CHAPTER THIRTY-ONE

To Market, To Market—2011

Joanne Bronson*, Murali Dhar†, William Ewing‡, Nils Lonberg§
*Bristol-Myers Squibb Company Wallingford, Connecticut, USA
†Bristol-Myers Squibb Company Princeton, New Jersey, USA
‡Bristol-Myers Squibb Company Pennington, New Jersey, USA
§Bristol-Myers Squibb Company Milpitas, California, USA

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OVERVIEW

This year's To-Market-To-Market chapter provides summaries for 26 new molecular entities (NMEs) that received first time approval world-wide in 2011.[1] Nineteen of these NMEs received their first approval in the United States. Three of the remaining first-time NMEs are from the European Union (EU), two are from Japan, one is from China, and one is from South Korea. It is noteworthy that the U.S. Food and Drug Administration (FDA) approved a total of 30 NMEs in 2011, a considerable increase from 21 approvals in 2010 and the highest number of approvals since 2004.[2] This total includes the 19 U.S.-approved NMEs covered in this chapter and 6 NMEs previously approved outside the United States, with the remainder being agents such as vaccines and imaging agents that are outside the scope of this chapter. Twenty one of the NMEs covered in the 2011 To-Market-To-Market chapter are small molecules and five are biologic agents. Anticancer agents topped the list in 2011 with seven first-time NMEs in total, of which five are small molecules and two are biologic agents. In the infectious disease area, three antiviral agents and one antibacterial agent were approved. There were three first-time NME drug approvals each for central nervous system, cardiovascular, and endocrine diseases. There were also three approvals in the immunology therapeutic area, with one small molecule and two biologic agents. The remaining NMEs include a biologic agent for macular degeneration, a small molecule for the rare disease transthyretin familial amyloidosis, and a small molecule for urinary incontinence. The following overview is organized by therapeutic area, with drugs covered in this year's chapter described first, followed by additional approvals that are of interest but not covered in detail.

Four of the five small molecules approved in the anticancer area are kinase inhibitors. Crizotinib (Xalkori®) is an ATP competitive, dual inhibitor of tyrosine kinases c-MET (mesenchymal–epithelial transition factor) kinase and anaplastic lymphoma kinase (ALK). The U.S. FDA approved crizotinib for the treatment of non-small-cell lung cancer at 250 mg administered orally twice daily. Ruxolitinib (Jakafi®) is the first approved oral inhibitor of JAK1 and JAK2 for the treatment of patients with intermediate or high-risk myelofibrosis. Ruxolitinib was approved in the U.S. at a recommended dose of 20 mg administered orally twice daily. Vandetanib (Caprelsa®) is an oral tyrosine kinase inhibitor that was approved by the U.S. FDA at 300 mg once daily for the treatment of symptomatic or

progressive medullary thyroid cancer (MTC) in adult patients with inoperable advanced or metastatic disease. Vemurafenib (Zelboraf®) is an inhibitor of B-raf kinase that is specifically recommended for the treatment of patients with the $BRAF^{V600E}$ mutation. Along with the human monoclonal antibody ipilimumab, vemurafenib is the second approved therapy in 2011 for the treatment of metastatic melanoma. The U.S. FDA approved vemurafenib at 960 mg administered orally twice daily for the treatment of patients with metastatic melanoma, as detected by the cobas 4800 BRAF V600 mutation test. Abiraterone acetate (Zytiga®) inhibits CYP17, a key enzyme in androgen biosynthesis, and is the third approved therapy in the past 2 years for the treatment of metastatic castration-resistant prostate cancer (mCRPC). The U.S. FDA approved abiraterone acetate for the treatment of mCRPC at 1000 mg once daily orally in combination with prednisone. Abiraterone acetate joins two therapies approved for prostate cancer in 2010, sipuleucel-T and cabazitaxel. The two biologic agents approved for cancer therapy are brentuximab (Adcetris™) and ipilimumab (Yervoy®). Brentuximab verdotin is an antibody–drug conjugate that binds to CD30 positive tumor cells and delivers the microtubule inhibitor monomethyl auristatin E (MMAE). It was approved as an intravenous infusion by the U.S. FDA for treatment of last-line Hodgkin's lymphoma (HL) and systemic anaplastic large cell leukemia (ALCL). Ipilimumab is an immunostimulatory antibody that was approved by the U.S. FDA as an intravenous infusion for treatment of unresectable or metastatic melanoma. The antibody augments host immune responses by blocking negative signaling mediated by the T cell surface molecule CTLA-4. The U.S. FDA also approved the orphan drug Erwinaze (asparaginase *Erwinia chrysanthemi*) as a component of a multiagent regimen for the treatment of patients with acute lymphoblastic leukemia who have developed hypersensitivity to the *E. coli*-derived enzyme.[3] Erwinaze is an enzyme that breaks down asparagine, which is essential for cell survival. Leukemia cells cannot produce this amino acid, whereas normal cells are able to make enough asparagine to survive.

