Drugs Fut 2006, 31(7): 641-659

CCC: 0377-8282/2006

Update 2006 - Treatment of Ophthalmic Disorders

(Source: Prous Science Integrity®)

Treatment of Ophthalmic Disorders by Condition

Condition	Phase	Drug	Source
Cataract	II	*N*-Acetylcarnosine	Innovative Vision Products
	II	OT-551	Othera Pharmaceuticals
Conjunctivitis, allergic	III	Alcaftadine	Vistakon Pharmaceuticals (Johnson & Johnson)
	II	EV-131	Evolutec
	II	K-123	Kowa
	I	Oralgen® Grass Pollen	Fornix BioSciences
Conjunctivitis, infective	L-2006	Tosufloxacin tosilate[1,2,3]	Otsuka
	III	ISV-401	InSite Vision
Corneal ulcer	Prereg.	Eyprotor®	Lee's Pharmaceuticals
	II	KK-220	Kowa
Dry eye	Prereg.	Diquafosol tetrasodium	Inspire Pharmaceuticals/Allergan
	III	Ciclosporin[1,2,3]	Novagali Pharma
	III	Icomucret	Alcon
	III	Nova-23006/Nova-23033	Novagali Pharma
	III	Rebamipide[1,2]	Otsuka/Novartis
	II	Diquafosol tetrasodium	Santen
	II	Ecabet sodium[1,2,3]	ISTA Pharmaceuticals/Senju
	II	NP-50301	Nascent Pharmaceuticals
	II	Pimecrolimus[1,2,3]	Novartis
	II	Rimexolone[1,2]	Alcon
	I	Gefarnate[1,3]	Santen
	I	Moli-1901	Lantibio
Glaucoma	L-2006	Bimatoprost/timolol maleate	Allergan
	L-2006	Travoprost/timolol	Alcon
	III	Eyepass™	GMP Companies
	III	Memantine hydrochloride[1,2]	Allergan
	III	Tafluprost	Santen/Asahi Glass
	II	Iganidipine hydrochloride[2]	Senju/ISTA Pharmaceuticals
	II	ISV-205	InSite Vision
	II	Lomerizine hydrochloride[1,2]	Santen/Nippon Organon
	II	Olmesartan hydrate	Santen/Daichi Sankyo
	I	BVT-28949	Biovitrum
	I	MK-0987	Merck & Co.
	I	MK-0994	Merck & Co.
	I	Nova-21027	Novagali Pharma
	I	RKI-983	Senju/Novartis
	I	Y-39983	Senju/Novartis
Hyphema	III	Aminocaproic acid[1,3]	ISTA Pharmaceuticals/Eastern Virginia Medical School
Keratitis, bacterial	II	Levofloxacin/prednisolone acetate	Santen/Daichii Sankyo
Keratoconjunctivitis, vernal	L-2006	Ciclosporin[1,2]	Santen
Keratopathy, diabetic	III	Risarestat[2]	Senju
Macular degeneration	L-2005	Pegaptanib sodium[1,2]	EyeTech/Pfizer
	L-2006	Ranibizumab[2]	Genentech/Novartis Ophthalmics
	L-2006	Anecortave acetate[2]	Alcon

Continuation

Treatment of Ophthalmic Disorders by Condition

Condition	Phase	Drug	Source
Macular degeneration	Prereg.	Rostaporfin	Miravant
	III	Squalamine lactate	Genaera
	II	Bevasiranib sodium	Acuity Pharmaceuticals
	II	Celecoxib[1,2]	National Institutes of Health
	II	Combretastatin A-4 phosphate	OxiGene
	II	NT-501	Neurotech
	II	OT-551	Othera Pharmaceuticals/National Eye Institute
	I/II	Talaporfin sodium[1]	Light Sciences
	I/II	Vatalanib succinate	Novartis
	I	267268	GlaxoSmithKline
	I	AdPEDF.11	GenVec
	I	Sirna-027	Sirna Therapeutics
	I	VEGF Trap	Regeneron/sanofi-aventis
	IND Filed	ATG-003	Athenagen
Macular edema	III	Fluocinolone acetonide[1,3]	Alimera Sciences/pSivida
	III	Pegaptanib sodium[1,2]	EyeTech
	III	Posurdex®	Allergan/Sanwa
	II	Bevasiranib sodium	Acuity Pharmaceuticals
	II	Microplasmin	ThromboGenics/NuVue Technologies
	II	Ranibizumab[2]	Genentech/Novartis Ophthalmics
	II	Ruboxistaurin mesilate hydrate[2]	Lilly
	I/II	BDM-E	BioDiem
	I/II	SK-0503	Sanwa
	I	Triamcinolone acetonide[1,3]	SurModics
	Discontinued	Denufosol tetrasodium	Inspire Pharmaceuticals
Ocular hypertension	III	Tafluprost	Santen/Asahi Glass
	II	Olmesartan hydrate	Santen/Daichi Sankyo
Ocular inflammation	L-2005	Loteprednol etabonate/tobramycin	Bausch & Lomb
	L-2005	Nepafenac	Alcon
	III	Tobramycin/prednisolone acetate	ISTA Pharmaceuticals
Pseudovitellium detachment	II	Anecortave acetate[2]	Alcon
Retinal telangiectasia (Coat's disease)	II	Anecortave acetate2	Alcon
Retinal vein occlusion	II	Pegaptanib sodium[1,2]	EyeTech
Retinitis	I	NT-501	Neurotech
Retinopathy, diabetic	Prereg.	Ruboxistaurin mesilate hydrate[2]	Takeda/Lilly
	III	Candesartan cilexetil[1,2]	Takeda/AstraZeneca
	II	Hyaluronidase[1]	ISTA Pharmaceuticals
	II	Microplasmin	ThromboGenics/NuVue Technologies
	I	Anecortave acetate[2]	Alcon
Uveitis	L-2005	Fluocinolone acetonide[1,3]	Bausch & Lomb/Novartis Ophthalmics
	Prereg.	Difluprednate[1,3]	Senju/Sirion Therapeutics
	III	Etanercept[1,2]	National Eye Institute
Uveitis	II	Daclizumab[1]	National Eye Institute
Vitreous bleeding	Prereg.	Hyaluronidase[1]	ISTA Pharmaceuticals

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

Treatment of Ophthalmic Disorders by Source

Source	Condition	Drug	Phase
Acuity Pharmaceuticals	Macular degeneration	Bevasiranib sodium	II
	Macular edema	Bevasiranib sodium	II
Alcon	Dry eye	Icomucret	III
		Rimexolone[1,2]	II
	Glaucoma	Travoprost/timolol	L-2006
	Macular degeneration	Anecortave acetate[2]	L-2006
	Ocular inflammation	Nepafenac	L-2005
	Pseudovitellium detachment	Anecortave acetate[2]	II
	Retinal telangiectasia (Coat's disease)	Anecortave acetate[2]	II
	Retinopathy, diabetic	Anecortave acetate[2]	I
Alimera Sciences	Macular edema	Fluocinolone acetonide[1,3]	III
Allergan	Dry eye	Diquafosol tetrasodium	Prereg.
	Glaucoma	Bimatoprost/timolol maleate	L-2006
		Memantine hydrochloride[1,2]	III
	Macular edema	Posurdex®	III
Asahi Glass	Glaucoma	Tafluprost	III
	Ocular hypertension	Tafluprost	III
AstraZeneca	Retinopathy, diabetic	Candesartan cilexetil[1,2]	III
Athenagen	Macular degeneration	ATG-003	IND Filed
Bausch & Lomb	Ocular inflammation	Loteprednol etabonate/tobramycin	L-2005
	Uveitis	Fluocinolone acetonide[1,3]	L-2005
BioDiem	Macular edema	BDM-E	I/II
Biovitrum	Glaucoma	BVT-28949	I
Daichii Sankyo	Glaucoma	Olmesartan hydrate	II
	Keratitis, bacterial	Levofloxacin/prednisolone acetate	II
	Ocular hypertension	Olmesartan hydrate	II
Eastern Virginia Medical School	Hyphema	Aminocaproic acid[1,3]	III
Evolutec	Conjunctivitis, allergic	EV-131	II
EyeTech	Macular degeneration	Pegaptanib sodium[1,2]	L-2005
	Macular edema	Pegaptanib sodium[1,2]	III
	Retinal vein occlusion	Pegaptanib sodium[1,2]	II
Fornix BioSciences	Conjunctivitis, allergic	Oralgen® Grass Pollen	I
Genaera	Macular degeneration	Squalamine lactate	III
Genentech	Macular degeneration	Ranibizumab[2]	L-2006
	Macular edema	Ranibizumab[2]	II
GenVec	Macular degeneration	AdPEDF.11	I
GlaxoSmithKline	Macular degeneration	267268	I
GMP Companies	Glaucoma	Eyepass™	III
Innovative Vision Products	Cataract	*N*-Acetylcarnosine	II
InSite Vision	Conjunctivitis, infective	ISV-401	III
	Glaucoma	ISV-205	II
Inspire Pharmaceuticals	Dry eye	Diquafosol tetrasodium	Prereg.
		Ecabet sodium[1,2,3]	II
ISTA Pharmaceuticals	Glaucoma	Iganidipine hydrochloride[2]	II
	Hyphema	Aminocaproic acid[1,3]	III
	Macular edema	Denufosol tetrasodium	Discontinued
	Ocular inflammation	Tobramycin/prednisolone acetate	III
	Retinopathy, diabetic	Hyaluronidase[1]	II
	Vitreous bleeding	Hyaluronidase[1]	Prereg.
Kowa	Conjunctivitis, allergic	K-123	II
	Corneal ulcer	KK-220	II
Lantibio	Dry eye	Moli-1901	I
Lee's Pharmaceuticals	Corneal ulcer	Eyprotor®	Prereg.
Light Sciences	Macular degeneration	Talaporfin sodium[1]	I/II
Lilly	Macular edema	Ruboxistaurin mesilate hydrate[2]	II
	Retinopathy, diabetic	Ruboxistaurin mesilate hydrate[2]	Prereg.
Merck & Co.	Glaucoma	MK-0987	I
		MK-0994	I
Miravant	Macular degeneration	Rostaporfin	Prereg.
Nascent Pharmaceuticals	Dry eye	NP-50301	II
National Eye Institute	Macular degeneration	OT-551	II
	Uveitis	Daclizumab[1]	II
		Etanercept[1,2]	III
National Institutes of Health	Macular degeneration	Celecoxib[1,2]	II
Neurotech	Macular degeneration	NT-501	II

