially reducing new blood vessel formation. This should reduce further progression of the disease in patients with AMD or diabetic retinopathy and may cause established abnormal blood vessels to regress. A reduction of new blood vessel formation and the selective regression of already established abnormal vessels have been demonstrated in preclinical AdPEDF studies conducted by GenVec and collaborators. The newly initiated multicenter, dose-escalating trial will enroll up to 51 patients with severe AMD to receive one of up to eight different dose levels. The primary endpoint is safety.

Photodynamic therapy

In February 2003, Miravant announced plans to file its an NDA for marketing approval of PhotoPoint™ SnET2 (**rostaporfin**) for the treatment of wet AMD. Miravant's PhotoPoint™ SnET2 is comprised of a light-activated drug designed to target abnormal blood vessels beneath the macula. By destroying these leaky blood vessels, the retina can potentially return to a more normal architecture. The company's decision to proceed with NDA filing follows analyses of phase III clinical data showing positive results in a significant number of drug-treated patients compared to placebo controls, and after discussions with the FDA.

Adjuncts to photodynamic therapy

The National Eye Institute is conducting a multicenter randomized phase I/II clinical study designed to determine whether the selective COX-2 inhibitor **celecoxib**

(Celebrex®) can help stabilize or improve vision in patients with AMD who are receiving verteporfin-enhanced photodynamic therapy. The study is based on several observations: 1) PDT usually does not cause vision to improve, and it has only a temporary effect, requiring several treatments over a 2-year period. Furthermore, PDT does not work in all patients and may actually cause some swelling and regrowth of blood vessels. Celecoxib is an antiinflammatory drug with additional antiangiogenic properties that, in animal studies, has prevented the growth of abnormal blood vessels associated with tumors and with injury to the cornea. Thus, the drug might reduce swelling and prevent vessel regrowth in AMD, enhancing the effectiveness of PDT.

Antiinflammatory steroids

Bausch & Lomb Incorporated and Control Delivery Systems have developed an implantable sustained-release drug delivery system using Envision TD™ technology. A surgeon places this implant directly into the back of the eye, where it delivers the steroid medicine **fluocinolone acetonide** into the vitreous cavity of the eye at a constant rate for about 3 years. Bausch & Lomb is evaluating the safety and efficacy of this implant (Retisert™) in phase II studies in patients with macular degeneration. Retisert™ is also in later-stage clinical trials for the indications of diabetic macular edema posterior uveitis (see below).

Macular edema

Macular edema is swelling of the macula, the small area of the retina responsible for central vision. The edema is caused by fluid leaking from retinal blood vessels. Central vision, used for reading and other close detail work, is affected. Because the macula is surrounded by many tiny blood vessels, anything affecting them, such as a medical condition affecting blood vessels elsewhere in the body or an abnormal condition originating in the eye, can cause macular edema. Retinal blood vessel obstruction, eye inflammation, diabetic retinopathy and age-related macular degeneration have all been associated with macular edema. The macula may also be affected by swelling following cataract extraction, although typically this resolves itself naturally.

Treatment seeks to remedy the underlying cause of the edema. Eye drops, injections of cortisone around the eye or laser surgery can be used to treat macular edema. Recovery depends on the severity of the condition causing the edema.

Antiinflammatory steroids

Oculex announced in December 2001 that patient enrollment in the company's phase II trial evaluating **Posurdex™** in persistent macular edema has been completed. More than 300 patients have been enrolled in this randomized, multicenter study at more than 25 U.S. centers. The trial will evaluate the potential improvement in visual acuity in patients who have persistent macular edema as a result of diseases such as diabetic retinopathy, retinal vein occlusion and uveitis. The study is scheduled to conclude in mid-2003. Posurdex™, based on Oculex's proprietary biodegradable ophthalmic drug delivery technology, is an implant that delivers dexamethasone for an extended period of time.

As mentioned above, Bausch & Lomb's Retisert™ implant, which directly delivers the steroid medicine **fluocinolone acetonide** into the vitreous cavity of the eye for about 3 years, is in phase III trials involving patients with diabetic macular edema who have experienced vision loss.

Angiogenesis inhibitors

As mentioned above, Pfizer and EyeTech Pharmaceuticals are jointly developing **pegaptanib sodium** (Macugen™, EYE-001), which is in phase II testing for diabetic macular edema. Pegaptanib sodium holds fast track status for this indication.

Protein kinase C inhibitors

Lilly announced in late 2002 that the company has decided to delay the European submission of its protein kinase C (PKCβ) inhibitor **ruboxistaurin mesilate hydrate** (LY-333531) for diabetic macular edema, which was planned for 2003, after results from a trial in this indication failed to meet their primary endpoints. In the trial, the overall rate of disease progression was much lower than expected in the placebo group and this was reflected in the results. Despite this, a prospectively defined analysis of the patients by the degree of their glucose control showed that patients with a baseline hemoglobin A1c of 11% or less experienced statistically significant and clinically important reductions in the time to progression to vision-threatening macular edema. Given these results, Lilly will begin additional registration trials in 2003 to investigate ruboxistaurin for diabetic macular edema.

Photodynamic therapy

The photosensitizing agent **verteporfin**, marketed since 1999 for the treatment of AMD, is being evaluated by Novartis Ophthalmics in phase I/II clinical trials for the treatment of diabetic macular edema.

Conjunctivitis

Conjunctivitis is an inflammation of the transparent membrane (conjunctiva) that lines the eyelids and part of

the eyeballs. It can be caused by a bacterial or viral infection, an allergic reaction or an incompletely opened tear drainage duct in newborns. In conjunctivitis, inflammation causes small blood vessels in the conjunctiva to become more prominent, resulting in a pinkish or reddish cast to the whites of the eyes, thus the reason it is sometimes called pinkeye and red eye.

Treatment of conjunctivitis includes antibiotic eyedrops if the infection is bacterial. If the irritation is allergic conjunctivitis, antihistamines, decongestants, mast cell stabilizers, steroids or antiinflammatory drops may be used.

Histamine H_1 receptor antagonists

A topical formulation of the potent and selective histamine H_1 receptor antagonist (antihistamine) **epinastine hydrochloride**, developed by Allergan, was recently approved in Europe as Relestat™ ophthalmic solution, 0.05% for the treatment of allergic conjunctivitis. An oral formulation of epinastine has been marketed by originator Nippon Boehringer Ingelheim since 1994 for the treatment of allergic rhinitis, bronchial asthma, urticaria, eczema and several other allergic skin conditions.

PAF antagonists

Santen is evaluating the platelet activating factor (PAF) antagonist **apafant** in Japanese phase II clinical trials as a potential treatment for allergic conjunctivitis.

Immunosuppressants

Sucampo Pharmaceuticals has signed a licensing agreement with Fujisawa granting the former rights to develop the potent immunosuppressive agent **tacrolimus** for ophthalmic indications in the U.S., Europe and much of the rest of the world, excluding major Asian markets. Fujisawa is evaluating the compound in phase II trials in Japan and Europe for the indications of vernal conjunctivitis (also called seasonal allergic conjunctivitis), a seasonal chronic form of conjunctival inflammation accompanied by photophobia and intense itching, and for perennial allergic conjunctivitis. Tacrolimus is marketed by Fujisawa in many countries, including the U.S., as the immunosuppressive agent Prograf® for prevention of organ graft rejection and under the trade name Protopic® for the treatment of atopic dermatitis.

Santen is developing an eye drop formulation of the immunomodulating and antiinflammatory agent **ciclosporin** in phase III trials in Japan for the indication of vernal keratoconjunctivitis.

Cytokine modulators

CAT-213 is a human IgG_4 monoclonal antibody that neutralizes $eotaxin_1$, a chemokine protein that acts to attract eosinophils into tissues, where they can degranulate and cause tissue damage. Eosinophils are believed to play a key role in causing the inflammation and tissue damage that occurs in a variety of allergic disorders. In November 2002 Cambridge Antibody Technology began recruitment for a phase I/II challenge study of CAT-213 in allergic conjunctivitis. Data from this study are expected to be available at the end of 2003.

Antiinfective agents

The U.S. FDA recently granted Allergan marketing approval for **gatifloxacin** 0.3% ophthalmic solution (Zymar™) for the treatment of bacterial conjunctivitis caused by susceptible strains of bacteria. The company launched the product soon thereafter. Senju is conducting phase III trials in Japan for the same indication. An oral formulation of gatifloxacin, codeveloped by Kyorin and Bristol-Myers Squibb, has been marketed for the treatment of bacterial infections since 1999.