In the infectious diseases area, boceprevir (Victrelis®) and telaprevir (Incivek®) were the first hepatitis C virus (HCV) NS3-4A protease inhibitors approved for the treatment of HCV infection. Boceprevir is a peptidomimetic HCV NS3-4A protease inhibitor that binds covalently, but reversibly, to the active site serine. The approved dose of boceprevir is 800 mg given orally three times daily in combination with peginterferon alfa plus ribavirin. The peptidomimetic telaprevir likewise acts as a covalent, reversible, inhibitor of HCV protease. The recommended dosage of

telaprevir (Incivek) is 750 mg taken orally three times a day with food in combination with peginterferon alfa plus ribavirin. For treatment of human immunodeficiency virus (HIV) infection, the non-nucleoside reverse transcriptase (RT) inhibitor rilpivirine (Edurant®) was approved as a 25-mg oral tablet to be taken once daily with a meal in combination with other antiretroviral agents. The U.S. FDA also approved the specific three-drug combination Complera®, a fixed dose combination of rilpivirine (25 mg) with emtricitabine (200 mg) and tenofovir (300 mg) to be given once daily taken orally with meals.[4] The macrolide natural product fidaxomicin (Dificid®) was approved by the U.S. FDA as an oral agent for the treatment of *Clostridium difficile*-associated diarrhea. The recommended dose is 200 mg twice daily for a treatment course of 10 days. There is a lower rate of recurrence of *C. difficile* infections (CDI) with fidaxomicin compared with other agents.

In the cardiovascular area, first-time approvals were achieved in 2011 for apixaban (Eliquis®) and edoxaban (Lixiana®), two antithrombotic drugs that act as direct inhibitors of Factor Xa (FXa), an enzyme with a central role in producing thrombin by both the intrinsic and extrinsic pathways of blood coagulation. The first approved FXa inhibitor was rivaroxaban (Xarelto®), which received EU approval in 2008 and, more recently, was approved in the United States in 2011 with a recommended dose of 10 mg once daily to reduce the risk of blood clots, deep vein thrombosis (DVT), and pulmonary embolism (PE) following knee or hip replacement surgery. Apixaban was approved in the EU for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. The recommended dose is 2.5 mg given orally twice daily. Edoxaban was approved in Japan at doses of 15 and 30 mg once daily for the prevention of venous thromboembolism after major orthopedic surgery. For lowering blood pressure in patients with hypertension, azilsartan medoxomil (Edarbi®), a potent and selective angiotensin II receptor antagonist, was approved by the U.S. FDA at 40 and 80 mg once daily. In late 2011, the U.S. FDA approved Edarbyclor™, a fixed dose combination of azilsartan medoxomil and the diuretic chlorthalidone in a once-daily, single tablet for patients with hypertension.[5] The recommended starting dose of Edarbyclor is 40 mg azilsartan medoxomil combined with 12.5 mg chlorthalidone; the maximum dose is a 40/25-mg azilsartan medoxomil/chlorthalidone combination.