Continuation

Treatment of Ophthalmic Disorders by Source

Source	Condition	Drug	Phase
Neurotech	Retinitis	NT-501	INippon
Organon	Glaucoma	Lomerizine hydrochloride[1,2]	II
Novagali Pharma	Dry eye	Ciclosporin[1,2,3]	III
		Nova-23006/Nova-23033	III
	Glaucoma	Nova-21027	I
Novartis	Dry eye	Pimecrolimus[1,2,3]	II
		Rebamipide[1,2]	III
	Glaucoma	RKI-983	I
		Y-39983	I
	Macular degeneration	Vatalanib succinate	I/II
Novartis Ophthalmics	Macular degeneration	Ranibizumab[2]	L-2006
	Macular edema	Ranibizumab[2]	II
	Uveitis	Fluocinolone acetonide[1,3]	L-2005
NuVue Technologies	Macular edema	Microplasmin	II
	Retinopathy, diabetic	Microplasmin	II
Othera Pharmaceuticals	Cataract	OT-551	II
	Macular degeneration	OT-551	II
Otsuka	Conjunctivitis, infective	Tosufloxacin tosilate[1,2,3]	L-2006
	Dry eye	Rebamipide[1,2]	III
OxiGene	Macular degeneration	Combretastatin A-4 phosphate	II
Pfizer	Macular degeneration	Pegaptanib sodium[1,2]	L-2005
pSivida	Macular edema	Fluocinolone acetonide[1,3]	III
Regeneron	Macular degeneration	VEGF Trap	I
Sanofi-aventis	Macular degeneration	VEGF Trap	I
Santen	Dry eye	Diquafosol tetrasodium	II
		Gefarnate[1,3]	I
	Glaucoma	Lomerizine hydrochloride[1,2]	II
		Olmesartan hydrate	II
		Tafluprost	III
	Keratitis, bacterial	Levofloxacin/prednisolone acetate	II
	Keratoconjunctivitis, vernal	Ciclosporin[1,2]	L-2006
	Ocular hypertension	Olmesartan hydrate	II
		Tafluprost	III
Sanwa	Macular edema	Posurdex®	III
		SK-0503	I/II
Senju	Dry eye	Ecabet sodium[1,2,3]	II
	Glaucoma	Iganidipine hydrochloride[2]	II
		RKI-983	I
		Y-39983	I
	Keratopathy, diabetic	Risarestat[2]	III
	Uveitis	Difluprednate[1,3]	Prereg.
Sirion Therapeutics	Uveitis	Difluprednate[1,3]	Prereg.
Sirna Therapeutics	Macular degeneration	Sirna-027	I
SurModics	Macular edema	Triamcinolone acetonide[1,3]	I
Takeda	Retinopathy, diabetic	Candesartan cilexetil[1,2]	III
		Ruboxistaurin mesilate hydrate[2]	Prereg.
ThromboGenics	Macular edema	Microplasmin	II
	Retinopathy, diabetic	Microplasmin	II
Vistakon Pharmaceuticals (Johnson & Johnson)	Conjunctivitis, allergic	Alcaftadine	III

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

Drugs Under Development for the Treatment of Ophthalmic Disorders

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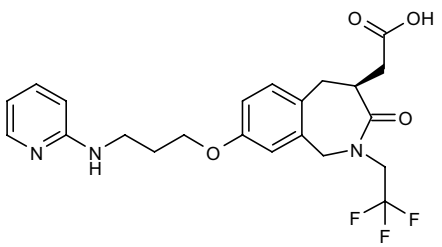
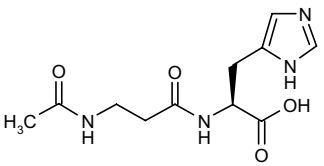
267268



267268, a vitronectin ($\alpha_v\beta_3$ integrin) antagonist, is currently undergoing phase I clinical trials at GlaxoSmithKline for the treatment of age-related macular degeneration (AMD).

N-Acetylcarnosine

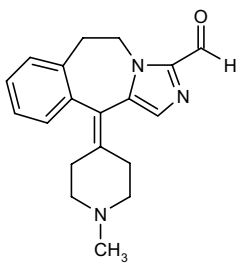


N-Acetylcarnosine is an antioxidant in phase II clinical trials at Innovative Vision Products for the treatment of cataracts. The drug candidate possesses the ability to protect cells from oxidative stress, both in the lipid phase of cellular membranes and in the aqueous environment. *N*-Acetylcarnosine, a prodrug of the antioxidant L-carnosine, acts in the aqueous humor of the eye, where it scavenges tryptophan/kynurenine and ascorbate radicals. It also partially cleaves the lifelong cross-linking (glycosylation) of lens proteins due to ascorbate, and is subsequently flushed out via Schlemm's canal. The compound has also demonstrated significant resistance to carnosinase hydrolysis.

AdPEDF.11

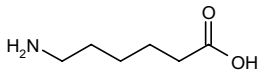
AdPEDF.11 is an angiogenesis inhibitor in early clinical trials at GenVec for the treatment of wet AMD. The drug candidate uses GenVec's proprietary adenovector, a DNA carrier, to deliver the human pigment epithelium-derived factor (*PEDF*) gene to the affected eye. PEDF is normally produced in the eye and serves two important functions: regulation of blood vessel growth and photoreceptor neuroprotection. AdPEDF.11 has also been studied for the treatment of diabetic retinopathy.

Alcaftadine



The histamine H_1 receptor antagonist alcaftadine is in phase III clinical trials at Vistakon Pharmaceuticals, a division of Johnson & Johnson Vision Care, for the treatment of allergic conjunctivitis.

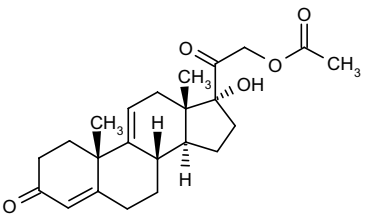
Aminocaproic Acid, New Indication/Formulation



Aminocaproic acid is a plasminogen activator inhibitor (PAI) that was launched by Xanodyne as Amicar® over

40 years ago for the treatment of excessive bleeding resulting from systemic hyperfibrinolysis and urinary fibrinolysis. A new topical gel formulation, Caprogel®, is currently undergoing phase III trials at ISTA Pharmaceuticals and Eastern Virginia Medical School for the topical treatment of traumatic hyphema of the eye. Results from *in vitro* studies indicate that the primary action of aminocaproic acid is inhibition of the activation of profibrinolysin, but that it also inhibits the action of fibrinolysin (plasmin). In low concentrations, the compound can inhibit the *in vitro* activation of human and bovine profibrinolysin by streptokinase, urokinase, and probably fibrinokinase. At higher concentrations, the drug inhibits the proteolytic activity of fibrinolysin and trypsin. Aminocaproic acid was originally developed at Wyeth Pharmaceuticals and was subsequently licensed to Eastern Virginia Medical School. In May 2002, the latter licensed the drug to ISTA Pharmaceuticals. Aminocaproic acid holds FDA orphan drug designation for the topical treatment of traumatic hyphema of the eye.

Anecortave Acetate



Anecortave acetate, presented as a suspension for depot injection, is an angiogenesis inhibitor developed by Alcon and launched in 2006 as Retaane® in Australia for the treatment of AMD. Alcon withdrew the MAA filed in 2004 in the E.U. for anecortave, stating research and development and marketing strategies as reasons for the withdrawal. The drug, an angiostatic cortisene derived from the steroid class, is engineered to remove chemical groups responsible for adverse effects, such as the development of cataracts and elevated intraocular pressure (IOP) leading to glaucoma. It is administered via a blunt-tipped, curved cannula which delivers the drug behind the eye without the risk of puncturing the eyeball. Preclinical studies suggest that the antiangiogenic effects of anecortave may be the result of significant downregulation of the expression of the matrix metalloproteinases MMP-2 and MMP-9. Phase II clinical trials are under way at the company for the treatment of retinal telangiectasia (Coat's disease) and pseudovitellium detachment. Phase I clinical trials are also ongoing for diabetic retinopathy.

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

ATG-003

Athenagen has filed an IND seeking approval to begin clinical evaluation of ATG-003 for the treatment of neovascular AMD. The drug candidate is a nicotinic receptor antagonist that works by inhibiting the angiogenesis that is characteristic of macular degeneration.

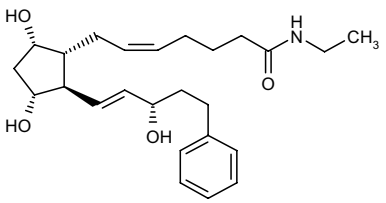
BDM-E

BDM-E is a small synthetic peptide under development at BioDiem for the treatment of retinal eye disease. Phase I/II clinical trials are under way for the s.c. treatment of diabetic macular edema. Preclinical studies are also evaluating the compound's potential for the treatment of AMD. *In vitro*, BDM-E has been shown to stimulate the growth of new retinal pigmented epithelial cells and inhibit the growth of choroidal endothelial cells associated with unwanted neovascularization.