Alcon has also recently received marketing approval from the FDA for **moxifloxacin hydrochloride** 0.5% ophthalmic solution (Vigamox™) as a treatment for bacterial conjunctivitis. This fourth-generation fluoroquinolone antibiotic is safe and effective for children as young as 1 year of age. The solution also shows enhanced coverage of difficult-to-treat Gram-positive bacteria and is highly active against *Chlamydia* and other emerging bacterial threats. Originator Bayer markets moxifloxacin in oral and injectable formulations for the treatment of a variety of infections including pneumonia, sinusitis and acute exacerbations of chronic bronchitis.

The naphthyridine antibacterial compound **tosufloxacin tosilate**, marketed for more than a decade in Japan as an oral formulation for the treatment of urinary and respiratory tract infections, is now being developed by Toyama and Nidek as an antibacterial ophthalmic drug.

InSite Vision is conducting U.S. phase II trials of **ISV-401**, an ophthalmic formulation of azithromycin based on the DuraSite® drug delivery system. ISV-401 is targeted for the treatment of acute bacterial conjunctivitis in patients aged 1 year and older.

Keratitis

Keratitis is a condition characterized by painful inflammation and infection of the cornea. It may result from damage to the cornea after a foreign object has penetrated the tissue, such as from a poke in the eye. At other times, bacteria or fungi from a contaminated contact lens can pass into the cornea. These infections can reduce visual clarity, produce corneal discharge and erode the cornea. Corneal infections can also lead to corneal scarring, which can impair vision and may require a corneal transplant.

As a general rule, the deeper the corneal infection, the more severe the symptoms and complications. Although

relatively infrequent, corneal infections are the most serious complication of contact lens wear.

Minor corneal infections are commonly treated with antibacterial eye drops. If the problem is severe, it may require more intensive antibiotic or antifungal treatment to eliminate the infection, as well as steroid eye drops to reduce inflammation.

Under license from Daiichi Pharmaceutical, Santen is developing **DE-094**, a novel agent for the treatment of infectious keratitis, in phase II clinical trials. DE-094 is a combination product incorporating levofloxacin, a quinolone antibacterial agent, and the steroid drug prednisolone A.

Myopia

Myopia is often called “nearsightedness.” People with myopia can see close objects clearly, while objects farther away appear blurred. All images that the eye can see are created by light rays that come from the image and enter the eye. In normal vision, light rays from an object are bent by the cornea and lens at the front of the eye so they focus on the retina. From the retina, the image of the object is transmitted to the brain by a nerve pathway. In myopic individuals, the eye lengthens abnormally and causes light rays to focus in front of the retina. This results in a blurred image. Myopia is most often caused by excessive lengthening of the eye during childhood. Recent studies have shown that a parental history of myopia is the strongest risk factor for the development and progression of myopia. Close-up work, such as reading, computer work and close television viewing may also influence the development of myopia.

Myopia affects approximately 25% of all children and adolescents in the U.S. and Europe, and an even higher proportion of youth in the Far East. In general, the onset of myopia occurs during the grade school years and progresses until growth of the eye is complete. The younger the child is at the time of onset of myopia, the more rapid the progression of the disease. The socio-economic costs related to myopia (eye exams and correction) exceed $4.6 billion annually in the U.S. A number of therapies, including contact lenses and multifocal lenses, have been advocated. However, no viable clinically acceptable therapy has been shown to be effective in slowing the rate of progression of myopia.

Valley Forge Pharmaceuticals is conducting a phase II clinical trial evaluating **pirenzepine** ophthalmic gel to halt the progression of myopia in nearsighted children. Studies of pirenzepine, a relatively selective muscarinic M_1 antagonist, in animals and humans indicate that the drug, applied twice daily, may slow progression of the axial length of the eye. In previously completed phase II trials, pirenzepine reduced the progression of myopia by at least 50% in the first 12 months of therapy in children who suffer from the condition. Novartis Ophthalmics has licensed exclusive rights to develop and commercialize pirenzepine for this indication.

Choroidal neovascularization

In the summer of 2001, Novartis Ophthalmics and QLT announced that Visudyne™ (**verteporfin** for injection) had been approved by the FDA for the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) due to pathologic myopia, ocular histoplasmosis syndrome, angoid streaks, CNV due to certain retinal abnormalities and idiopathic causes. Verteporfin is the only drug available for these ocular conditions. In phase III trials of patients with CNV caused by pathologic myopia, vision was stabilized or improved in 72% of verteporfin-treated patients as compared to 44% of patients given placebo. In an open-label study in patients with ocular histoplasmosis, 28% of patients had an improvement in visual acuity of three lines or more on a standard eye chart at 12 months. Verteporfin is marketed in some 50 countries for the treatment of classic CNV due to AMD.

Cataract

A cataract is a clouding of the normally clear lens of the eye. Cataracts commonly affect distance vision and cause problems with glare. They generally do not cause pain, double vision with both eyes or abnormal tearing. The most common type of cataract is related to aging. Almost all Americans aged 65 and older have some degree of clouding of the lens. Although most cataracts develop slowly and do not disturb eyesight early on, as the clouding progresses, the cataract eventually interferes with clear vision and can lead to blindness. Approximately 17 million people worldwide are blind as a result of cataracts.

The only effective treatment for a cataract is surgery to remove the clouded lens and replace it with a clear lens implant. Surgical methods used to remove cataracts include phacoemulsification and extracapsular cataract extraction.

Antioxidants

Innovative Vision Products has developed ***N*-acetylcarnosine**, an ophthalmic drug conceived as a nonsurgical alternative for the treatment of age-related cataracts. This molecule protects the crystalline lens from oxidative stress-induced damage. In a recent placebo-controlled clinical trial enrolling 49 patients with senile cataract, *N*-acetylcarnosine was shown to safely and effectively produce long-term improvements in sight.

Retinitis pigmentosa

Retinitis pigmentosa (RP) is the name given to a group of inherited eye diseases that affect the retina. RP causes the degeneration of photoreceptor cells in the

retina. Photoreceptor cells capture and process light helping us to see. As these cells degenerate and die, patients experience progressive vision loss. The most common feature of all forms of RP is a gradual degeneration of the rods and cones. Most forms of RP first cause the degeneration of rod cells. These forms of RP, sometimes called rod-cone dystrophy, usually begin with night blindness. As the disease progresses and more rod cells degenerate, patients lose their peripheral vision. Patients with RP often experience a ring of vision loss in their mid-periphery with small islands of vision in their very far periphery. Others report the sensation of tunnel vision, as though they see the world through a straw. Many patients with RP retain a small degree of central vision throughout their life. Other forms of RP, sometimes called cone-rod dystrophy, first affect central vision. Patients first experience a loss of central vision that cannot be corrected with glasses or contact lenses. With the loss of cone cells also comes disturbances in color perception. As the disease progresses, rod cells degenerate causing night blindness and peripheral vision.

The worldwide prevalence of RP is approximately 1 in 4000. Symptoms of RP are most often recognized in children, adolescents and young adults, with progression of the disease continuing throughout the individual's life. The pattern and degree of visual loss are variable, but a majority of people with RP are legally blind by the age of 40.

As yet, there is no known cure for RP. However, intensive research is currently under way to discover the cause, prevention and treatment of RP. At this time, RP researchers have identified a first step in managing RP. While not a cure, certain doses of vitamin A have been found to slightly slow the progression of RP in some individuals.

Apoptosis inhibitors

Epithalone, a synthetic pineal tetrapeptide from the Russian Academy of Medical Sciences, is potentially useful for the treatment of retinitis pigmentosa. In rats with congenital retinitis pigmentosa, a single daily dose of 1 mg/kg injected into the parabulbar region of the eye for 72 days produced morphological and electrophysiological improvement by day 41 and prolonged retinal functional activity by 43.9%; significant retinal preservation was seen, and the time for complete destruction of the retinal layers was prolonged from 41 days (in control animals) to 72 days. In a study in patients with pigmented retinal degeneration, epithalone stopped the development of pathology in 100% of cases and increased visual function in 80% of cases. Phase II testing of the compound is under way.

