

## 2010 FDA Approved New Drugs

Charles Z Ding



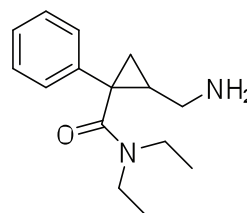
**About the Author:** Dr. Charles Z. Ding was born and raised in China. He got his bachelor degree in Chemistry from Lanzhou University in China in 1983 before coming to the States for graduate education. He got his Ph.D. in organic chemistry from State University of New York at Buffalo in 1989 and did his postdoctoral training at Northwestern University. His first industry job is with Bristol-Myers Squibb, subsequently he was attracted to small biotech companies. He is currently a Director, Medicinal Chemistry in Anacor Pharmaceuticals based in Palo Alto, CA. He has accumulated 18 years of drug discovery and development experience in both large pharmaceutical and small biotech companies. He invented and co-invented multiple IND in numerous therapeutic areas, including cardiovascular, oncology, metabolic disease and anti-infectives.

### Introduction

The total new drug approvals by US FDA remain low of 26 new molecular entities (NME) in year 2009. Of these new approvals, there are seven biologics, and the number appears to be trending higher year-over-year, when compared with 3 in year 2008 and 2 in year 2007. Neuroscience and oncology therapeutics dominated the small molecules approvals, while oncology drugs and immunomodulators were prevalent in approved biologics. US based large pharmaceuticals were less fortunate than the European counterparts in numbers of approvals. Novartis scored the most wins in 2009 US approval with total of 4 NME approvals, followed by GlaxoSmithKline with 2 approvals. Small biotech companies continue to show their success in bringing innovative products to approval stage.

### 2009 New Drug Approvals (NDA) or Biologic License Approvals (BLA) in chronological order

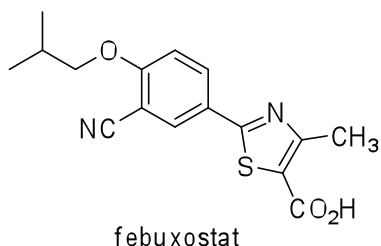
Drug	Savella (milnacipran HCl) <sup>1</sup>
Indication	Fibromyalgia
Company	Forest Laboratories, Cypress Bioscience
Approval Date	Jan. 14, 2009



milnacipran

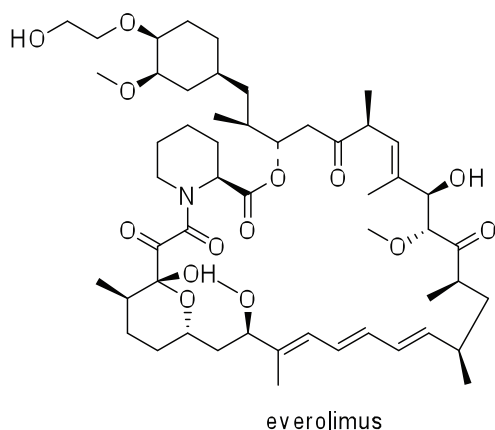
Savella (milnacipran HCl), is a new treatment option for fibromyalgia from Forest and Cypress, in competition with Pfizer's Lyrica and Eli Lilly's Cymbalta, both drugs are blockbusters. The disease affects about 6 million Americans, and is characterized as a chronic condition in joint and muscle pain and decreased physical functioning. The mechanism of action for milnacipran is different from that of Lyrica and Cymbalta. Milnacipran is a selective norepinephrine and serotonin inhibitor, inhibiting norepinephrine in a greater potency than serotonin. The chemical name of milnacipran is (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride. It exists as a racemic mixture.

Drug	Uloric (febuxostat) <sup>2</sup>
Indication	Gout
Company	Takeda
Approval Date	Feb. 13, 2009



Uloric (febuxostat) is a new drug for treatment of gout in 40 years. The drug was discovered originally by Teijin Pharma. Uloric is a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. Uloric is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations. The active ingredient in Uloric is febuxostat, its chemical name is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

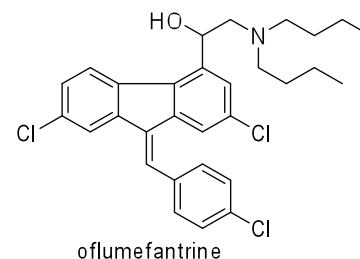
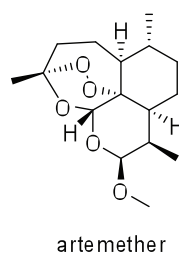
Drug	Afinitor (everolimus) <sup>3</sup>
Indication	Renal Cell Carcinoma
Company	Novartis
Approval Date	March 30, 2009