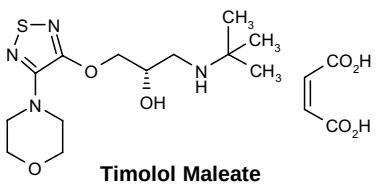
Bevasiranib Sodium

The VEGF inhibitor bevasiranib sodium (formerly Cand5), a first-in-class small interfering RNA (siRNA) therapeutic, is in phase II clinical trials at Acuity Pharmaceuticals for the treatment of wet AMD and diabetic macular edema by direct injection into the back of the eye. Research has shown that the VEGF protein is a factor in the development of abnormal blood vessels in eyes with wet AMD. Bevasiranib reduces the production of VEGF by a newly discovered technology known as RNA interference. The drug has been shown to reduce VEGF in human retinal pigment epithelial cells and to slow the growth and leakage of abnormal blood vessels in disease models of wet AMD.

Bimatoprost/Timolol Maleate



Bimatoprost



Timolol Maleate

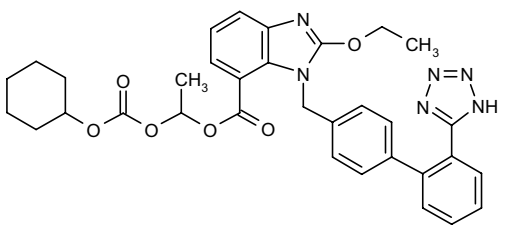
The combination bimatoprost/timolol maleate was launched by Allergan n the U.K. as Ganfort earlier this year and has been preregistered in the U.S. for the reduction of IOP in patients with glaucoma or ocular hypertension. In March 2006, the Committee for Medicinal Products for Human Use (CHMP) recommended approval in the E.U. Bimatoprost is a synthetic structural

analogue of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances known as prostamides. The analogue is believed to lower IOP in humans by increasing aqueous humor outflow through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Timolol is a nonselective β_1- and β_2-adrenoceptor blocker. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous humor formation. In some studies, a slight increase in outflow facility was also observed.

BVT-28949

Biovitrum is conducting early clinical trials with BVT-28949, a 5-HT_{2A} receptor antagonist for the treatment of glaucoma. The drug candidate, formulated as eyedrops, is designed to reduce IOP by increasing aqueous humor outflow.

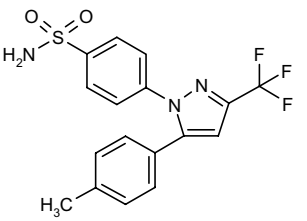
Candesartan Cilexetil, New Indication



Candesartan cilexetil, an angiotensin AT_1 receptor blocker, was launched in 1997 in several European countries by AstraZeneca and Takeda for the oral treatment of hypertension. In 2004, the drug was approved for both hypertension and chronic heart failure (CHF) in the E.U., and approval in the U.S. and Japan for CHF was granted in 2005. In terms of current clinical development, candesartan cilexetil is undergoing phase III trials for the treatment of diabetic retinopathy and phase II trials for the treatment of diabetic nephropathy. AstraZeneca is also evaluating in phase III clinical trials the effectiveness of candesartan in reducing the risk of death or major vascular events in patients with acute stroke and elevated blood pressure, and phase II trials are under way for the treatment of cluster headache. Originally developed by Takeda, candesartan cilexetil is now being developed and marketed in collaboration with AstraZeneca, which holds exclusive marketing rights to the product in certain European countries, Australia, Canada and the U.S. Candesartan cilexetil is currently approved for use in the once-daily treatment of hypertension in 50 countries and is commercially available in 25 countries.

Original monograph – Drugs Fut 1993, 18(7): 609.

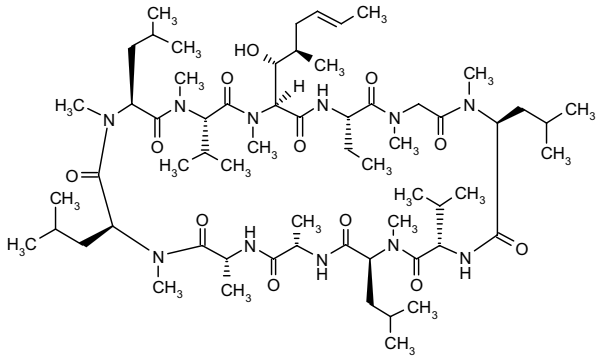
Celecoxib, New Indication



The nonsteroidal antiinflammatory drug (NSAID) celecoxib was launched by Pfizer in 1999 in the U.S. for the treatment of rheumatoid arthritis, osteoarthritis and familial adenomatous polyposis. The drug was launched again by Pfizer in 2002 for the treatment of dysmenorrhea and pain, and was approved there for the treatment of ankylosing spondylitis in 2005. At present, Astellas Pharma is awaiting approval in Japan for the treatment of lower back pain. Celecoxib is in phase III clinical trials at Pfizer for the treatment of urethral colic, and at the European Organization for Research and Treatment of Cancer (EORTC) for the treatment of colorectal cancer. The drug is being studied extensively by the U.S. National Cancer Institute (NCI), including phase III trials for the treatment of oral and salivary gland cancer, phase II/III trials for bladder cancer and actinic keratosis, phase II trials for the treatment of metastatic colorectal cancer, solid tumors, non-small cell lung cancer (NSCLC; in collaboration with Cornell University) and glioblastoma multiforme, and phase I trials for the treatment of cancer-related cachexia. The National Institutes of Health (NIH) is evaluating the potential of the drug in phase II trials for the treatment of macular degeneration, and clinical trials are under way at the M.D. Anderson Cancer Center for the treatment of lung cancer. The mechanism of action of celecoxib is believed to be inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans the compound does not inhibit the cyclooxygenase-1 (COX-1) isozyme. Originally developed at Searle (now Pfizer), Yamanouchi (now Astellas Pharma) obtained rights to the drug pursuant to a co-development agreement signed in April 1996. In October 2000, celecoxib received orphan drug designation for the treatment of familial adenomatous polyposis. Currently, the drug is being distributed by Pfizer in Canada, France, Germany, Italy, the U.K. and the U.S.

Original monograph – Drugs Fut 1997, 22(7): 711.

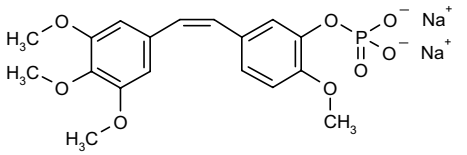
Ciclosporin, New Indication/Formulation



Ciclosporin is a potent immunosupressant that has been available for more than 20 years for the prevention of graft rejection following kidney, liver, heart, heart-lung, lung, pancreas or bone marrow transplantation and for the prevention and treatment of graft-*versus*-host disease (GVHD). The drug is also indicated for the treatment of severe atopic dermatitis, steroid-dependent or resistant nephrotic syndrome, severe psoriasis, severe rheumatoid arthritis refractory to other agents and general immunosuppression. In 2003, ciclosporin was launched jointly by Allergan and Inspire Pharmaceuticals in the U.S. for the treatment of the underlying inflammation associated with dry eye, and in 2006 it was introduced by Santen in Japan as Papilock for the treatment of vernal keratoconjunctivitis. Currently, the drug is preregistered in the U.S. and the E.U. for the prevention of chronic allogeneic lung transplant rejection in an aerosolized formulation. A regulatory application has also been filed in Japan seeking approval for the treatment of myasthenia gravis. Phase II clinical trials are under way at the NCI for the treatment of chemotherapy/radiotherapy-induced cytopenia in patients with myelodysplastic syndromes and for the treatment of cancer-associated disorders in patients with T-cell large granular lymphocytic leukemia. Ciclosporin is a cyclic polypeptide immunosuppressant consisting of 11 amino acids. It is produced as a metabolite by the fungal species *Beauveria nivea*. *In vivo*, the compound binds to cyclophillin. This complex then inhibits calcineurin, which is normally responsible for activating the transcription of IL-2. The drug inhibits lymphokine production and release, including IL-2 and T-cell growth factor (TCGF), alleviating the inflammatory symptoms of many disorders. The drug is also a potent immunosuppressive agent. Experimental evidence suggests that the effectiveness of the drug is due to specific and reversible inhibition of immunocompetent lymphocytes in the G0 or G1 phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Ciclosporin was originally developed at Novartis and was subsequently licensed to Allergan in the U.S., Santen in Japan and Recordati in Italy. In August 1999, the compound was designated an orphan drug in Japan for the treatment of vernal keratoconjunctivitis that cannot be adequately controlled by antiallergic drugs. In July 2001, Allergan and Inspire Pharmaceuticals agreed to a licensing, development and marketing agreement, giving Inspire the right to co-promote ciclosporin in the U.S. Allergan went on to sign a promotion agreement with NPS Pharmaceuticals in April 2003. Chiron, in April 2003, acquired exclusive development and commercialization rights from Novartis to aerosolized ciclosporin. Novagali Pharma also developed a proprietary cationic emulsion using its Novasorb™ technology platform, enabling an optimal penetration of the drug in tissues of the eye surface. Nova-22007 is in phase III clinical testing in Sjögren's patients with moderate to severe dry eye.

Original monograph – Drugs Fut 1982, 7(3): 591.