Retinal detachment

Retinal detachment is a serious eye condition that almost always leads to blindness if not treated promptly. Retinal detachment occurs when the retina separates from the choroid, a thin layer of blood vessels that supplies oxygen and nutrients to the retina. Unless the detached retina is surgically reattached, a permanent loss of vision in the affected eye can result. Each year the condition affects about 30,000 people in the U.S.

Three surgical procedures are commonly used to repair retinal detachment: pneumatic retinopexy, scleral buckling and vitrectomy. Some of these procedures are done in conjunction with cryopexy. The purpose of these treatments is to close any retinal holes or tears and to reduce the tug on the retina from a shrinking vitreous.

$P2Y_2$ agonists

INS-37217 Ophthalmic, delivered as an intravitreal injection, is a second-generation $P2Y_2$ receptor agonist from Inspire Pharmaceuticals that has been shown in preclinical studies to enhance the reabsorption of fluid across the retinal pigment epithelium and stimulate the removal of extraneous fluid from the subretinal space. If successfully developed, INS-37217 Ophthalmic could facilitate retinal reattachment without the need for surgery, and may improve visual outcome. INS-37217 Ophthalmic may also be used as an adjunct to improve success rates when retinal detachment surgery is employed. The U.S. IND for INS-37217 Ophthalmic for the treatment of retinal disease was filed in December 2000. Results of a phase I/II trial were announced in October 2002, and demonstrated that intravitreal injection of INS-37217 Ophthalmic was very well tolerated. In addition, patients treated with INS-37217 Ophthalmic showed improvement in extent of retinal reattachment as demonstrated by two independent, quantitative measures. Patients treated with placebo showed no improvement as determined by the same two measures. A definitive phase II clinical trial is being planned for initiation in the second half of 2003.

Hyphema

Hyphema is a condition characterized by blood in the front chamber of the eye and is usually caused by trauma to the eye, which may be a blunt or perforating injury. Severe inflammation of the iris, a blood vessel abnormality or cancer of the eye may occasionally cause bleeding into the front chamber.

In mild cases, no treatment is required, and the blood is absorbed within a few days. Bed rest, eye patching and sedation to minimize activity and reduce the likelihood of recurrent bleeding are often prescribed. Eye drops to decrease the inflammation or lower the IOP may be used, and removal of the blood by an ophthalmologist may be necessary, especially if the IOP is severely increased or the blood is slow to resorb.

Antifibrinolytic agents

In May 2002, ISTA Pharmaceuticals acquired substantially all the assets of AcSentient, thereby adding the product Caprogel™ (**aminocaproic acid**) for the treatment of hyphema to its R&D pipeline. Researchers at Eastern Virginia Medical School discovered that the antifibrinolytic agent aminocaproic acid reduces recurrent hyphema, and licensed the technology to AcSentient and Senju.

Uveitis

Uveitis, the third leading cause of blindness in the U.S. after diabetic retinopathy and macular degeneration, is the inflammation of the inside of the eye, specifically affecting one or more of the three parts of the eye that make up the uvea: the iris, the ciliary body and the choroid. The symptoms of uveitis can include light sensitivity, blurred vision, pain, redness of the eye and "floaters" that temporarily impair vision. Anterior uveitis, the most common form, accounts for 75% of cases. It is often referred to as iritis as the iris is the part of the uvea that is usually inflamed. Intermediate uveitis affects the area just behind the ciliary body (pars plana) and also the most forward edge of the retina. This is the second most common type of uveitis. In patients with posterior uveitis, inflammation affects the part of the uvea at the back of the eye, the choroid. Often the retina is affected in this group. Posterior uveitis is commonly slower in onset and may last longer, and it is often more difficult to treat and is often associated with progressive loss of vision. Diffuse uveitis implies inflammation involving all parts of the eye, including anterior, intermediate and posterior structures.

Ocular complications of uveitis may result in irreversible loss of vision, especially when the condition is unrecognized or improperly treated. The most frequent complications include cataract, glaucoma, retinal detachment, neovascularization of the retina, optic nerve or iris, and cystoid macular edema. The latter is the most common cause of decreased vision from uveitis. Given the potential seriousness of the condition, patients suspected of having uveitis should be referred immediately for complete ophthalmologic evaluation.

Uveitis usually responds well to treatment; however, there may be a tendency for the condition to recur. Treatment usually includes prescription eye drops, which dilate the pupils, in combination with antiinflammatory drugs, especially steroids. Treatment may take several days or up to several weeks.

Antiinflammatory steroids

As mentioned earlier, Bausch & Lomb's Retisert™ implant, which directly delivers **fluocinolone acetonide** into the vitreous cavity of the eye at a constant rate for about 3 years, is being evaluated in patients with noninfectious uveitis affecting the back of the eye. NDA filing for the posterior uveitis indication, initially slated for mid-2003, has been deferred approximately 1 year. Pivotal clinical trials continue to generate data to support the NDA filing.

Cytokine modulators

Daclizumab is a humanized antibody that binds to the interleukin-2 receptor on activated T-cells, thereby blocking the binding of IL-2 to its receptor and inhibiting immune responses. Protein Design Labs, in collaboration with the National Eye Institute, has conducted phase I/II testing of daclizumab in patients with severe, sight-threatening uveitis. Uveitis is an autoimmune condition that is believed to be caused by the action of activated T-cells, the target of daclizumab. Further study of daclizumab in this indication is ongoing.

Vitreous bleeding

Vitreous hemorrhage, a vision-distorting accumulation of blood within the vitreous humor, most often results as a complication of diabetes, although it can also occur following retinal disorders or trauma. Currently the only treatment for this condition is surgery.

Hyaluronidase-based treatments

In addition to diabetic retinopathy, as mentioned above, ISTA Pharmaceuticals' lead investigational product candidate **Vitrase®** is also being developed for the treatment of severe vitreous hemorrhage. As a result of encouraging clinical trial results, and in consideration of the current absence of effective nonsurgical alternatives, Vitrase® has received fast-track designation from the U.S. FDA for the treatment of vitreous hemorrhage. The product, which is currently under FDA review for this indication, is being codeveloped by ISTA and Allergan. Providing that Vitrase® receives regulatory approval, Allergan will sell, market and distribute the product worldwide, except in Mexico before 2004, and Japan.

Dry eyes

Dry eye syndrome (also referred to as dry eyes), occurs when not enough tears are produced or when tears do not have the proper chemical composition. Often, dry eyes are part of the natural aging process. They can also be caused by blinking or eyelid problems, medications like antihistamines, oral contraceptives and antidepressants, a dry climate, wind and dust, general health problems like arthritis, diabetes or Sjögren's syndrome and chemical or thermal burns to the eye. Symptoms of dry eyes include irritated, scratchy, dry,

uncomfortable or red eyes, a burning sensation or feeling of something foreign in the eyes and blurred vision. Excessive dry eyes may damage eye tissue, scar the cornea and impair vision and make contact lens wear difficult. It is estimated that over one million Americans suffer from chronic dry eye syndrome, and approximately 60 million people worldwide use artificial tears.

Treatment for dry eyes includes over-the-counter artificial tears and ointments, collagen or silicone plugs for the tear ducts to prevent tears from draining, thermal cautery, steroid eye drops and antiinflammatory drugs.

Plug devices

In mid-2001, Medennium received CE Mark approval from the E.U. for its **SmartPlug™**, a one-size-fits-all device to treat dry eyes without the potential of the irritation and discomfort of conventional rigid punctum plugs. The SmartPlug™ is unique in that it is made of thermodynamic acrylic polymer that is a thin rigid rod when removed from the package, but seconds after insertion into the punctum it transforms into a soft gel-like, long-term plug that conforms itself to the patient's punctum. This approval allows the SmartPlug™ to be sold throughout the E.U.

Immunosuppressants

Following its approval by the FDA in December, Allergan's Restasis™ (**ciclosporin** ophthalmic emulsion) is now available as a treatment for keratoconjunctivitis sicca, or chronic dry eye syndrome, in patients whose tear production is presumed to be suppressed due to ocular inflammation. While the exact mechanism of action of Restasis™ is unknown, it is thought to act as a partial immunomodulator with antiinflammatory effects. Restasis™ was developed in collaboration with Inspire Pharmaceuticals. Allergan is also evaluating the product in European phase III trials, while Santen is conducting phase III testing in Japan.

As mentioned above, Fujisawa has granted Sucampo Pharmaceuticals the rights to develop **tacrolimus** for ophthalmic indications in the U.S., Europe and much of the rest of the world. Sucampo is developing the drug in European phase II trials for the treatment of dry eyes.