Afinitor (everolimus) from Novartis was approved for the treatment of advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Everolimus is an inhibitor of mTOR (mammalian target of

rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies. The spectrum of kinase inhibition, therefore its mechanism of anticancer activity, is different from that of Pfizer's Sutent (sunitinib malate) or Onyx Pharmaceuticals' Nexavar (sorafenib). Afinitor (everolimus) is a rapamycin analog and has a chemical name of (1R,9S,12S,15R,16E, 18R,19R,21R,23S, 24E,26E,28E,30S, 32S,35R) -1,18- dihydroxy-12-{{(1R)-2-[(1S,3R,4R)- 4-(2hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0<sup>4,9</sup>]hexatriaconta16,24, 26,28-tetraene-2,3,10,14,20-pentaone.

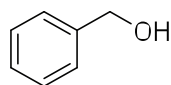
Drug	Coartem (artemeter/lumefantrine) <sup>4</sup>
Indication	Malaria
Company	Novartis
Approval Date	April 7, 2009



Coartem (artemeter/lumefantrine) was approved for the treatment of malaria infections caused by the parasite *P. falciparum*. Before its approval in US, Coartem was already in use in some 80 countries to treat malaria infections. Coartem is a combo pill contains a fixed dose of two antimalarial active ingredients, artemether, an artemisinin derivative, and lumefantrine. Both components are blood schizontocides. The chemical name of

artemether is (3R,5aS,6R,8aS,9R,10S,12R,12aR)decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepine. The chemical name of lumefantrine is (Z)-2-dibutylamino-1-(2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluorene-4-yl)ethanol. Artemether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). The anti-malarial activity of artemether and DHA has been attributed to its endoperoxide moiety in the molecule. The exact mechanism by which lumefantrine exerts its anti-malarial effect is not well understood. Available data suggest lumefantrine inhibits the formation of  $\beta$ -hematin by forming a complex with hemozoin. Both artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis.

Drug	Ulesfia (benzyl alcohol) <sup>5</sup>
Indication	Head Lice
Company	Sciele
Approval Date	April 9, 2009



benzyl alcohol

Ulesfia (benzyl alcohol) is the first and only prescription medication that kills head lice by asphyxiation without potential neurotoxic side effect. *In vitro* studies of Ulesfia Lotion on native, captured lice suggest that benzyl alcohol inhibits lice from closing their respiratory spiracles, allowing the vehicle to obstruct the spiracles and causing the lice to asphyxiate.

Drug	Simponi (golimumab) <sup>6</sup>
Indication	Rheumatoid Arthritis
Company	Centocor Ortho Biotech/J&J
Approval Date	April 24, 2009

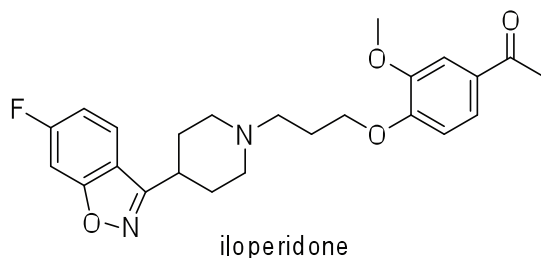
Simponi (golimumab), from Centocor, a unit of Johnson & Johnson, was approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF $\alpha$ . This interaction prevents the binding of TNF $\alpha$  to its receptors, thereby inhibiting the biological activity of TNF $\alpha$  (a cytokine protein). Elevated TNF $\alpha$  levels in the blood, synovium, and joints

have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF $\alpha$  is an important mediator of the articular inflammation that is characteristic of these diseases. Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF). Simponi (golimumab) was found using genetically engineered mice immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. It is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Drug	Dysport (Abobotulinum toxin A) <sup>7</sup>
Indication	Cervical Dystonia and Frown Lines
Company	Ipsen and Medicis
Approval Date	April 14, 2009

Dysport is botulinum toxin type A from Ipsen, Medicis approved to treat both cervical dystonia--a condition whose symptoms include involuntary contracting of the neck muscles--and to temporarily improve the look of frown lines. Medicis has the right to market it for aesthetic use, in competition with Botox. Dysport's active ingredient botulinum toxin type A is a purified neurotoxin type A complex produced by fermentation of the bacterium *Clostridium botulinum* type A, Hall strain. It is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps. In terms of mechanism of action, botulinum toxin type A inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings. This leads to therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves.