Combretastatin A-4 Phosphate



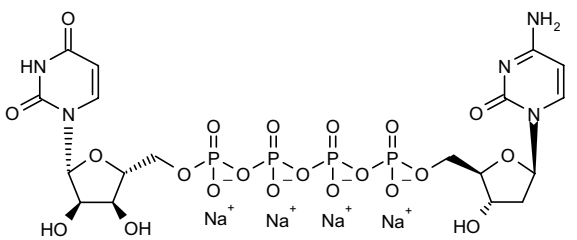
A phosphate prodrug of combretastatin A-4, combretastatin A-4 phosphate (CA4P) is a vascular targeting agent under development by OxiGene for several indications. CA4P, one of several compounds licensed from Arizona State University in 1997, was originally derived from the root bark of the *Combretum caffrum* tree, also known as the Cape bushwillow. CA4P, which is rapidly converted to the active compound in the bloodstream, enters the endothelial cells of tumor-associated blood vessels, where it affects the microtubules that form the cytoskeleton of the endothelial cells lining the tumor vasculature. When this tubulin structure is disrupted, the endothelial cells change shape from flat to round, stopping blood flow through the capillary, starving the tumor of nutrients and causing tumor cell death. This mechanism of action differentiates CA4P from angiogenesis inhibitors, which are designed to work by preventing the growth of sprouting new blood vessels. The company is evaluating CA4P in phase III trials in patients with inoperable stage IIIB/IV NSCLC, a subset of patients not deemed suitable for curative treatment with concurrent radiotherapy. OxiGene is studying CA4P in phase II trials as monotherapy for the treatment of anaplastic thyroid cancer. The company is also evaluating combination therapy of CA4P with other chemotherapeutic agents in phase I/II for the treatment of anaplastic thyroid cancer and advanced ovarian cancer and in phase II for the treatment of breast and lung cancer. A phase I/II trial is under way with CA4P in combination with the iodine-labeled antibody A5B7 for the treatment of gastrointestinal and

colorectal cancer. Additional phase I/II trials include CA4P in combination with radiotherapy for the treatment of head and neck cancer and prostate cancer. Phase II trials are under way as monotherapy for the treatment of myopic macular degeneration. Oxigene is also evaluating the drug in early clinical studies as monotherapy for cervical cancer and in combination with carboplatin and paclitaxel for the treatment of solid tumors. Preclinical studies are under way at the company with CA4P in combination with bevacizumab for the treatment of colorectal cancer. In 2003, CA4P was granted orphan drug designation by the FDA for the treatment of anaplastic thyroid cancer, medullary thyroid cancer and stage IV papillary or follicular thyroid cancer, and in 2006 it was granted orphan drug designation for the treatment of ovarian cancer.

Daclizumab, New Indication

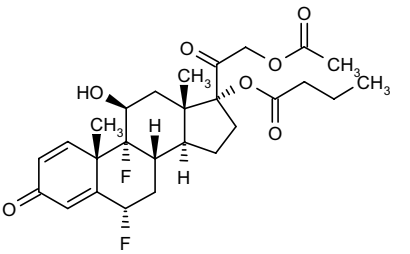
Daclizumab is a humanized monoclonal antibody that binds to the IL-2 receptor (α subunit, CD25) on activated T-cells and inhibits IL-2-mediated activation of lymphocytes, preventing the activation of the inflammatory cytokine response common to transplant rejection and autoimmune and inflammatory diseases. Daclizumab was first approved in December 1997 by the FDA as Zenapax® for use in combination with ciclosporin and corticosteroids to prevent acute organ rejection in kidney transplant patients. The antibody was originally created by Protein Design Labs, which licensed it to Roche for co-development and worldwide marketing. The antibody is in phase II evaluation at Protein Design Labs and Roche for the treatment of asthma. Protein Design Labs and Biogen Idec are also conducting phase II clinical trials of daclizumab for the treatment of multiple sclerosis. The National Eye Institute is conducting several phase I and II studies for the treatment of uveitis.

Denufosol Tetrasodium



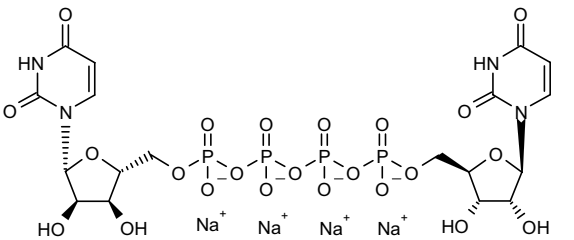
Denufosol tetrasodium (INS-37217) is a $P2Y_2$ receptor agonist in phase II clinical trials at Inspire Pharmaceuticals for the treatment of cystic fibrosis as an inhalable formulation. Development for macular edema was discontinued in January 2006 when data from two pilot trials were reviewed, demonstrating neither reduction of retinal thickness nor improvement in visual acuity following administration of denufosol. In 2001, the drug was granted orphan drug status in the U.S. for the treatment of cystic fibrosis, and the EMEA followed suit in January 2006 with E.U. orphan drug designation for the same indication.

Difluprednate, New Indication/Formulation



Senju has filed a regulatory application in Japan seeking approval for an ophthalmic emulsion of the topical corticosteroid difluprednate for the treatment of uveitis. The company recently licensed the product to Sirion Therapeutics for the U.S. market. Difluprednate is currently available in Japan from Mitsubishi Pharma for the topical treatment of skin inflammation.

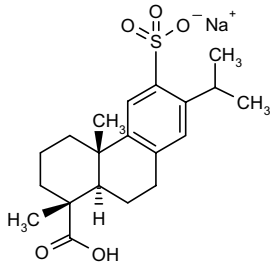
Diquafosol Tetrasodium



Diquafosol tetrasodium (DE-089, INS-365, Prolacria™) is a dinucleotide developed by Inspire Pharmaceuticals and Allergan as an ophthalmic solution for the treatment of dry eye disease. An NDA was submitted in 2003 followed by an amendment in June 2005, and the companies received the second approvable letter from the FDA late last year. Diquafosol tetrasodium is a $P2Y_2$ purinergic receptor agonist that activates these receptors on the ocular surface, leading to rehydration. The overall effect of the compound is to provide a rapid receptor-mediated rehydration of the ocular surface through the coordinated production of salt, water, mucin and lipids, thus restoring the major natural components of the tear film. In December 1998, Inspire established a development, license and supply agreement with Santen granting the company an exclusive license to market diquafosol for ocular surface diseases in Japan, China, South Korea, the Philippines, Thailand, Vietnam, Taiwan, Singapore, Malaysia and Indonesia. Santen recently

completed phase II testing in Asia. In June 2001, Inspire entered into a joint license, development and marketing agreement with Allergan, pursuant to which Allergan obtained an exclusive license to develop and commercialize diquafosol worldwide, with the exception of Japan and the aforementioned Asian countries.

Ecabet Sodium, New Indication/Formulation



A urease inhibitor, ecabet sodium is a gastrointestinal mucoprotective agent that was launched in 1993 in Japan as Gastrom® byTanabe Seiyaku for the oral treatment of peptic ulcer. At present, the compound is being evaluated as an enema for the treatment of ulcerative colitis in phase III trials by Tanabe Seiyaku, and phase II trials are under way at ISTA Pharmaceuticals and Senju to test an eyedrop formulation for the treatment of dry eye syndrome. As an ocular agent, ecabet sodium represents a new class of molecules that increase the quantity and quality of mucin produced by conjunctival goblet cells and corneal epithelia. Ecabet sodium is expected to be combined with other late-stage or currently marketed products for the treatment of dry eye syndrome.

Original monograph – Drugs Fut 1988, 13(11): 966.

Etanercept, New Indication

Etanercept is a fully human TNF-α antagonist, a recombinant fusion protein comprising the soluble human p75 tumor necrosis factor (TNF) receptor linked to the Fc portion of human IgG_1, that acts by binding TNF and rendering the bound TNF biologically inactive, resulting in a significant reduction in inflammatory activity. Etanercept was originally launched in 1998 by Wyeth and Amgen in the U.S. as Enbrel® for the reduction of the signs and symptoms of moderately to severely active rheumatoid arthritis in patients responding inadequately to one or more disease-modifying antirheumatic drugs (DMARDS). In 1999, the indication was expanded to include juvenile rheumatoid arthritis. E.U. approval of these indications followed in 2000 and launch in the U.K. took place the same year. In 2002, Wyeth and Amgen launched Enbrel® in the U.S. for the reduction of the signs and symptoms of active arthritis in patients with psoriatic arthritis and Enbrel® was commercialized in the U.S. in 2003 and 2004, respectively, for ankylosing spondylitis and for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In 2004, Enbrel® was approved in the E.U. for the treatment of psoriasis, rheumatoid arthritis (in combination with methotrexate) and ankylosing spondylitis. In March 2005, Wyeth and Takeda, comarketer in Japan, launched Enbrel® for injection for the treatment of rheumatoid arthritis. The NCI is conducting phase III clinical trials for the treatment of cancer-related cachexia and anorexia in patients with advanced disease. Additional phase III trials are ongoing at the National Eye Institute for the treatment of uveitis associated with juvenile rheumatoid arthritis. Etanercept is also in phase II evaluation by Wyeth Pharmaceuticals for the treatment of asthma and idiopathic pulmonary fibrosis and by Amgen for the treatment of hidradenitis suppurativa.

Original monograph – Drugs Fut 1998, 23(9): 951.

EV-131

Evolutec's EV-131 is a novel histamine-binding protein that prevents the activation of histamine receptors, including the H_4 receptor, and is in phase II trials for the treatment of allergic rhinitis and allergic conjunctivitis and in preclinical evaluation for asthma, acute respiratory distress syndrome (ARDS), postoperative cataracts and ocular inflammation. EV-131 is a major component of the saliva of feeding ticks that binds to histamine and blocks mast cell degranulation, thereby limiting the inflammatory reaction of the host at the feeding site. The protein shows activity in both early and late phases of inflammation, an advantage over widely prescribed antihistamines and corticosteroid therapies which show activity in early- and late-phase inflammation, respectively. Furthermore, EV-131 can be delivered by several different routes, another advantage over existing therapies.