Antiinflammatory drugs

In June 2002, CollaGenex initiated a multicenter, double-blind, placebo-controlled clinical study to evaluate the efficacy of Periostat®, a proprietary formulation of **doxycycline hyclate**, for the treatment of meibomianitis, also known as ocular rosacea and characterized by symptoms of dry eyes. Periostat®, which has been marketed by CollaGenex since 1998 for the treatment of periodontitis, has demonstrated the ability to inhibit a number of destructive proteases and cytokines involved in inflammatory processes.

$P2Y_2$ agonists

Inspire Pharmaceuticals' **diquafosol tetrasodium** (INS-365 Ophthalmic) is a $P2Y_2$ receptor agonist that activates receptors on the ocular surface and inner lining of the eyelid to stimulate the release of water, salt, mucin and lipids – the key components of natural tears. An NDA for diquafosol tetrasodium ophthalmic solution will be submitted in 2003. One phase II trial and two phase III trials have been conducted, and a phase IIIb trial is ongoing. The phase IIIb study may support the NDA, but will not be required for the initial filing. A pre-NDA meeting was held with the FDA on January 6, 2003 and an NDA will be filed in mid-2003. In June 2001, Inspire entered into a partnership with Allergan for the development and commercialization of diquafosol tetrasodium outside of Asia. Santen is developing diquafosol in Japan and nine other Asian countries.

Miscellaneous treatments

Allergan is conducting phase III clinical trials evaluating **Androgen Tear** as a treatment for dry eye syndrome.

Information sources on the internet

American Academy of Ophthalmology
http://www.aao.org

American Optometric Association
http://www.aoanet.org

Diabetic Retinopathy Foundation
http://www.retinopathy.org/

Foundation Fighting Blindness
http://www.blindness.org/

Macular Degeneration Foundation
http://www.eyesight.org/

Macular Degeneration Network
http://www.macular-degeneration.org

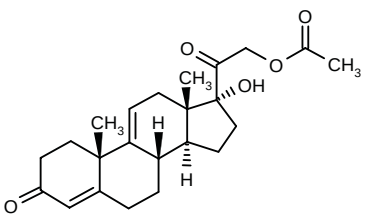
National Keratoconus Foundation
http://www.nkcf.org/

The American Macular Degeneration Foundation
http://www.macular.org/disease.html

Monograph Updates of Ophthalmic Drugs

N.E. Mealy, M Bayés
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

Anecorvate Acetate



Anecortave acetate (AL-3789) is an angiostatic steroid developed by Alcon and currently in phase III trials for the treatment of age-related macular degeneration (AMD). The drug slows or stops new blood vessel growth beneath the retina by inhibiting the production of certain enzymes that allow new cells to move through the blood vessel walls into new tissue areas.

A phase III study of anecortave acetate was recently begun in patients with AMD. Some 500 patients will be enrolled at 40-50 sites in the U.S., Canada, Australia and Europe. Vision outcomes will be compared in predominantly classic wet AMD patients treated with anecortave acetate 15 mg and in those treated with Visudyne® photodynamic therapy (PDT), the current method of treatment. Meanwhile, 12-month data from Alcon's ongoing phase II/III trial of anecortave acetate have confirmed 6-month data showing its efficacy in treating AMD. Six-month results indicate that a single application of 15 mg of anecortave acetate behind the eye resulted in 92% of patients with predominantly classic AMD maintaining functional vision, compared to only 65% of those receiving no drug. In addition, 18% of patients receiving anecortave acetate had improved vision, compared to no improvement in the control group. At 12 months, anecortave's superiority to placebo in maintaining vision and preventing significant vision loss was evident. The drug also maintained its positive safety profile at 12 months. Of patients treated with anecortave acetate, 79% lost fewer than 3 lines of vision from baseline to 12 months, compared to 53% of placebo patients. In the subgroup of patients with predominantly classic lesions, the 12-month clinical efficacy was even greater, with 84% of treated patients maintaining vision within 3 lines compared to 50% for the placebo group (1, 2).

Patients with exudative AMD were administered single posterior juxtascleral injections of 3, 15 or 30 mg anecortave acetate every 6 months in a phase II study with (classic) or without (occult) PDT. The parent drug was rapidly hydrolyzed to its active alcohol metabolite AL-4940, concentrations of which were dose-related in patients receiving PDT. Mean C_{max} values were similar: 4.27 ± 2.90 ng/ml *vs.* 3.30 ± 1.42 ng/ml with and without PDT, respectively. According to these results, the effect of anecortave is not influenced by PDT and is similar in classic and occult AMD patients (3).

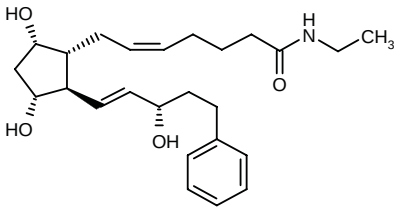
1. *New phase III study for anecortave acetate in AMD*. DailyDrugNews.com (Daily Essentials) Sept 5, 2002.

2. *Twelve-month data shows efficacy of anecortave acetate in wet AMD*. DailyDrugNews.com (Daily Essentials) Oct 2, 2002.

3. Patil, S.D., Dahlin, D.C., Simpson, G., Schaffer, H., Clifford, W., Curtis, M., Faulkner, R. *Pharmacokinetics of anecortave acetate following posterior juxtascleral injections in patients with age-related macular degeneration (ARMD)*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 10-14, Toronto) 2002, Abst W5245.

Original monograph - Drugs Fut 2002, 27(11): 1039.

Bimatoprost



The potent, long-acting synthetic prostamide bimatoprost (AGN-192024), first introduced in the U.S. in 2001, was launched last year by Allergan in several other markets, including the U.K., Germany and Italy, as an ophthalmic solution for reducing elevated intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension.

An *in vitro* study characterized the agonist activity of several prostaglandin FP receptor agonists at an FP receptor cloned from human ciliary body. The most potent agonist was travoprost acid (EC_{50} = 3.2 ± 0.6 nM), followed by bimatoprost free acid (EC_{50} = 5.8 ± 2.6 nM), fluprostenol (EC_{50} = 6.1 ± 1.5 nM) and latanoprost free acid (EC_{50} = 54.6 ± 12.4 nM); both unoprostone and S-1033 were significantly weaker than travoprost acid. The amide prodrug of bimatoprost displayed intermediate potency (EC_{50} = 126 ± 347 nM) and agonist activity was observed with the isopropyl ester prodrugs of travoprost (EC_{50} = 42.3 ± 6.7 nM), latanoprost (EC_{50} = 126 ± 347 nM) and unoprostone (EC_{50} = 9100 ± 2870 nM). PGI_2, bradykinin, histamine and 5-HT had no effect. AL-8810, an FP receptor antagonist, reversed the agonist activity of bimatoprost, unoprostone, fluprostenol, travoprost acid and latanoprost acid (1).

The functional activity of bimatoprost, travoprost, unoprostone and other prostaglandin FP receptor-selective agonists was demonstrated in human trabecular meshwork cells. Concentration-dependent turnover of [^{3}H]-inositol phosphates was demonstrated, with a decreasing order of potency (EC_{50}) of: travoprost acid (2.4 nM), cloprostenol (4.5 nM), (±)-fluprostenol (10.8 nM), latanoprost (34.7 nM), bimatoprost acid (112 nM), $PGF_{2\alpha}$ (120 nM), unoprostone (3280 nM) and S-1033 (4570 nM). Rapid, concentration-dependent increases in intracellular Ca^{2+} mobilization were also observed with travoprost acid, $PGF_{2\alpha}$, unoprostone and S-1033 (2).

In binding studies, bimatoprost and its hydrolytic product bimatoprost free acid bound to the prostaglandin FP receptor and displaced [^{3}H]-travoprost acid with respective K_i values of 9250 ± 846 and 59 ± 6 nM. Bimatoprost, bimatoprost 0.03% ophthalmic solution and bimatoprost acid mobilized intracellular calcium in HEK293 cells expressing the cloned human ciliary body FP receptor with respective EC_{50} values of 3070 ± 1330, 1150 ± 93 and 15 ± 3 nM, an effect that was concentration-dependently antagonized by AL-8810. The results demonstrate that bimatoprost acts as an FP receptor agonist (3).