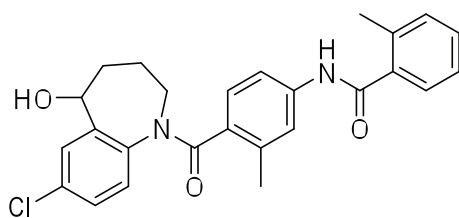
Drug	Fanapt (iloperidone) <sup>8</sup>
Indication	Schizophrenia
Company	Vanda Pharmaceuticals
Approval Date	May 6, 2009



iloperidone

Fanapt (iloperidone) from Vanda Pharmaceuticals was approved to treat schizophrenia. Fanapt is a psychotropic agent belonging to the chemical class of piperidyl-benzisoxazole derivatives. Its chemical name is 4'-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone. The mechanism of action of Fanapt is still unknown. However it is suggested that the therapeutic efficacy of Fanapt is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT<sub>2</sub>) receptor antagonisms.

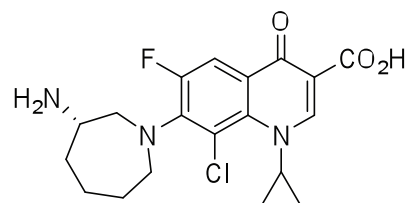
Drug	Samsca (tolvaptan) <sup>9</sup>
Indication	Hyponatremia
Company	Otsuka
Approval Date	May 19, 2009



tolvaptan

Samsca (tolvaptan) from Otsuka Pharmaceuticals was approved for hyponatremia, an electrolyte disorder that affects 6 million people in the U.S. annually. Tolvaptan's chemical name is (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carbonyl]-o-tolu-m-toluidide. It is a selective vasopressin V<sub>2</sub>-receptor antagonist with an affinity for the V<sub>2</sub>-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V<sub>2</sub>-receptor is 29 times greater than for the V<sub>1a</sub>-receptor. Tolvaptan antagonizes the effect of vasopressin and cause an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations.

Drug	Besivance (besifloxacin HCl) <sup>10</sup>
Indication	Bacterial Conjunctivitis
Company	Bausch & Lomb
Approval Date	May 29, 2009



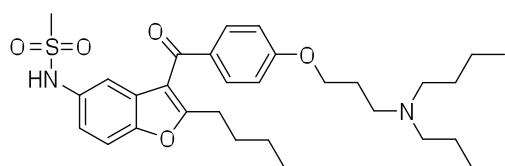
besifloxacin

Besivance™ (besifloxacin ophthalmic suspension) 0.6%, from Bausch & Lomb was approved to treat bacterial conjunctivitis, also known as pink eye. It is the first fluoroquinolone specifically developed for ophthalmic use and is the first and only ophthalmic fluoroquinolone with no previous systemic use. Other representative fluoroquinolone class of antibiotics developed for systemic uses are ciprofloxacin, levofloxacin and moxifloxacin. Besifloxacin's chemical name is (+)-7-[(3R)-3-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use, apparently no phototoxicity concern.

Drug	Ilaris (canakinumab) <sup>11</sup>
Indication	Cryopyrin-Associated Periodic Syndrome(CAPS)
Company	Novartis
Approval Date	June 17, 2009

Ilaris (canakinumab) was approved for the treatment of children and adults with cryopyrin-associated periodic syndrome (CAPS), which includes a number of rare but life-long auto-inflammatory disorders. Canakinumab is a recombinant, human anti-human-IL-1 $\beta$  monoclonal antibody that belongs to the IgG1/ $\kappa$  isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Canakinumab binds to human IL-1 $\beta$  and neutralizes its activity by blocking its interaction with IL-1 receptors selectively results its pharmacological effects.

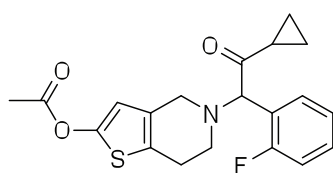
Drug	Multaq (dronedarone HCl) <sup>12</sup>
Indication	Atrial Fibrillation
Company	Sanofi-Aventis
Approval Date	July 1, 2009



dronedarone

Multaq (dronedarone HCl) from Sanofi-Aventis was approved for atrial fibrillation. Dronedarone HCl is a benzofuran derivative with the following chemical name: N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl} methanesulfonamide, hydrochloride. The exact mechanism of action of dronedarone is unknown. Dronedarone has antiarrhythmic properties belonging to all four Vaughan-Williams classes, but the contribution of each of these activities to the clinical effect is unknown.