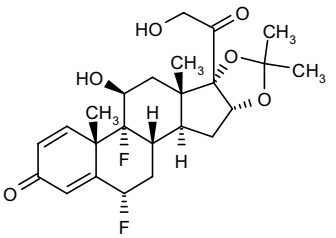
Eyepass™

The Eyepass™ implant is a microsurgical implantable device that is in phase III clinical trials at GMP Companies for the treatment of glaucoma.

Eyprotor®

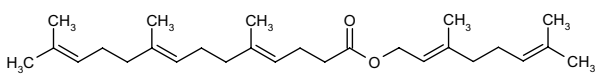
Eyprotor® is a protein-free calf blood extract eye gel, submitted for regulatory approval by Lee's Pharmaceuticals in China for the treatment of corneal epithelium abrasion.

Fluocinolone Acetonide, New Indication/Formulation



The glucocorticoid fluocinolone acetonide was launched over 45 years ago for the topical treatment of steroid-responsive dermatoses. The product was commercialized as Retisert™ in 2005 by Bausch & Lomb as an intravitreal implant using the company's proprietary Envision TD™ reservoir for the treatment of chronic, noninfectious posterior uveitis. The implant is a tiny polymer shell containing about 2 mg of fluocinolone, placed on the end of a plastic strip. Once the device is secure, a tiny port in the polymer shell slowly releases the drug into the eye for up to 3 years, reducing retinal inflammation. Currently, the drug is in phase III clinical trials at Alimera Sciences and pSivida for the treatment of diabetic macular edema as an implant formulation called Medidur™. Like the Envision TD™ reservoir, Medidur™ is small enough to be injected through a needle during an in-office procedure and is expected to provide sustained delivery of fluocinolone to the back of the eye for up to 3 years. In February 2005, Alimera Sciences and pSivida entered into a worldwide agreement to co-develop and market the Medidur™ formulation of fluocinolone to treat diabetic macular edema. In February 2006, Bausch & Lomb signed an agreement with Novartis Ophthalmics pursuant to which the companies co-promote the product for the treatment of posterior uveitis in the U.S. Orphan drug designation was assigned to fluocinolone in the U.S. and the E.U. for the treatment of noninfectious posterior uveitis in 2000 and 2005, respectively.

Gefarnate, New Indication/Formulation



Gefarnate (DE-099) is in early clinical trials at Santen for the topical treatment of corneal and conjunctival epithelial disorders associated with dry eye. The compound acts by stimulating mucin secretion and promoting corneal epithelial migration. Originally developed and launched (Gefanil) for the treatment of ulcers by the former Sumitomo, now Dainippon Sumitomo Pharma, the drug candidate was subsequently acquired by Santen.

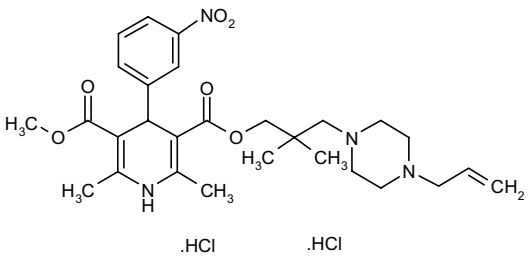
Hyaluronidase, New Indication

Vitrase®/Vitragan™, ISTA Pharmaceuticals' proprietary formulation of highly purified ovine hyaluronidase, is a natural proteoglycan-digesting enzyme that was launched in 2005 in the U.S. for use as a spreading agent for hypodermoclysis and as an adjunct in subcutaneous urography. The drug is preregistered in the E.U. and the U.S. as an injection for the treatment of severe vitreous hemorrhage and is currently undergoing phase II clinical trials for the induction of postvitreous detachment in diabetic retinopathy. Hyaluronidase is a spreading or diffusing substance that modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. When injected into the vitreous humor, Vitrase®/Vitragan™ breaks down the proteoglycan matrix, causing the vitreous humor to liquefy. ISTA granted exclusive rights to Otsuka for development and commercialization of hyaluronidase in Japan in December 2001. In October 2004, ISTA and Allergan revised a previous collaboration agreement with the result that ISTA re-acquired all rights to market and sell hyaluronidase for all uses in the U.S. and other markets worldwide, while Allergan retained an option to commercialize the product for the posterior segment of the eye in Europe.

Icomucret

Icomucret is currently undergoing phase III clinical trials at Alcon for the treatment of dry eye.

Iganidipine Hydrochloride



The calcium channel blocker iganidipine hydrochloride is being evaluated in phase II clinical trials as an ophthalmic solution at Senju for the treatment of glaucoma. The drug candidate was originally developed at Kyoto Pharmaceutical and Senju just recently licensed the product to ISTA Pharmaceuticals for development and marketing in the U.S.

Original monograph – Drugs Fut 1997, 22(1): 23.

ISV-205

A high-concentration formulation of diclofenac, ISV-205 is in phase II clinical trials at InSite Vision for the treatment of steroid-induced glaucoma in an eyedrop formulation that incorporates InSite's proprietary DuraSite® delivery system. DuraSite® is a sustained-release delivery vehicle that extends the effects of the drug to several hours. ISV-205 is also undergoing preclinical trials at InSite for the treatment of ocular inflammation. The drug candidate, an NSAID, can block steroid-induced IOP elevation in the eye by inhibiting the production of the TIGR protein, which appears to affect the fluid balance in the eye. ISV-205 delivers concentrations of diclofenac that have demonstrated clinically significant effects in cell culture systems. ISV-205 was licensed to InSite by the University of California at Oakland.

ISV-401

ISV-401 is a proprietary ophthalmic formulation of azithromycin, a broad-spectrum antibiotic, that incorporates InSite Vision's DuraSite® drug delivery technology for prolonged release of the active ingredient. The drug candidate is in phase III clinical trials for the treatment of acute bacterial conjunctivitis in patients aged 1 year and older.

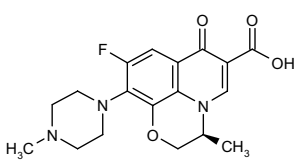
K-123

Phase II clinical trials are in progress at Kowa with K-123, a histamine H_1 receptor antagonist and phosphodiesterase type 3 (PDE3) inhibitor with potential for the treatment of allergic conjunctivitis.

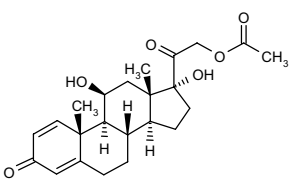
KK-220

Kowa's KK-220 is a recombinant human annexin A5 in phase II clinical trials for the treatment of corneal ulcer.

Levofloxacin/Prednisolone Acetate



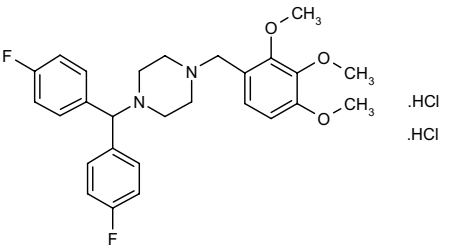
Levofloxacin



Prednisolone Acetate

The combination of levofloxacin/prednisolone acetate (DE-094) is in phase II clinical trials at Santen for the treatment of infectious bacterial keratitis. Originally developed at the former Daiichi Pharmaceutical, now Daiichi Sankyo, the drug candidate is licensed to Santen.

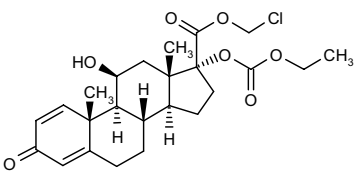
Lomerizine Hydrochloride, New Indication



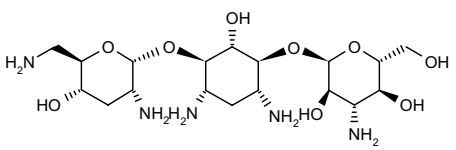
Lomerizine hydrochloride is a calcium channel blocker and a P-glycoprotein (MDR-1) inhibitor that was launched in 1999 by Nippon Organon and Pfizer for the oral prophylaxis of migraine. The drug is currently in phase II clinical trials at Santen (DE-090) for the oral treatment of glaucoma. According to Santen, basic research on lomerizine indicates that it could improve the blood supply to the retina and the optic nerves by enlarging the blood vessels in the eye, which could retard the gradual deterioration of vision associated with glaucoma. This vasodilatation is reportedly due to the drug's calcium-antagonist effect. Originally co-developed by Kanebo (now part of Nippon Organon) and Pharmacia, Pfizer obtained rights to lomerizine in April 2003 when the company merged with Pharmacia. Worldwide development and marketing rights to the drug were licensed to Santen in February 2001 pursuant to an agreement with Nippon Organon.

Original monograph – Drugs Fut 1988, 13(4): 312.

Loteprednol Etabonate/ Tobramycin



Loteprednol Etabonate

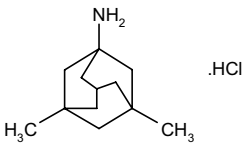


Tobramycin

Loteprednol etabonate/tobramycin (LE-tobramycin, Zylet®) is an antiinflammatory/antibiotic combination

product that was launched in 2005 by Bausch & Lomb as an ophthalmic suspension for the treatment of steroid-responsive inflammatory ocular conditions in patients who have or are at risk of developing superficial bacterial ocular infections. The drug combines the corticosteroid loteprednol etabonate and the antibiotic tobramycin to combat both inflammation and infection. In October 2001, Bausch & Lomb acquired all rights to the loteprednol etabonate ophthalmic business from Pharmos. This is the third Baush & Lomb product containing loteprednol etabonate that has been approved by the FDA.