The eyes of glaucomatous beagle dogs treated with bimatoprost (0.03%) once in the morning or evening, or twice daily, demonstrated significant decreases in IOP and pupil size. On day 4 of treatment, respective mean diurnal changes in IOP from baseline were 26.0 ± 3.2, 27.3 ± 2.6 and 39.6 ± 2.1 mmHg, which were significantly different from control eyes. Miosis of varying duration was frequently observed during the study (4).

In male Dutch-belted rabbits and cynomolgus monkeys given a single ocular dose of bimatoprost 0.03%, bimatoprost was hydrolyzed to 17-phenyl-$PGF_{2\alpha}$, with greater hydrolysis seen in rabbits than in monkeys (5).

Two multicenter, randomized, double-blind trials lasting 1 year each assessed lowering of IOP with once- and twice-daily bimatoprost 0.03% and twice-daily timolol 0.5% in 957 patients with glaucoma or ocular hypertension. Reductions in IOP were significantly greater throughout the studies with once-daily bimatoprost compared with timolol. Twice-daily bimatoprost was also effective, but less so than once-daily drug (6). The results of this study and two of the following studies are summarized in Table I.

Bimatoprost 0.03% and latanoprost 0.005% given once daily were compared in a 6-month, multicenter, randomized trial in 269 patients with ocular hypertension or glaucoma. Bimatoprost was superior in lowering IOP throughout the study, with significantly greater reductions from baseline figures. Both treatments were well tolerated (7).

Three patients with uncontrolled glaucoma treated with ocular hypotensive lipids (unoprostone, travoprost and bimatoprost) developed cystoid macular edema which resolved with steroid and antiinflammatory treatment and withdrawal of hypotensive lipids (8).

Bimatoprost 0.03% once and twice daily was compared to timolol 0.5% twice daily in 240 patients with ocular hypertension or glaucoma in a multicenter, randomized, double-blind trial. Bimatoprost given once daily was the most effective treatment at 3 months in terms of lowering IOP, with a significant difference in efficacy over timolol (reductions of 8 mmHg and 5.5 mmHg for bimatoprost 0.03% once daily and timolol 0.5% b.i.d., respectively) (9).

1. Sharif, N.A., Kelly, C.R., Crider, J.Y. *Agonist activity of bimatoprost, travoprost, latanoprost, unoprostone isopropyl ester and other prostaglandin analogs at the cloned human ciliary body FP prostaglandin receptor*. J Ocular Pharmacol Ther 2002, 18(4): 313.

2. Sharif, N.A., Kelly, C.R., Crider, J.Y. *Human trabecular meshwork cell responses induced by bimatoprost, travoprost, unoprostone, and other FP prostaglandin receptor agonist analogues*. Invest Ophthalmol Visual Sci 2003, 44(2): 715.

Table I: Clinical studies of bimatoprost (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Glaucoma, ocular hypertension	Randomized, double-blind, multicenter, pooled/meta-analysis	Bimatoprost 0.03% top od x 1 y (n=474) Bimatoprost 0.03% top bid x 1 y (n=483) Timolol 0.5% top bid x 1 y (n=241)	1198	Results showed that bimatoprost once daily was safe, well tolerated and more effective than timolol b.i.d. in decreasing intraocular pressure in patients with glaucoma or ocular hypertension	6
Glaucoma, ocular hypertension	Randomized, multicenter	Bimatoprost 0.03%, od x 6 mo (n=133) Latanoprost 0.005%, od x 6 mo (n=136)	269	Although both treatments were well tolerated, bimatoprost demonstrated superior intraocular pressure-lowering efficacy	7
Glaucoma, ocular hypertension	Randomized, double-blind, multicenter	Bimatoprost 0.03%, drops instilled od x 1 y (n=234) Bimatoprost 0.03%, drops instilled bid x 1 y (n=243) Timolol 0.5%, drops instilled bid x 1 y (n=119)	596	Bimatoprost 0.03% once daily had superior efficacy to timolol 0.5% twice daily in the treatment of glaucoma or ocular hypertension	9

3. Sharif, N.A., Kelly, C.R., Williams, G.W. *Bimatoprost (Lumigan®) is an agonist at the cloned human ocular FP prostaglandin receptor: Real-time FLIPR-based intracellular Ca^{2+} mobilization studies*. Prostaglandins Leukot Essent Fatty Acids 2003, 68(1): 27.

4. Gelatt, K.N., MacKay, E.O. *Effect of different dose schedules of bimatoprost on intraocular pressure and pupil size in the glaucomatous beagle*. J Ocular Pharmacol Ther 2002, 18(6): 525.

5. Dahlin, D.C., Bergamini, M.V.W., Curtis, M.A., Dean, T.R., Kiehlbauch, C.C., Chastain, J.E. *Bimatoprost hydrolysis to 17-phenyl $PGF_{2\alpha}$ by rabbit and monkey ocular tissues, in vivo*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4109.

6. Higginbotham, E.J., Schuman, J.S., Goldberg, I., Gross, R.L., VanDenburgh, A.M., Chen, K., Whitcup, S.M. *One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension*. Arch Ophthalmol 2002, 120(10): 1286.

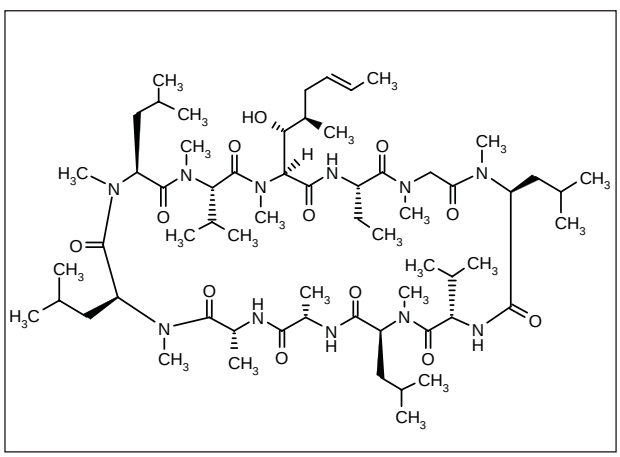
7. Noecker, R.S., Dirks, M.S., Choplin, N.T., Bernstein, P., Batoosingh, A.L., Whitcup, S.M. *A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma*. Am J Ophthalmol 2003, 135(1): 55.

8. Wand, M., Gaudio, A.R. *Cystoid macular edema associated with ocular hypotensive lipids*. Am J Ophthalmol 2002, 133(3): 403.

9. Whitcup, S.M., Cantor, L.B., VanDenburgh, A.M., Chen, K. *A randomised, double masked, multicentre clinical trial comparing bimatoprost and timolol for the treatment of glaucoma and ocular hypertension*. Br J Ophthalmol 2003, 87(1): 57.

Original monograph - Drugs Fut 2001, 26(5): 433.

Ciclosporin



The FDA recently approved and Allergan has now introduced Restasis™ (ciclosporin ophthalmic emulsion, 0.05%) for patients with keratoconjunctivitis sicca, or chronic dry eye syndrome, whose tear production is presumed to be suppressed due to ocular inflammation. A launch is expected in the second quarter of 2003. While the exact mechanism of action of Restasis™ is unknown, it is thought to act as a partial immunomodulator with antiinflammatory effects. In pivotal phase III trials, Restasis™ produced statistically significant and clinically relevant increases in Schirmer wetting *versus* vehicle at 6 months (1). Allergan has a partnership agreement with Inspire for the development and commercialization of Restasis™ outside Asia.

Ciclosporin 2% eyedrops were used to treat 24 children with severe vernal keratoconjunctivitis, with therapy beginning in the spring and lasting for 4 months. During an initial double-blind phase, 1 eye received ciclosporin and the other vehicle for 2 weeks. Ciclosporin was administered to both eyes thereafter. Ocular signs and symptoms were significantly decreased at 2 weeks with ciclosporin treatment, and symptoms continued to gradually decline over 3 months. No major side effects were noted (2). The results of this study and the following study are summarized in Table II.