Drug	Effient(prasugrel HCl) <sup>13</sup>
Indication	Blood thinner
Company	Daiichi Sankyo/Eli Lilly
Approval Date	July 10, 2009

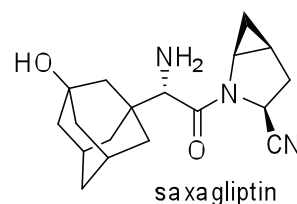


prasugrel

Effient (prasugrel HCl) was approved for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome. This drug comes from Eli Lilly and Daiichi Sankyo is meant to compete against the blockbuster drug Plavix (clopidogrel bisulfate), which is marketed by Sanofi-Aventis and Bristol-Myers Squibb. The active ingredient, prasugrel, is a thienopyridine class inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP receptor. Prasugrel's chemical name is 5-[(1RS)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-

4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride. It is a racemate mixture.

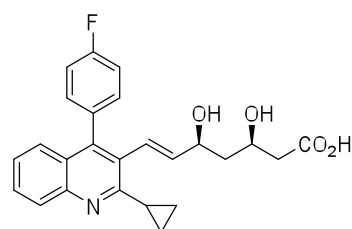
Drug	Onglyza (saxagliptin) <sup>14</sup>
Indication	Type 2 Diabetes
Company	Bristol-Myers Squibb/AstraZeneca
Approval Date	July 31, 2009



saxagliptin

Onglyza (saxagliptin) from Bristol-Myers Squibb and AstraZeneca, was approved for management of type 2 diabetes mellitus. The drug was invented by Bristol-Myers Squibb, and co-developed with AstraZeneca. Saxagliptin belongs to a class of drugs known as DPP-4 inhibitors, which stimulate the pancreas to make more insulin after eating a meal. It will compete with Januvia from Merck, the only other DPP-4 on the market. Saxagliptin is chemically known as (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1<sup>3,7</sup>]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. Saxagliptin is a competitive DPP4 inhibitor that preserves the incretin hormones in bloodstream and reduces fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

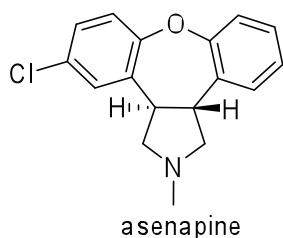
Drug	Livalo (pitavastatin) <sup>15</sup>
Indication	Cholesterol Lowering
Company	Kowa Research Institute
Approval Date	Aug 3, 2009



pitavastatin

Livalo (pitavastatin) from Kowa Research Institute was the newest statin approved to treat high cholesterol. The drug differs from other statins in that it's more effective at inhibiting cholesterol production and it's only minimally metabolized by the liver through the cytochrome P450 pathway. Like other statins, pitavastatin is an inhibitor of HMG-CoA reductase, which stops biosynthesis of cholesterol. It is a synthetic lipid-lowering agent for oral administration. The chemical name for pitavastatin is (+)monocalcium bis{( $\beta R$ ,  $5S$ ,  $6E$ )-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}.

Drug	Saphris (asenapine) <sup>16</sup>
Indication	Bipolar Disorder/Schizophrenia
Company	Organon/Merck
Approval Date	August 13, 2009



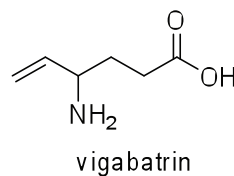
Saphris (asenapine) from Organon USA (now owned by Merck) was approved for episodes related to bipolar I disorder; acute schizophrenia. Saphris is similar to current antipsychotics, but boasts an improved safety profile that could lead to blockbuster sales. Saphris will compete with Risperdal from J&J and Zyprexa from Eli Lilly. The exact mechanism of action of asenapine is unknown. It has been suggested that the efficacy of asenapine in schizophrenia is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors. Asenapine belongs to the chemical class dibenzo-oxepino pyrroles. The chemical name is (3a*R*,5,12b*R*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*dibenzo[2,3:6,7]oxepino[4,5-*d*]pyrrole.