In the endocrine disease therapeutic area, there were approvals for treatment of diabetes, erectile dysfunction (ED), and osteoporosis. Linagliptin (Tradjenta®) is an inhibitor of dipeptidyl peptidase-4 (DPP-4)

that was approved by the U.S. FDA to treat Type 2 diabetes along with diet and exercise. The recommended dose of linagliptin is 5 mg given orally once daily. Tradjenta® is the fifth marketed inhibitor of DPP-4. In 2011, the U.S. FDA approved Juvisync®, the first fixed-dose combination of a DPP-4 inhibitor (sitagliptin) with a cholesterol-lowering agent (simvastatin) for use in adults who need both agents.[6] Tablets containing different doses of sitagliptin and simvastatin in fixed-dose combination were developed to meet the different needs of individual patients. The type 5 phosphodiesterase (PDE5) inhibitor avanafil (Zepeed) was approved in South Korea for the treatment of ED at doses of 100 and 200 mg. Avanafil is reported to have a fast onset of action and to be the most selective PDE5 inhibitor on the market. The vitamin D analogue eldecalcitol (Edirol®) was approved in Japan for once daily oral treatment of osteoporosis at 0.5 and 0.75 μg doses. Eldecalcitol binds more potently to the vitamin D receptor than calcitrol, the active form of vitamin D.

Approvals in the central nervous system therapeutic area cover a range of disorders, including epilepsy, depression, and restless legs syndrome (RLS). Retigabine was approved in early 2011 in the EU (Trobalt) and in mid-2011 in the U.S. (Ezogabine/Potiga™) for the adjunctive treatment of partial-onset seizures in adults who have epilepsy. Retigabine acts as a selective positive allosteric modulator of KCNQ2-5 potassium channels, which are key regulators of neuronal excitability. The recommended dose of retigabine is 300 mg/day tid increasing by 150 mg/day tid in 1-week intervals up to 600 mg/day tid to 1200 mg/day tid depending on tolerability. Vilazodone (Viibryd®), a novel antidepressant agent that combines potent serotonin reuptake inhibition with partial agonist functional activity at 5-HT1A receptors, was approved in the U.S. for the treatment of major depressive disorder (MDD). The recommended dose of vilazodone is 40 mg once daily following titration from 10 mg for 7 days to 20 mg for 7 days. Gabapentin enacarbil (Horizant®), a novel prodrug of gabapentin, was approved in the U.S. for the treatment of moderate-to-severe RLS in adults. The recommended dose is 600 mg taken orally once daily taken with food at about 5 p.m. Although gabapentin has shown evidence of efficacy in RLS, its mechanism of action remains unclear.

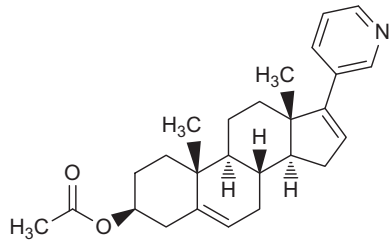
In the immunology area, first-time NMEs were approved for organ transplant rejection, lupus, and rheumatoid arthritis (RA). Belatacept (Nulojix®), a recombinant fusion protein that blocks CD28-mediated T-cell costimulation, is a selective immunosuppressive that was approved by the U.S. FDA for

prophylactic prevention of rejection in kidney transplant recipients. Belatacept is formulated as a lyophilized powder for intravenous infusion and is dosed at 10 mg/kg during an initial phase and 5 mg/kg during a maintenance phase. Belimumab (Benlysta®), a monoclonal antibody that binds to human B lymphocyte stimulator protein, became the first new drug approved by the U.S. FDA in over 50 years for treating the autoimmune disease systemic lupus erythematosus (SLE). The soluble factor neutralized by belimumab stimulates cell proliferation and antibody secretion in B lineage cells. Belimumab is formulated as a lyophilizate for intravenous infusion, and is administered as a 1-h infusion at 10 mg/kg every 2 weeks for the first three doses, followed by a maintenance regimen of 10 mg/kg every 4 weeks. Iguratimod (Iremod) was approved in China as an oral, disease modifying antirheumatic drug (DMARD) for treatment of RA, taken orally at 25 mg twice daily. Iguratimod inhibits PGE_2 production and COX-2 m-RNA expression in cultured fibroblasts.