Memantine Hydrochloride, New Indication



The NMDA antagonist memantine hydrochloride was originally launched over 20 years ago by originator Merz for the oral treatment of spasticity. The additional indication of dementia was approved years later, and in 2002, Merz and partner Lundbeck launched the drug for the treatment of moderately severe and severe Alzheimer's-type dementia. An oral formulation of memantine is in phase III trials at Allergan for protecting the eye from damage caused by glaucoma. Forest and the National Institute on Drug Abuse (NIDA) are also conducting phase III trials for the treatment of neuropathic pain and as an aid in smoking cessation, respectively. The NIDA is also evaluating the potential of memantine for the treatment of cocaine dependency. Research indicates that NMDA receptor antagonists have the potential to prevent injury and death of neurons related to a variety of conditions, including neuropathic pain, Alzheimer's disease, Huntington's disease and AIDS-related dementia. This is a result of their ability to block the flow of toxic levels of calcium released due to excessive amounts of glutamate present as a result of damaged neurons. Memantine's mechanism of action appears to be unique in that it blocks the flow of excess calcium into nerve cells for short periods of time with little impairment of normal function, unlike other NMDA receptor antagonists which either prevent glutamate from binding to the NMDA receptor or block the NMDA receptor channel for relatively long periods of time, leading to profound psychotic side effects.

Original monograph – Drugs Fut 1976, 1(9): 427.

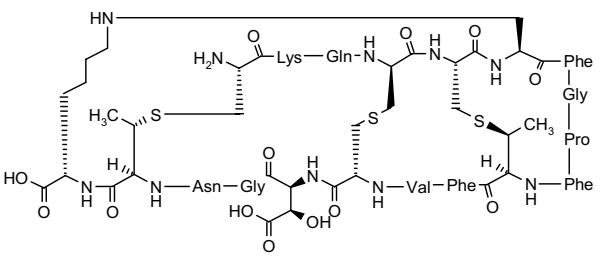
Microplasmin

Recombinant microplasmin, a truncated form of the human protein plasmin, is undergoing phase II clinical trials at ThromboGenics as an intravitreal injection to simplify vitrectomy, a surgical procedure that involves the separation of the vitreous from the retina, thereby inducing posterior vitreous detachment (PVD). This technique is considered beneficial in patients with numerous retinal conditions, including diabetic retinopathy and macular edema. Intravenous or intra-arterial administration of microplasmin is also in phase II trials for the treatment of acute stroke and peripheral arterial obstructive disease (PAOD). In 2004, the FDA granted ThromboGenics orphan drug status for the use of microplasmin in pediatric eye surgery to treat retinal disorders that cause visual impairment and blindness in children. The procedure using plasmin for induction of PVD was invented by the founders of NuVue Technologies, which owns exclusive rights for the use of plasmin in ophthalmic applications.

MK-0987/MK-0994

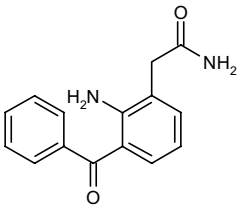
Merck & Co. is conducting early clinical trials with two compounds –MK-0987 and MK-09940– for the treatment of glaucoma.

Moli-1901



A 19-amino-acid polycyclic peptide produced from the fermentation of *Streptomyces cinnamoneus,* Moli-1901 (duramycin) promotes the hydration of epithelial tissue by opening an alternate salt channel. Moli-1901 binds the polar head of the phospholipid phosphatidylethanolamine in the cellular membrane and induces changes in intracellular calcium levels, which in turn activates calcium-dependent chloride channels. These alternate calcium-activated chloride channels produce an output of chloride and water. Lantibio (formerly known as MoliChem Medicines) licensed duramycin for the treatment of respiratory indications from Glaxo and the University of North Carolina at Chapel Hill and developed the product up to phase II clinical trials for the treatment of cystic fibrosis. In May 2004, Lantibio outlicensed development and commercialization rights to duramycin for the treatment of cystic fibrosis in the E.U. and Eastern Europe to AOP Orphan Pharmaceuticals. Currently, Lantibio is evaluating Moli-1901 in a European phase I trial for the treatment of dry eye and the company filed an IND in 2004 to begin clinical trials in the U.S.

Nepafenac



Alcon launched the NSAID nepafenac (Nevanac™) as an ophthalmic suspension in 2005 for the treatment of pain and inflammation associated with cataract surgery. The drug, which rapidly penetrates ocular tissues, is the first ophthalmic NSAID prodrug to receive FDA approval. Nepafenac was originally developed at Wyeth Consumer Healthcare.

Nova-21027

Nova-21027, a cationic emulsion, is undergoing phase I clinical trials at Novagali Pharma for the treatment of glaucoma.

Nova-23006/Nova-23033

Novagali Pharma's cationic emulsion Nova-23006/Nova-23033 (E.U./U.S. designations; Cationorm™) is an artificial tear agent in phase III clinical development for the treatment of mild dry eye. The company is preparing for product registration in both the U.S. and the E.U.

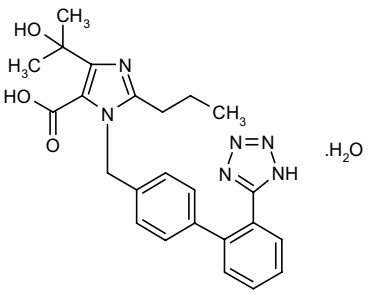
NP-50301

The estrogen ester NP-50301 is in phase II trials at Nascent Pharmaceuticals for the topical treatment of dry eye syndrome in postmenopausal women. The compound is believed to act by multiple mechanisms, including influencing the health of the cornea, the meibomian glands and the conjunctiva. Nascent plans to seek a strategic partner for continued clinical development and commercialization.

NT-501

Phase II clinical trials are being conducted at Neurotech for NT-501, an intraocular polymer implant for the treatment of dry AMD, and phase I trials are also under way for the treatment of retinitis pigmentosa. The implant consists of a 6-mm long, hollow, semipermeable fiber membrane with a suture loop at one end to anchor it to the sclera, allowing for ease of retrieval. It contains genetically modified human cells that continuously secrete ciliary neurotrophic factor (CNTF), a protein that was found in preclinical studies to be effective in retarding vision loss due to photoreceptor cell death. This method effectively overcomes the challenge of delivering therapeutic medications directly to the retina, as the placement of the implant in the vitreous body allows the CNTF to bypass the blood-retina barrier. NT-501 was originally developed at Amgen. In 2002, Neurotech signed an exclusive license agreement to develop and market CNTF for local delivery in ophthalmology indications.

Olmesartan Hydrate



The angiotensin II AT_1 receptor antagonist olmesartan hydrate (DE-092) is in phase II development at Santen for the treatment of ocular hypertension. Additional phase II trials for lowering IOP in glaucoma have been completed in the U.S., while trials in Japan for this indication are still ongoing. Results from the U.S. trial indicate that, although some IOP reduction was reported, efficacy was insufficient and no clear dose-response relationship was seen for the olmesartan concentrations. Based on these findings and pending phase II results from a trial in Japan, Santen will consider development options, such as conducting additional studies or repositioning olmesartan in the U.S. and Europe. Angiotensin II causes an increase in blood pressure by constricting blood vessels. The global development, manufacturing and marketing rights to the ophthalmic formulation of olmesartan hydrate, originally developed by the former Sankyo, now Daiichi Sankyo, were licensed to Santen in March 2002.

Oralgen® Grass Pollen

Oralgen® Grass Pollen is currently undergoing phase I clinical trials at Fornix BioSciences for the treatment of allergic conjunctivitis and allergic rhinitis in children with rhinoconjunctivitis. The product consists of a mixture of aqueous extracts of the pollen of five grass pollen species.

OT-551

OT-551 is a catalytic antioxidant scavenger being developed in phase II clinical trials at Othera

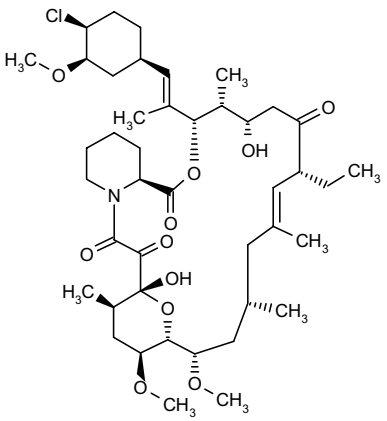
Pharmaceuticals to arrest the progression of or prevent cataracts in patients who have undergone vitrectomy surgery. In collaboration with the National Eye Institute, the company is conducting additional phase II trials for the treatment of patients with geographic atrophy, a sign of dry or atrophic AMD. The eyedrop formulation in which OT-551 is presented allows the drug to be metabolized to the active agent TP-H. TP-H, in turn, acts to protect cells from free radical damage, supplementing the body's natural defenses which become compromised by age or injury. Inside the eye, TP-H permeates tissues at both the lens and retina due to the high ocular bioavailability of the compound, providing antioxidant protection. Unlike many scavenger antioxidants, TP-H is not itself consumed in scavenging free radicals, but rather it is rapidly regenerated in a catalytic reaction by natural enzymes in the eye. The chemical properties of TP-H endow it with improved bioactivity over vitamins E and C. Additionally, the agent has affinity for both water and lipids, allowing it to regenerate more rapidly than either vitamin.