Patients with keratoconjunctivitis sicca (n=128) were treated with ciclosporin 0.05% or 0.1% eyedrops or vehicle twice daily for 6 months in a multicenter, randomized,

Table II: Clinical studies of ciclosporin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Kerato-conjunctivitis	Randomized, double-blind	Ciclosporin 2% eyedrops, 1 drop [0.8 mg] qid in 1 eye + Placebo eyedrops, 1 drop qid in the other eye x 2 wk → Ciclosporin 2% eyedrops, 1 drop [0.8 mg] qid in both eyes x 14 wk	24	Ciclosporin eyedrops were safe and significantly effective in children with vernal keratoconjunctivitis	2
Kerato-conjunctivitis	Randomized, double-blind, multicenter	Ciclosporin 0.05% eyedrops bid x 1 y Ciclosporin 0.1% eyedrops bid x 1 y Placebo x 6 mo → Ciclosporin 0.1% eyedrops bid x 6 mo	128	Systemic exposure to ciclosporin after long-term treatment was not quantifiable or low in patients with dry eye syndrome	3

double-blind phase III trial. In an additional phase, patients continued their ciclosporin regimens or were crossed over from vehicle to ciclosporin 0.1% for 6 months. Blood sample analysis showed that systemic exposure to ciclosporin after treatment with therapeutically effective doses was not quantifiable at the lower concentration. It was not quantifiable in 121 of 128 blood samples from patients given the 0.1% concentration and was otherwise low (3).

The topical administration of a composition comprising a macrolide IL-2 inhibitor, such as ciclosporin or FK-506 or pharmaceutically acceptable salts thereof, and a quinolone antimicrobial agent has been claimed for the treatment of inflammatory conditions and/or infections such as allergic conjunctivitis, allergic dermatitis and allergic rhinitis (4).

1. *Restasis receives FDA approval*. DailyDrugNews.com (Daily Essentials) Jan 7, 2003.

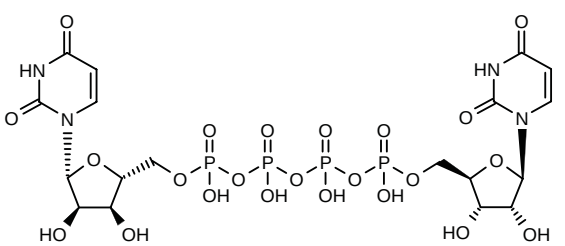
2. Pucci, N., Novembre, E., Cianferoni, A., Lombardi, E., Bernardini, R., Caputo, R., Campa, L., Vierucci, A. *Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis*. Ann Allergy Asthma Immunol 2002, 89(3): 298.

3. Small, D.S., Acheampong, A., Reis, B. et al. *Blood concentrations of cyclosporin A during long-term treatment with cyclosporin A ophthalmic emulsions in patients with moderate to severe dry eye disease*. J Ocular Pharmacol Ther 2002, 18(5): 411.

4. Ueno, R. (Sucampo Pharma AG). *Compsn. for topical administration*. WO 0304098.

Original monograph - Drugs Fut 1979, 4(8): 567.

Diquafosol Tetrasodium



Diquafosol tetrasodium (INS-365 Ophthalmic) is a $P2Y_2$ receptor agonist developed at Inspire as a treatment for dry eye syndrome, or keratoconjunctivitis sicca. Following a pre-NDA meeting with the FDA held on January 6, 2003, Inspire announced that it will submit an NDA for diquafosol for the treatment of dry eyes around mid-year. In phase II and III trials including approximately 1,200 patients, diquafosol ophthalmic solution demonstrated statistically significant improvements compared to placebo in corneal staining, further supported by statistically significant improvements in conjunctival staining, and excellent safety and tolerability were reported (1, 2). Inspire and Allergan entered into a partnership agreement in 2001 relating to diquafosol tetrasodium outside Asia and Santen holds rights to the product in Japan and certain other Asian markets.

A recent study reported the efficacy of diquafosol *in vivo* in stimulating mucin-like glycoprotein release and protecting against desiccation-induced corneal damage in normal rabbit eyes. At 2-15 min after treatment with the agent (8.5% w/v, 50 mcl into the conjunctival sac), an approximate 44% reduction in the area of conjunctival goblet cells staining positive was observed, indicating increased secretion of mucin-like glycoproteins from cells; dose-dependent reductions (0.001-0.1% w/v) were seen, with a maximum reduction at 5 min postdosing of approximately 40%. Diquafosol (0.1-1% w/v) also significantly inhibited desiccation-induced corneal damage. These results indicate that diquafosol may be effective in the treatment of dry eye syndrome (3).

Phase III results for diquafosol in dry eye syndrome have shown a highly statistically significant improvement over placebo for the primary objective endpoint of corneal staining. The 6-month, multicenter, double-masked trial compared diquafosol 1 and 2% eyedrops to placebo in 527 patients across 34 U.S sites. Diquafosol 2% showed a highly statistically significant improvement in corneal staining as early as 2 weeks, at the primary 6-week endpoint and consistently throughout the 24-week study. There was also a statistically significant improvement in the secondary endpoint of conjunctival staining. The results were consistent with those achieved in a previous

phase II study. The primary subjective endpoint, clearing of the ocular symptom of foreign body sensation at week 6, did not reach, but approached, statistical significance. The number of patients who cleared foreign body sensation was consistently higher on treatment compared to placebo throughout the study. There was a statistically significant improvement in this endpoint for the study drug at other time points for the greater than 80% of patients who complied with the protocol. Diquafosol was also associated with statistically significant improvements in other ocular symptoms at multiple time points and had an excellent safety profile (4).

1. *Inspire prepares to submit NDA for diquafosol by mid-2003*. DailyDrugNews.com (Daily Essentials) Jan 14, 2003.

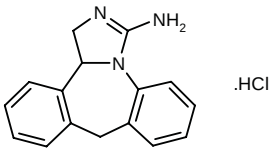
2. *Inspire plans to file INS-365 Ophthalmic NDA based on existing data*. DailyDrugNews.com (Daily Essentials) Oct 31, 2002.

3. Fujihara, T., Murakami, T., Nagano, T., Nakamura, M., Nakata, K. *INS365 suppresses loss of corneal epithelial integrity by secretion of mucin-like glycoprotein in a rabbit short-term dry eye model.* J Ocular Pharmacol Ther 2002, 18(4): 363.

4. *Phase III results announced for INS-365 Ophthalmic in dry eye*. DailyDrugNews.com (Daily Essentials) June 19, 2002.

Original monograph - Drugs Fut 1999, 24(7): 759.

Epinastine Hydrochloride



Epinastine hydrochloride is a histamine H_1 receptor antagonist which is marketed as an oral formulation by Boehringer Ingelheim for the treatment of seasonal allergies under the trade names Flurinol® and Alesion®. Allergan holds the rights to develop and commercialize ophthalmic formulations for ocular allergy and has just received European approval to market the drug as Relestat™ (ophthalmic solution, 0.05%) for this indication, with launch anticipated in the fourth quarter of 2003.

Preclinical safety studies on epinastine ophthalmic solution (0.05-0.5% t.i.d. for 6 months) were carried out in rabbits and monkeys. Treatment was well tolerated, with no ocular or systemic toxicity or drug-related adverse events observed. Pharmacokinetic parameters indicated very low and dose-dependent systemic exposure (1).

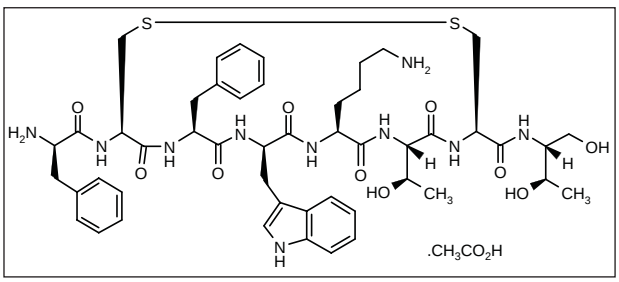
Epinastine showed promise as a treatment for allergic conjunctivitis in a double-blind, vehicle-controlled phase III trial. The severity of ocular itching, conjunctival hyperemia, ciliary and episcleral hyperemia, chemosis and lid swelling was significantly reduced at all time points following treatment with epinastine. No adverse events were observed (2).

1. Brar, B., Vangyi, C., Tarlo, K., Short, B. *Preclinical safety of ophthalmic epinastine in rabbits and monkeys*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 108.

2. Schiffman, R.M., Abelson, M.B., Crampton, H.J., Slugg, A.P., Michaelson, C., Bradford, R.R., Kim, B., Lue, J.C., Whitcup, S.M. *Efficacy and safety of ophthalmic epinastine evaluated using the conjunctival antigen challenge model in patients with a history of allergic conjunctivitis*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 107.

Original monograph - Drugs Fut 1987, 12(12): 1106.