Additional approvals in 2011 include drugs for macular degeneration, a rare amyloidosis disease and urinary incontinence. The recombinant fusion protein aflibercept (Eylea®), administered as an intravitreal injection, was approved in the U.S. for treatment of patients with neovascular (wet) age-related macular degeneration (AMD). Aflibercept acts as a soluble decoy receptor that binds all VEGF isoforms more tightly than their native receptors, thereby diverting VEGF from its normal function. The recommended dose for aflibercept is 2 mg administered by intravitreal injection every 4 weeks for the first 3 months, and then every 8 weeks thereafter. Tafamidis meglumine (Vyndaqel®) was approved in the EU for the treatment of Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) in adult patients with stage 1 symptomatic polyneuropathy. It is the first approved medicine for TTR-FAP, which is a rare, progressive, and fatal disorder characterized by neuropathy, cardiomyopathy, renal failure, and blindness. Tafamidis has a novel mechanism of action in that it stabilizes both the wild type and mutant forms of the transthyretin tetramer and prevents tetramer dissociation by noncooperatively binding to the two thyroxine binding sites. The recommended dose of tafamidis is 20 mg orally once daily. Mirabegron (Betanis®) was approved in Japan for the treatment of urgency, urinary frequency, and urinary urge urinary incontinence associated with overactive bladder (OAB). Mirabegron activates the β3-adrenoceptor (β3-AR) receptor, which is located on the bladder and involved in bladder smooth muscle relaxation. The recommended dose of mirabegron is 50 mg once daily.

1. ABIRATERONE ACETATE (ANTICANCER)[7–14]

Class:	Cytochrome P450 17A inhibitor
Country of origin:	United Kingdom
Originator:	Institute of Cancer Research, London
First introduction:	United States
Introduced by:	Janssen Biotech Inc.
Trade name:	Zytiga®
CAS registry no:	154229-18-2
Molecular weight:	391.55



In April 2011, the United States FDA approved abiraterone acetate (CB7630) in combination with the steroid prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) for patients who were previously treated with a docetaxel containing regimen for late-stage disease. Prostate cancer is the leading cause of cancer death in American men: 2010 statistics from the U.S. National Cancer Institute indicate that ~ 220,000 men were diagnosed with prostate cancer.[7] Chemotherapeutic options include docetaxel-based therapy with a median survival time of ~18 months. Surgical castration by androgen deprivation therapy is the cornerstone treatment for advanced prostate cancer. Although tumor growth is initially blocked, patients eventually develop disease progression resulting in a lethal drug resistant stage called castration-resistant prostate cancer (CRPC). However, many patients with CRPC respond to administration of secondary hormonal manipulations suggesting tumors are still dependent on the androgen receptor (AR) for signaling. Abiraterone acetate affects prostate, testicular, and adrenal androgens by irreversibly inhibiting both the lyase and hydroxylase activity of cytochrome P450 17A (CYP17) signaling pathways ($IC_{50's}$ of 2.9 and 4 nM, respectively) thereby decreasing testosterone levels.[8,9] The 16,17-double bond of the steroid scaffold of abiraterone acetate imparts irreversible binding to CYP17,

while the 3-pyridyl substitution confers specificity in binding to CYP17.[10] Abiraterone was developed as a prodrug (abiraterone acetate) to improve its bioavailability—the acetate moiety is rapidly cleaved *in vivo* leading to the generation of abiraterone. The key step in a reported large-scale synthesis of abiraterone acetate[11] involves a palladium-catalyzed cross coupling reaction between diethyl(3-pyridy1)borane and a vinyl iodide derived from dehydroepiandrosterone. Preclinical *in vivo* studies in mice indicated that abiraterone acetate reduced plasma testosterone to less than 0.1 nmol/L despite a three- to fourfold increase in the plasma levels of luteinizing hormone. There were no significant adrenal weight changes suggesting no significant inhibition of corticosterone production or a compensatory increase in the adrenocorticotropic hormone.[12]