Pegaptanib Sodium

Pegaptanib sodium (Macugen®), a selective VEGF antagonist, was launched by EyeTech (a subsidiary of OSI Pharmaceuticals) and Pfizer in 2005 for the treatment of subfoveal choroidal neovascularization secondary to neovascular AMD. The drug is also in phase III clinical trials at EyeTech for the treatment of macular edema in diabetic patients and phase II trials for the treatment of retinal vein occlusion. The product that is currently marketed incorporates Nektar Therapeutics' proprietary PEGylation technology to attach polyethylene glycol (PEG) polymer chains to the drug molecule. In an aqueous medium, the long, chain-like PEG molecule is heavily hydrated and in rapid motion. This rapid motion causes the PEG to sweep out a large volume and prevents the approach and interference of other molecules. As a result, PEG polymer chains can protect drug molecules from immune responses and other clearance mechanisms, sustaining drug bioavailability. A sustained-release formulation using PR Pharmaceuticals' proprietary ProPhase™ encapsulation technology is also in development at PR and EyeTech under a collaboration agreement signed in January 2006 by the two companies. VEGF is a secreted protein that selectively binds and activates receptors located primarily on the surface of vascular endothelial cells. VEGF induces angiogenesis and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of AMD, a leading cause of blindness. VEGF has been implicated in blood-retinal barrier breakdown and pathological ocular neovascularization. Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular VEGF. Under *in vitro* testing, pegaptanib binds to the major pathological VEGF isoform, extracellular VEGF165, by targeting the heparin-binding domain (HBD), thereby inhibiting VEGF165 binding to its VEGF receptors. In April 2000, EyeTech entered into a licensing agreement for pegaptanib with originator Gilead Sciences, whereby EyeTech obtained worldwide commercial rights to the compound. Pfizer and EyeTech in turn entered an agreement to jointly develop and commercialize the product in December 2002. In December 2004, the FDA granted pegaptanib fast track designation for the treatment of wet AMD.

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

Pimecrolimus, New Indication/Formulation



Novartis's pimecrolimus is a cytokine production inhibitor first introduced on the market in 2002 in the U.S. as Elidel® topical cream for the short-term treatment of the signs and symptoms of atopic dermatitis and intermittent long-term treatment to prevent progression to flares in patients aged 3 months and older. Elidel® is approved in approximately 90 countries, including many E.U. markets. At present, pimecrolimus cream is in phase III development for the treatment of chronic hand dermatitis, atopic dermatitis in infants and as prophylactic treatment of severe atopic dermatitis. Novartis is also evaluating the product in phase II clinical trials as eyedrops for the treatment of dry eye. A cream formulation for the treatment of seborrheic dermatitis in infants is also under development.

Original monograph – Drugs Fut 1998, 23(5): 508.

Posurdex®

Posurdex® is an implantable device in phase III clinical trials at Allergan for the treatment of persistent macular edema associated with diabetes and other conditions. It is an intravitreal, biodegradable, extended-release implant that delivers therapeutic levels of dexamethasone

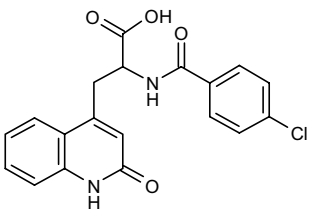
to the targeted disease site at the back of the eye. In April 2005, Allergan entered into an exclusive licensing agreement with Sanwa Kagaku Kenkyusho to develop and commercialize Posurdex® for the ophthalmic specialty market in Japan.

Ranibizumab

A humanized monoclonal antibody fragment targeting VEGF, ranibizumab (Lucentis™) was introduced in the U.S. by Genentech this year for the treatment of wet age-related macular degeneration (AMD). Genentech and partner Novartis Ophthalmics are conducting phase II clinical trials for its use in diabetic macular edema and early clinical trials are also under way at the National Eye Institute for the treatment of Von Hippel-Lindau syndrome. Ranibizumab, which binds and inhibits VEGF-A, is designed to block new blood vessel growth and leakiness, which lead to wet AMD disease progression and vision loss. In June 2003, Genentech and Novartis Ophthalmics, the eye health unit of Novartis, established an agreement pursuant to which Novartis Ophthalmics received an exclusive license to develop and market ranibizumab worldwide, with the exception of North America, for indications related to diseases of the eye.

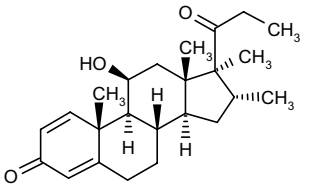
Original monograph – Drugs Fut 2003, 28(6): 541.

Rebamipide, New Indication



The quinolone derivative rebamipide was launched over 15 years ago by Otsuka in Japan for the oral treatment of *Helicobacter pylori*-induced gastric inflammation after eradication therapy and peptic ulcer. Currently, Otsuka is conducting phase II and phase III clinical trials for the treatment of Sjögren's syndrome and dry eye, respectively. The phase III trials are being conducted in collaboration with Novartis. Rebamipide, a potent antioxidant and free radical scavenger, works by enhancing tear secretion and increasing the levels of mucin covering the conjunctiva and cornea of the eye, improving tear quality and corneal health. In preclinical studies, the drug was also shown to concentration- and time-dependently increase the secretion of high-molecular-weight glycoconjugates (HMWGLs) from cultured rat conjunctival goblet cells. Originally developed at Otsuka, rebamipide was licensed to Novartis in February 2005 on a worldwide basis, excluding Japan and selected Asian countries.

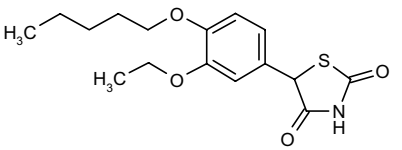
Rimexolone, New Indication



Rimexolone is a corticosteroid originally launched by Alcon as an ophthalmic suspension for the treatment of postoperative eye inflammation. At present, the company is evaluating the compound's potential for the treatment of dry eye in phase II clinical trials. Rimexolone was originally developed by Organon.

Original monograph – Drugs Fut 1977, 2(10): 695.

Risarestat



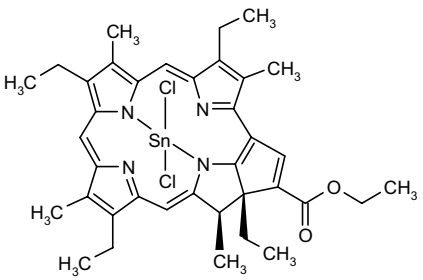
The aldose reductase inhibitor risarestat (CF-1122) is in phase III clinical development at Senju for the treatment of diabetic keratopathy.

Original monograph – Drugs Fut 1991, 16(10): 895.

RKI-983

A Rho kinase inhibitor, RKI-983 is currently undergoing phase I clinical trials for the treatment of glaucoma. Originally discovered by Senju, the compound was acquired by Novartis in 2005 for development and commercialization outside Japan.

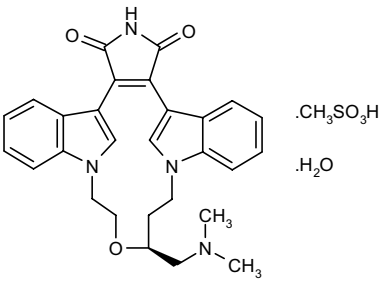
Rostaporfin



Miravant's light-activated drug rostaporfin (Photrex™) is designed to selectively destroy the abnormal blood vessels associated with wet AMD. The product candidate is awaiting regulatory approval in the U.S. Fifteen minutes after Photrex™ is administered, a low-power, nonthermal

red light is directed into the eye to activate the drug. In addition to wet AMD, rostaporfin has also been studied for the treatment of prostate cancer and AIDS-associated cutaneous Kaposi's sarcoma. The FDA granted fast track status to rostaporfin for the treatment of AMD in 1998.

Ruboxistaurin Mesilate Hydrate



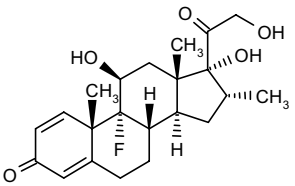
Lilly has filed an NDA for ruboxistaurin mesilate hydrate (Arxxant™), a protein kinase C β (PKCβ) inhibitor, in the U.S. for the oral treatment of diabetic retinopathy. Phase III trials are also under way for diabetic nephropathy, and phase II trials are evaluating the compound for the treatment of macular edema and diabetic peripheral neuropathy. In hyperglycemic diabetic patients, PKCβ becomes overactive and has been implicated in angiogenesis and vascular flow abnormalities. This leads to the various microvascular complications associated with diabetes. Phase III clinical trials have demonstrated that ruboxistaurin, through specific inhibition of PKCβ, significantly reduces the occurrence of vision loss in patients with diabetic retinopathy. In December 2003, Lilly and Takeda signed an agreement to jointly develop and market the drug for the treatment of diabetic retinopathy and diabetic peripheral neuropathy in the Japanese market.

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

Sirna-027

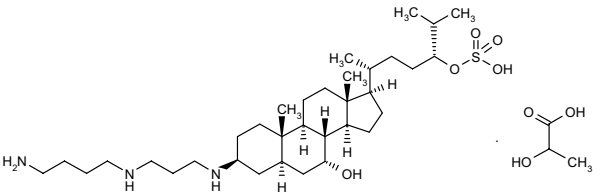
Sirna-027 is a chemically modified short interfering RNA (siRNA) targeting VEGFR-1. The drug is currently in early clinical trials at Sirna Therapeutics for the treatment by intravitreal injection of wet AMD. VEGFR-1, a key component of the clinically validated VEGF pathway, is found primarily on vascular endothelial cells and is stimulated by both VEGF and placental growth factor (PlGF), resulting in the growth of new blood vessels. By targeting VEGFR-1, Sirna-027 is designed to shut down activation of pathological angiogenesis initiated by both VEGF and PlGF. In October 2005, Sirna, originator of the drug, and Allergan established an agreement for the development of Sirna-027, as well as for the discovery and development of other novel RNAi-based therapeutics against select gene targets in ophthalmic diseases.

SK-0503



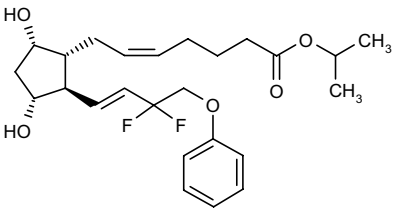
Sanwa Kagaku Kenkyusho is evaluating the safety and efficacy of SK-0503, an intravitreal implant of sustained-release dexamethasone, in phase II trials for the treatment of macular edema associated with branch retinal vein occlusion and diabetic retinopathy.