Octreotide Acetate



Octreotide acetate (injectable suspension; Sandostatin®, Sandostatin LAR®) is currently marketed by Novartis for various indications, including the control of symptoms in patients with metastatic carcinoid and vasoactive intestinal peptide-secreting tumors (VIPomas) and for the treatment of acromegaly. The company is also developing the depot formulation Sandostatin LAR® for diabetic retinopathy.

A study in guinea pigs evaluated the protective effects of melatonin, vitamin E and octreotide in the retina during ischemia-reperfusion. A total dose of 10 mg/kg melatonin, 150 mg/kg vitamin E and 22 μg/kg octreotide was administered 5 min prior to retinal ischemia for 1.5 h and at 6, 12 and 18 h during 24 h of reperfusion. Melatonin offered the most protection against retinal damage due to ischemia-reperfusion and all three agents

significantly protected against malondialdehyde formation (1, 2).

In a mouse model of oxygen-induced retinopathy, Woc4D (50 μg/kg/day s.c.) and octreotide (20 μg/kg/day s.c. b.i.d.) equally inhibited retinal neovascularization. Both agents decreased blood vessel tufts and markedly reduced oxygen-induced elevated growth hormone mRNA expression, without affecting body weight. The results support the use of somatostatin analogues in the treatment of retinopathy (3).

Using a guinea pig model of retinal ischemia-reperfusion injury, the effect of octreotide (50 μg/kg i.p.) on nitric oxide (NO) activity was evaluated. Mean retinal nitrate levels in the control, ischemia and ischemia + octreotide groups were 157.6 ± 25.2, 106.4 ± 20.1 and 96.4 ± 17.7 μmol/l, respectively. Retinal histopathological changes induced during ischemia-reperfusion were not significantly affected by octreotide treatment compared with the control group. The results indicate that octreotide treatment is without effect on NO activity in the retina (4).

To investigate the effect of octreotide on retinal lipid peroxidation and histopathological changes during ischemia-reperfusion (I/R), guinea pigs were administered 10 μg/kg at 6-h intervals starting 15 min prior to an ischemic assault and 24 h of reperfusion. Significant increases in the levels of retinal malondialdehyde and the thickness of the overall retina, inner retina, ganglion cell layer, inner plexiform layer and inner nuclear layer induced by ischemia were prevented by treatment with octreotide. It was concluded that octreotide may have potential as an alternative therapeutic in retinal diseases involving I/R injury (5).

1. Celebi, S., Dilsiz, N., Yilmaz, T., Kukner, S. *Effects of melatonin, vitamin E and octreotide on lipid peroxidation during ischemia-reperfusion in the guinea pig retina*. Eur J Ophthalmol 2002, 12(2): 77.

2. Yilmaz, T., Celebi, S., Kukner, A.S. *The protective effects of melatonin, vitamin E and octreotide on retinal edema during ischemia-reperfusion in the guinea pig retina*. Eur J Ophthalmol 2002, 12(6): 443.

3. Higgins, R.D., Yan, Y., Schrier, B.K. *Somatostatin analogs inhibit neonatal retinal neovascularization*. Exp Eye Res 2002, 74(5): 553.

4. Celiker, U., Ilhan, N. *Nitric oxide and octreotide in retinal ischemia-reperfusion injury*. Doc Ophthalmol 2002, 105(3): 327.

5. Celiker, U., Ilhan, N., Ozercan, I., Demir, T., Celiker, H. *Octreotide reduces ischaemia-reperfusion injury in the retina*. Acta Ophthalmol Scand 2002, 80(4): 395.

Original monograph - Drugs Fut 1984, 9(5): 342.

Pegaptanib Sodium

EyeTech Pharmaceuticals has completed patient enrollment ahead of schedule in two pivotal phase III trials of pegaptanib sodium (Macugen™, formerly EYE-001, NX-1838) for the treatment of exudative (wet) AMD. The trials enrolled 1,196 patients at 117 sites in the U.S., Canada, South America, Europe, Israel and Australia, and are evaluating vision stabilization and/or improvement associated with pegaptanib as stand-alone treatment or in combination with PDT in patients eligible for PDT. In the U.S., pegaptanib has fast track designation for the treatment of wet AMD and diabetic macular edema (DME). Phase II trials are also being conducted in DME. Pegaptanib is an aptamer that binds to and neutralizes vascular endothelial growth factor (VEGF). EyeTech acquired the rights to the aptamer from Gilead in 2000. The company recently entered into a joint development and commercialization agreement with Pfizer. In early clinical trials, it inhibited abnormal blood vessel growth, stabilized and/or reversed blood vessel leakage and improved vision by 3 lines or more in 26% of patients (1, 2).

Due to the invasive nature of delivering pegaptanib sodium via intravitreal injection, an alternative delivery method was proposed. Using an oil-in-oil solvent evaporation process, scientists have developed poly(lactic-co-glycolic)acid (PLGA) microspheres containing pegaptanib in the solid state and evaluated the stability and bioavailability of the microspheres. The PLGA microspheres exhibited controlled release of the drug at an average rate of 2 μg/day over 20 days and the retained activity of the drug was confirmed by the inhibition of endothelial cell proliferation following incubation with the microspheres. Furthermore, the delivery of pegaptanib through the sclera was confirmed following the application of the RNA aptamer-containing microspheres packed into a sealed chamber and placed onto the sclera of rabbits (3).

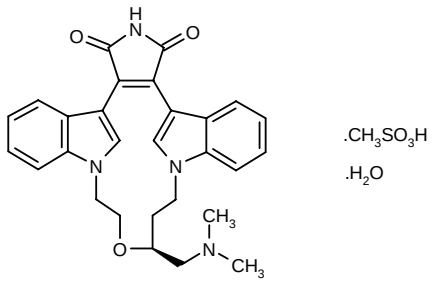
1. *EyeTech completes enrollment in two pivotal Macugen trials*. DailyDrugNews.com (Daily Essentials) Aug 12, 2002.

2. *Pfizer and Eyetech form collaboration to develop and commercialize Macugen*. DailyDrugNews.com (Daily Essentials) Dec 30, 2002.

3. Carrasquillo, K.G., Ricker, J.A., Rigas, I.K., Miller, J.W., Gragoudas, E.S., Adamis, A.P. *Controlled delivery of the anti-VEGF aptamer EYE001 with poly(lactic-co-glycolic) acid microspheres*. Invest Ophthalmol Visual Sci 2003, 44(1): 290.

Original monograph - Drugs Fut 2002, 27(9): 841.

Ruboxistaurin Mesilate Hydrate



A selective inhibitor of protein kinase C β (PKC-β), ruboxistaurin mesilate hydrate (LY-333531; Lilly) is in phase III clinical trials at Lilly for the treatment of macular edema and diabetic retinopathy.

Lilly has decided to delay the European submission for ruboxistaurin, which was planned for 2003, after results from two trials in these indications failed to meet their primary endpoints. In both trials, the overall rate of disease progression was much lower than expected in the placebo groups and this was reflected in the results. Despite this, in the diabetic macular edema trial, a prospectively defined analysis of the patients by the degree of their glucose control showed that patients with a baseline hemoglobin A1c of 11% or less experienced statistically significant and clinically important reductions in the time to progression to vision-threatening macular edema. Furthermore, in the diabetic retinopathy trial, the use of ruboxistaurin was associated with a decrease in the number of patients with sustained visual loss as measured by visual acuity assessment. Given these results, Lilly will begin additional registration trials this year to investigate ruboxistaurin for diabetic retinopathy and diabetic macular edema. The first European submission for ruboxistaurin will now be for the treatment of symptoms of diabetic peripheral neuropathy in 2004. Lilly also plans to make a U.S. submission in 2004 for this indication. Both will take place once ongoing phase III trials for diabetic peripheral neuropathy have been completed (1).

The *in vivo* effects of ruboxistaurin were examined in streptozotocin-diabetic rats which were treated with the compound at a dose of 10 mg/kg/day in the diet for 2 weeks following 6 weeks of diabetes. Treatment with the PKC-β inhibitor reversed the deficits in sciatic motor and saphenous nerve sensory conduction velocity and the reductions in sciatic nerve and superior cervical ganglion blood flow. Ruboxistaurin treatment also attenuated the diabetes-induced deficits in endothelium-dependent vasodilating responses to acetylcholine and phenylephrine in the mesenteric vascular bed. Furthermore, although ruboxistaurin had no effect on the mechanical hyperalgesia developing in the diabetic rats, it corrected the thermal hyperalgesia in these animals. These findings also provide solid evidence for the involvement of PKC-β in neural and vascular complications of diabetes (2).