Drug	Extavia(interferon beta-1b) <sup>17</sup>
Indication	Multiple Sclerosis
Company	Novartis
Approval Date	August 14, 2009

Extavia (interferon beta-1b) from Novartis was approved for the management of relapsing symptom of

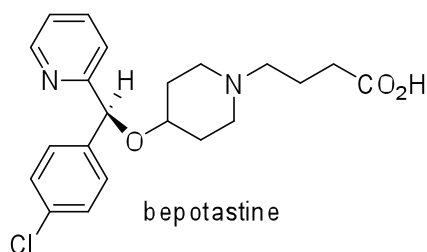
multiple sclerosis. The mechanism of action of interferon beta-1b in patients with multiple sclerosis is unknown. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta-ser17. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural protein.

Drug	Sabril (vigabatrin) <sup>18</sup>
Indication	Seizures
Company	Lundbeck
Approval Date	Aug. 21, 2009



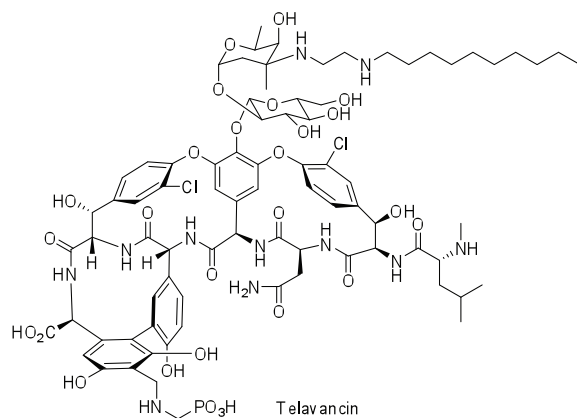
Sabril (vigabatrin) from Lundbeck was approved for refractory complex partial seizure in adults as adjunctive therapy. It is not intended to be a first line agent for complex partial seizure, but for patient who have inadequately responded to several alternative treatments and the potential benefits outweigh the risk of vision loss. The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of  $\gamma$ -aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system. Vigabatrin is an oral antiepileptic drug with the chemical name ( $\pm$ ) 4-amino-5-hexenoic acid

Drug	Bepreve(bepotastine ophthalmic solution) <sup>19</sup>
Indication	Itchy Eyes
Company	Ista Pharmaceuticals
Approval Date	Sept 8, 2009



Bepreve (bepotastine ophthalmic solution) from Ista Pharmaceuticals was approved for the treatment of itchy eyes triggered by pollen, plants and other irritants. The drug was approved in Japan in 2000, where it is marketed by Mitsubishi Tanabe Pharma. Senju Pharmaceutical has granted worldwide rights to the drug (except in Asia), and Ista in turn licensed the drug from Senju in 2006. Bepotastine is a histamine H1 receptor antagonist, its chemical name is (+)-4-[[[(S)-p-chloro- $\alpha$ -2-pyridyl-benzyl]oxy]-1-piperidinebutyric acid.

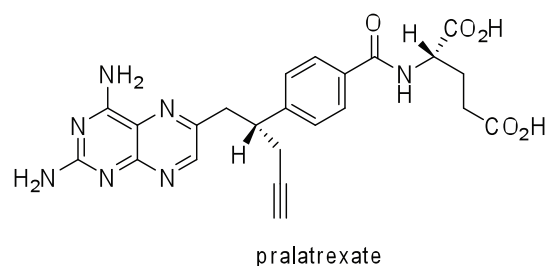
Drug	Vibativ (telavancin) <sup>20</sup>
Indication	Complicated Skin and Skin Structure Infections(cSSSI)
Company	Theravance/Astellas Pharmaceuticals
Approval Date	Sept. 11, 2009



Vibativ (telavancin) from Theravance and Astellas Pharma was approved for treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. The drug was invented by Theravance targeting super bugs, like MRSA, VISA etc and co-developed with Astellas. Vibativ inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan. It also binds

to the bacterial membrane and disrupts membrane barrier function. Vibativ's active ingredient, telavancin, is a lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. The chemical name of telavancin is vancomycin,N3''-[2-(decylamino)ethyl]-29-[[[(phosphono-methyl)-amino]-methyl]- hydrochloride.