Squalamine Lactate



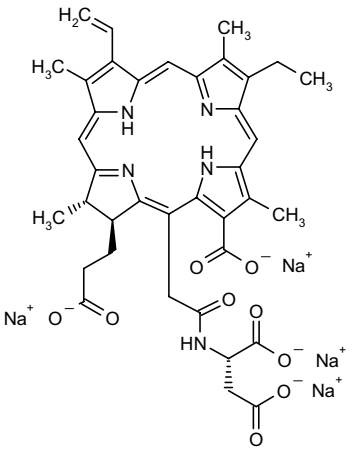
Squalamine lactate (Evizon™) is a novel antiagiogenic aminosterol that directly blocks endothelial cell activation, migration and proliferation by multiple growth factors, including VEGF, as well as cytoskeletal formation and integrin expression. The compound is in phase III development at Genaera for the treatment of choroidal neovascularization associated with age-related macular degeneration (wet AMD) and in conjunction with antiandrogen therapy in patients with prostate cancer undergoing radical prostatectomy. Another phase II trial is evaluating squalamine with concomitant photodynamic therapy (PDT) with Visudyne®. In 2004, the FDA granted fast track designation to squalamine for the treatment of wet AMD.

Tafluprost



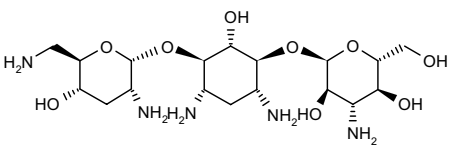
Tafluprost (DE-085) is a novel prostaglandin drug candidate in phase III clinical trials at Santen and Asahi Glass for the treatment of ocular hypertension and for the reduction of IOP in primary open-angle glaucoma. The compound was jointly discovered by Santen and Asahi. Santen is conducting pharmaceutical and clinical development, while Asahi is responsible for the manufacture of the active ingredient.

Talaporfin Sodium, New Indication

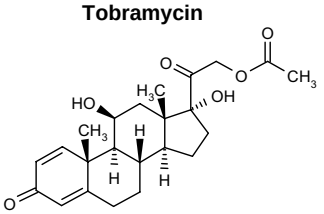


Talaporfin sodium (LS-11) is a next-generation PDT that is applied using Light Sciences' Light Infusion Technology™ (Litx™), specifically the light-emitting diode (LED)-based light infusion device, to activate the drug. The therapy platform (Laserphyrin®) was launched in Japan by Meiji Seika in 2004 as PDT for lung cancer (endobronchial carcinoma). Phase I/II trials are under way at Light Sciences to evaluate talaporfin for the treatment of advanced age-related macular degeneration (AMD). The company is also conducting phase I/II trials for the treatment of inoperable hepatocellular carcinoma. Advantages of Litx™ include less delay prior to treatment and a lower risk of photosensitivity, providing a more profound photoactivation that is maintained for a longer period than light delivered by a laser. Light Sciences licensed Laserphyrin® from Nippon Petrochemicals and Meiji Seika in early 2000, and has exclusive rights to develop, manufacture and commercialize the compound for use in PDT in multiple therapeutic applications worldwide, outside Japan.

Tobramycin/Prednisolone Acetate



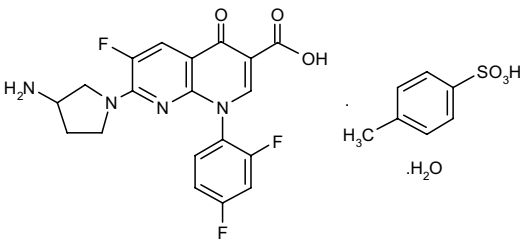
Tobramycin



Prednisolone Acetate

The combination tobramycin/prednisolone acetate is an antiinfective/antiinflammatory product in phase III clinical trials at ISTA Pharmaceuticals for the treatment of steroid-responsive inflammatory ocular conditions where the risk of bacterial infection exists. The ophthalmic product is a fixed combination in a proprietary formulation. Both of the active ingredients are approved drugs.

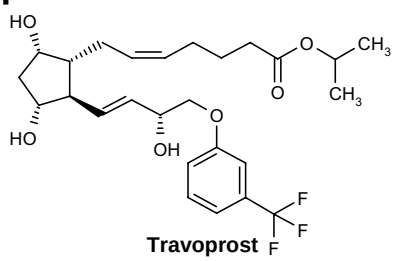
Tosufloxacin Tosilate, New Indication/Formulation



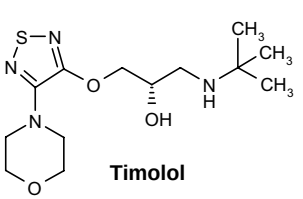
Launched over 15 years ago in Japan for the oral treatment of bacterial infections, tosufloxacin tosilate was more recently launched in Japan for the treatment of chlamydial conjunctivitis as eye drops in 2006. Tosufloxacin, a member of the naphthyridine family, exhibits potent antibacterial activity against the main pathogens that cause eye infections based on its ability to inhibit DNA gyrase and DNA topoisomerase IV. It has demonstrated efficacy against *Staphylococcus, Streptococcus, Streptococcus pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae* and *Chlamydia*. Originally developed at Toyama, the patent to tosufloxacin tosilate was licensed to Abbott in Japan and the U.S. in 1988. In 1997, Toyama entered into a business alliance with Nidek to jointly develop the compound. In 2003, Toyama granted marketing rights to Otsuka in Japan for the ophthalmic indication. Dong-A obtained rights to tosufloxacin in Korea in February 2004.

Original monograph – Drugs Fut 1989, 14(6): 536.

Travoprost/Timolol



Travoprost

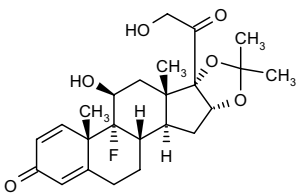


Timolol

Travoprost/timolol is a combination therapy developed by Alcon and launched earlier this year as

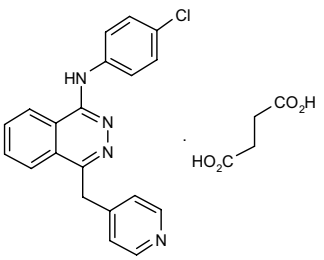
DuoTrav™ in Canada, Germany and the U.K. for the treatment of glaucoma. It was approved last year in Australia and is undergoing regulatory review in the U.S., where it will be known as Extravan®. The drug is a fixed combination of a prostaglandin analogue (travoprost) and a β-blocker (timolol) and has demonstrated the ability to reduce IOP in clinical trials.

Triamcinolone Acetonide, New Indication/Formulation



The glucocorticoid triamcinolone acetonide was launched over 45 years ago by sanofi-aventis for the treatment of allergic asthma and allergic rhinitis, by Forest for the treatment of osteoarthritis, pain and rheumatoid arthritis, and by Wyeth Pharmaceuticals for the treatment of other dermatological disorders. Over 40 years ago, the drug was launched by Bristol-Myers Squibb for the treatment of arthritis, and Rottapharm has marketed triamcinolone for over 10 years for the treatment of stomatitis. The product is also marketed for the treatment of allergy under a collaboration among Azwell, Takeda and Wyeth, and Kos Pharmaceuticals has launched it for the treatment of asthma. SurModics is currently conducting early clinical trials for the treatment of macular edema of an I-vation™ sustained-release intravitreal implant formulation. The implant utilizes SurModics' Bravo™ drug delivery polymer coating and a nonbiodegradable coil designed for implantation into the posterior chamber of the eye. The unique helical design of the implant maximizes the surface area available for drug delivery and ensures secure anchoring of the implant against the sclera, keeping it out of the visual field and facilitating retrieval.

Vatalanib Succinate



Vatalanib succinate is a novel once-daily oral angiogenesis signaling of all known VEGF pathways at the receptors VEGFR-1, VEGFR-2 and VEGFR-3, regardless of the growth factor (VEGF A-E). The drug is in phase III development by Novartis, development partner Schering AG and the NCI for the treatment of metastatic colorectal cancer. Additional phase III trials are also under way in combination with letrozole for the treatment of breast cancer in postmenopausal women. Schering AG is also developing vatalanib succinate in phase II clinical trials as second-line monotherapy in patients with stage IIIB/IV NSCLC. Additional phase II development is under way at the NCI for the treatment of myelodysplasia, and Novartis and Schering AG are conducting early clinical trials for the treatment of solid tumors. Novartis is also performing several phase II clinical trials for the treatment of acute myelogenous leukemia (AML), agnogenic myeloid metaplasia, chronic myelogenous leukemia in blastic phase (CML-BP) and multiple myeloma. The compound in combination with gemcitabine and verteporfin PDT is also in phase I/II trials for the treatment of pancreatic cancer and macular degeneration, respectively.

VEGF Trap

Regeneron's lead antiangiogenesis compound VEGF Trap is undergoing early clinical development with partner sanofi-aventis for the intravenous treatment of solid tumors. Regeneron is also studying the drug candidate in early clinical trials for the treatment of non-Hodgkin's lymphoma (NHL). The companies intend to evaluate VEGF Trap for a variety of cancers, both as monotherapy and in combination with chemotherapy. Regeneron is also evaluating VEGF Trap in phase I trials for the treatment of wet age-related macular degeneration (wet AMD).

Y-39983

Y-39983 is a Rho-associated coiled coil-forming protein kinase (ROCK) inhibitor in early clinical trials at Senju Pharmaceuticals for the topical treatment of glaucoma. In preclinical trials, the drug was shown to induce a significant dose-dependent decrease in IOP. Originally developed at Mitsubishi Pharma, Y-39983 was subsequently licensed to Senju. In November 2005, Novartis obtained global development and commercialization rights, with the exception of Japan.