The results from a study using human liver microsomes indicate that a single enzyme is responsible for the biotransformation of ruboxistaurin to *N*-desmethyl LY-333531, with a K_m value of 1 μM. Cytochrome CY3A4 appeared to be the most likely candidate, demonstrating a rate of *N*-desmethyl LY-333531 formation 57-fold greater than CYP2D6; the biotransformation was completely inhibited in the presence of ketoconazole, but not quinidine. Further studies revealed ruboxistaurin and *N*-desmethyl LY-333531 to completely inhibit CYP2D6, with respective K_i values of 0.17 and 1.0 μM (3).

The disposition of ruboxistaurin was found to be similar in rats and dogs following oral dosing. For both species, the primary route of elimination was in the feces: at least 90% of the administered dose was eliminated via this route by 120 and 96 h in rats and dogs, respectively. Following a single oral dose of 5 mg/kg to rats and dogs, C_{max} values were 14.7 and 245 ± 94 ng/ml, AUC values were 60.8 and 1419 ± 463 ng/h/ml, and $t_{1/2}$ values were 2.5 and 5.7 h, respectively (4).

1. *Lilly's E.U. submission for ruboxistaurin delayed by phase III trial results*. DailyDrugNews.com (Daily Essentials) Dec 19, 2002.

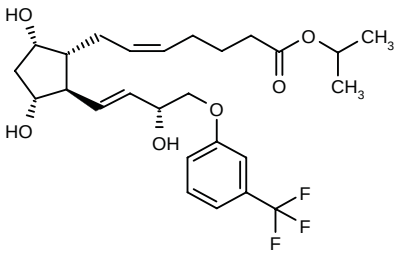
2. Cotter, M.A., Jack, A.M., Cameron, N.E. *Effects of the protein kinase C beta inhibitor LY333531 on neural and vascular function in rats with streptozotocin-induced diabetes*. Clin Sci 2002, 103(3): 311.

3. Ring, B.J., Gillespie, J.S., Binkley, S.N., Campanale, K.M., Wrighton, S.A. *The interactions of a selective protein kinase C beta inhibitor with the human cytochromes P450*. Drug Metab Dispos 2002, 30(9): 957.

4. Burkey, J.L., Campanale, K.M., O'Bannon, D.D., Cramer, J.W., Farid, N.A. *Disposition of LY333531, a selective protein kinase C beta inhibitor, in the Fischer 344 rat and beagle dog*. Xenobiotica 2002, 32(11): 1045.

Original monograph - Drugs Fut 2000, 25(10): 1017.

Travoprost



Since the last report, Alcon has launched its prostaglandin $PGF_{2\alpha}$ analogue and full FP receptor agonist travoprost (Travatan® ophthalmic solution) in Germany for reducing elevated IOP as monotherapy or adjunctive therapy in patients with ocular hypertension or open-angle glaucoma who are intolerant of or insufficiently responsive to another IOP-lowering medication. Travoprost is also available in the U.S. and the U.K (1).

An *in vitro* study characterized the agonist activity of several prostaglandin FP receptor agonists at an FP receptor cloned from human ciliary body. The most potent agonist was travoprost acid (EC_{50} = 3.2 ± 0.6 nM) followed by bimatoprost free acid (EC_{50} = 5.8 ± 2.6 nM), fluprostenol (EC_{50} = 6.1 ± 1.5 nM) and latanoprost free acid (EC_{50} = 54.6 ± 12.4 nM); both unoprostone and S-1033 were significantly weaker than travoprost acid. The amide prodrug of bimatoprost displayed intermediate potency (EC_{50} = 126 ± 347 nM) and agonist activity was observed with the isopropyl ester prodrugs of travoprost (EC_{50} = 42.3 ± 6.7 nM), latanoprost (EC_{50} = 126 ± 347 nM) and unoprostone (EC_{50} = 9100 ± 2870 nM). PGI_2, bradykinin, histamine and 5-HT had no effect. AL-8810, an FP receptor antagonist, reversed the agonist activity of bimatoprost, unoprostone, fluprostenol and travoprost acid and latanoprost acid (2).

The functional activity of bimatoprost, travoprost, unoprostone and other prostaglandin FP receptor-selective agonists was demonstrated in human trabecular meshwork cells. Concentration-dependent turnover of [^{3}H]-inositol phosphates was demonstrated, with a decreasing order of potency (EC_{50}) of: travoprost acid (2.4 nM), cloprostenol (4.5 nM), (±)-fluprostenol (10.8 nM), latanoprost (34.7 nM), bimatoprost acid (112 nM), $PGF_{2\alpha}$ (120 nM), unoprostone (3280 nM) and S-1033 (4570 nM). Rapid, concentration-dependent increases in intracellular Ca^{2+} mobilization were also observed with travoprost acid, $PGF_{2\alpha}$, unoprostone and S-1033 (3).

Analysis of results from 132 black patients of 596 patients with open-angle glaucoma or ocular hypertension entered into a randomized, double-blind phase III trial indicated that the patients treated with travoprost 0.004% or 0.0015%, in comparison to latanoprost 0.005% or timolol 0.5%, had the lowest mean IOP at 12 months, as well as a lower incidence of visual field progression. This may signify cost savings for travoprost over latanoprost and timolol in the black population (4). The results of this study and the following study are summarized in Table III.

Three patients with uncontrolled glaucoma treated with ocular hypotensive lipids (unoprostone, travoprost and bimatoprost) developed cystoid macular edema which resolved with steroid and antiinflammatory treatment and withdrawal of hypotensive lipids (5).

Travoprost 0.0015% and 0.004% once daily and timolol 0.5% b.i.d. were compared in a multicenter, randomized, double-blind phase III trial in 605 patients with open-angle glaucoma or ocular hypertension. Travoprost demonstrated superior IOP-lowering effects throughout this 6-month study (6).

1. *Another major launch for Alcon's prostaglandin analogue for glaucoma*. DailyDrugNews.com (Daily Essentials) July 15, 2002.

2. Sharif, N.A., Kelly, C.R., Crider, J.Y. *Agonist activity of bimatoprost, travoprost, latanoprost, unoprostone isopropyl ester and other prostaglandin analogs at the cloned human ciliary body FP prostaglandin receptor*. J Ocular Pharmacol Ther 2002, 18(4): 313.

Table III: Clinical studies of travoprost (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Open-angle glaucoma, ocular hypertension	Randomized, double-blind	Travoprost 0.004% or 0.0015%, od x 12 mo (n=49) Latanoprost 0.005%, od x 12 mo (n=43) Timolol 0.5%, bid x 12 mo (n=40)	132	The superior efficacy of travoprost in black patients with glaucoma or intraocular hypertension may translate into cost savings over latanaprost and timolol	4
Open-angle glaucoma, ocular hypertension	Randomized, double-blind, multicenter	Placebo (AM) → Travoprost 0.0015% od (PM) x 6 mo (n=202) Placebo (AM) → Travoprost 0.004% od (PM) x 6 mo (n=201) Timolol 0.5% bid x 6 mo (n=202)	605	Both concentrations of travoprost were safe and well tolerated and induced greater reductions in intraocular pressure than timolol in patients with open-angle glaucoma or ocular hypertension	6

3. Sharif, N.A., Kelly, C.R., Crider, J.Y. *Human trabecular meshwork cell responses induced by bimatoprost, travoprost, unoprostone, and other FP prostaglandin receptor agonist analogues*. Invest Ophthalmol Visual Sci 2003, 44(2): 715.

4. Halpern, M.T., Covert, D.W., Robin, A.L. *Projected impact of travoprost versus both timolol and latanoprost on visual field deficit progression and costs among black glaucoma subjects*. Trans Am Ophthalmol Soc 2002, 100: 109.

5. Wand, M., Gaudio, A.R. *Cystoid macular edema associated with ocular hypotensive lipids*. Am J Ophthalmol 2002, 133(3): 403.

6. Fellman, R.L., Sullivan, E.K., Ratliff, M., Silver, L.H., Whitson, J.T., Turner, F.D., Weiner, A.L., Davis, A.A. *Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: A 6-month, masked, multicenter trial*. Ophthalmology 2002, 109(5): 998.

Original monograph - Drugs Fut 2000, 25(1): 41.