Drug	Folotylin(pralatrexate) <sup>21</sup>
Indication	Peripheral T-cell Lymphoma(PTCL)
Company	Allos Therapeutics
Approval Date	Sept 24, 2009



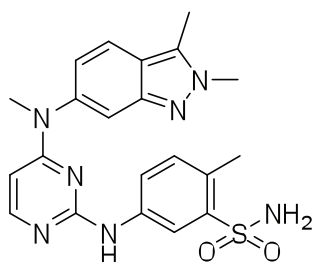
Folotylin (pralatrexate) from Allos Therapeutics was approved for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). The condition is a rare form of blood cancer that has a poor prognosis and a high relapse rate. The drug has a high price tag, but the company insists that it was priced similarly to other rare disease drugs. Pralatrexate is an antineoplastic folate analog that competitively inhibits dihydrofolate reductase. It is also a competitive inhibitor for polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other biological molecules the synthesis of which depends on single carbon transfer. Pralatrexate has a chemical name (2S)-2-[[4-[(1RS)-1-[(2, 4-diaminopteridin-6-yl)methyl]but-3 ynyl]benzoyl]amino]pentanedioic acid. It is a racemate mixture.

Drug	Stelara(ustekinumab) <sup>22</sup>
Indication	Plaque Psoriasis
Company	Centocor Ortho Biotech/J&J
Approval Date	Sept. 25, 2009

Stelara (ustekinumab) from Centocor was approved for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates

for phototherapy or systemic therapy. Because of less frequent dosing, this is a new competitor to like Enbrel and Humira, which require more frequent dosing. Stelara (ustekinumab) is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. It comprises of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12 β1.

Drug	Votrient(pazopanib) <sup>23</sup>
Indication	Renal Cell Carcinoma
Company	GlaxoSmithKline
Approval Date	Oct. 19, 2009



pazopanib

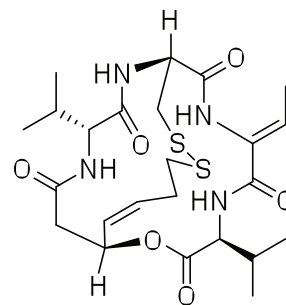
Votrient (pazopanib) from GlaxoSmithKline was approved for the treatment of advanced renal cell carcinoma. Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR-β receptors. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice. It will compete with treatments like Nexavar, but boasts different side effects that may be more acceptable to physicians and patients. Pazopanib has a chemical name 5-[[4-[(2,3-dimethyl-2H-

indazol-6333 yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride.

Drug	Arzerra (ofatumumab) <sup>24</sup>
Indication	Chronic Lymphocytic Leukemia(CLL)
Company	GlaxoSmithKline
Approval Date	Oct. 26, 2009

Arzerra (ofatumumab) from GlaxoSmithKline was approved for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. GSK licensed the drug in 2007 with a high price tag. Arzerra (ofatumumab) is an IgG1κ human monoclonal antibody with a molecular weight of approximately 149 kDa. The antibody was generated via transgenic mouse and hybridoma and is produced in a recombinant murine cell line (NS0) using standard mammalian cell cultivation and purification. Ofatumumab binds specifically to both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is expressed on normal B lymphocytes (pre-B- to mature B-lymphocyte) and on B-cell CLL. The CD20 molecule is not shed from the cell surface and is not internalized following antibody binding. Data suggest that possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity.

Drug	Istodax (romidepsin) <sup>25</sup>
Indication	Cutaneous T-cell Lymphoma
Company	Gloucester Pharmaceuticals
Approval Date	Nov. 5, 2009



romidepsin

Istodax (romidepsin) from Gloucester Pharmaceutical was approved for cutaneous T-cell lymphoma.

Romidepsin is a histone deacetylase (HDAC) inhibitor. Histone deacetylase HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. In vitro, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC50 values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized. Romidepsin is described chemically as (1*S*,4*S*,7*Z*,10*S*,16*E*,21*R*)-7-ethylidene-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16ene-3,6,9,19,22-pentone.

Drug	Kalbitor (ecallantide) <sup>26</sup>
Indication	Hereditary Angioedema(HAE)
Company	Dyax
Approval Date	Nov. 27, 2009

Kalbitor (ecallantide) from Dyax was approved for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. This is a rare and often lethal genetic disease characterized by pain and swelling in the face, lungs and upper airway. Kalbitor (ecallantide) is a human plasma kallikrein inhibitor, it is a 60-amino-acid protein produced in *Pichia pastor* yeast cells by recombinant DNA technology. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of High Molecular Weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE patients, normal regulation of plasma kallikrein activity and the classical complement cascade is absent. During attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Kalbitor (ecallantide) is a potent (Ki = 25 pM), selective, reversible inhibitor of plasma kallikrein. It binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin. By directly inhibiting plasma kallikrein, reduction of level of bradykinin and thereby treats symptom of the disease during acute episodic attacks of HAE.

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