In Phase I clinical trials, it was shown that abiraterone acetate is rapidly absorbed and deacetylated in the liver to abiraterone. There was a nonlinear increase in AUC and C_{max} with increasing doses. The mean terminal half-life was 10.3 h and clearance in fed state was 307 L/h. Coadministration of abiraterone acetate with food led to significant increases in both C_{max} and AUC. Abiraterone acetate is highly protein bound (>99%) and has a steady-state Vss (mean ± SD) of 19,669 ± 13,358 L. The safety and efficacy of abiraterone acetate was assessed in randomized, placebo-controlled multicenter Phase III trials in patients with mCRPC who had received prior chemotherapy containing docetaxel. A total of 1195 patients were randomized 2:1 to receive either abiraterone acetate (1000 mg once daily, oral dosing) in combination with prednisone (5 mg, twice daily, oral dosing) or placebo (once daily) plus prednisone (5 mg, twice daily, oral dosing). The median overall survival (OS) (primary end point) was 15.8 months for patients in the abiraterone acetate treatment group compared to 11.2 months for patients in the placebo group. Interim analysis of prostate-specific antigen (PSA) progression (secondary end point) clearly showed the superiority of abiraterone acetate compared to placebo (10.2 months compared to 6.6 months). The PSA response rate was also high: 29% compared to 6% for placebo.[13] Most common serious adverse events for abiraterone acetate versus placebo included fluid retention (30.5% vs. 22.3%), hypokalemia (17.1% vs. 8.4%), hypertension (9.7% vs. 7.9%), hepatic transaminase abnormalities (10.4% vs. 8.1%), and cardiac abnormalities (13.3% vs. 10.4%).[14] The recommended dose of abiraterone acetate is 1000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily.

2. AFLIBERCEPT (OPHTHALMOLOGIC, MACULAR DEGENERATION)[15–22]

Class:	Recombinant fusion protein
Country of origin:	United States
Originator:	Regeneron Pharmaceuticals
First introduction:	United States
Introduced by:	Regeneron Pharmaceuticals
Trade name:	Eylea®
Expression system:	Recombinant Chinese hamster ovary CHO-cell line
CAS registry no:	862111-32-8
Molecular weight:	~115 kDa

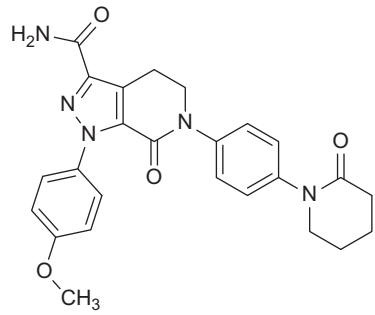
In November 2011, the U.S. FDA approved the recombinant fusion protein aflibercept, administered as an intravitreal injection, for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD).[15] Macular degeneration results from damage to the macula, the part of the eye responsible for sharp, detailed central vision.[16] AMD, which is the most common cause of vision loss in people over 60, is classified as nonneovascular (dry) or neovascular (wet). All cases of AMD begin as the dry form, but 10% progress to the wet form. Wet AMD results from abnormal growth of blood vessels in the retina. Damage due to leakage of blood and fluid can occur rapidly and lead to scarring of the retina and severe central vision loss. About 200,000 new cases of wet AMD are diagnosed each year in North America; the U.S. National Eye Institute estimates that the prevalence of advanced AMD will grow to nearly 3 million by 2020.[16] One approach for treatment of AMD involves inhibition of vascular endothelial growth factor (VEGF), which plays a key role in ocular neovascularization (angiogenesis).[17] Previously approved anti-VEGF agents developed for ophthalmic use are pegaptanib, an aptamer targeting the $VEGF_{165}$ isoform, and ranibizumab, a recombinant VEGF-specific antibody fragment. In addition, the anticancer agent bevacizumab (Avastin), a monoclonal VEGF-specific antibody, has been used off-label to treat wet AMD. Aflibercept differs from these agents in that it acts as a soluble decoy receptor that binds all VEGF isoforms more tightly than their native receptors, thereby diverting VEGF from its normal function.[18] Aflibercept consists of a fusion of the second Ig

domain of human VEGF receptor 1 and the third Ig domain of human VEGF receptor 2 fused to the constant region of (Fc) of human immunoglobulin G1. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kDa and glycoside molecular weight of 18 kDa. It is produced in recombinant Chinese hamster ovary (CHO) cells that overexpress the fusion protein. Aflibercept has subpicomolar affinity for VEGF-A ($K_D = 0.66$ pM for VEGF-A_{165} and 0.19 pM for VEGF-A_{121}), the major driver of pathological angiogenesis and vascular leak in wet AMD.[19] Ranibizumab and bevacizumab bind VEGF-A_{165} with lower affinity ($K_D = 20.6$ and 35.1 pM, respectively). In addition, the association rate for aflibercept binding to VEGF-A was orders of magnitude faster than for ranibizumab and bevacizumab.

Following intravitreal administration of aflibercept to patients with wet AMD, the C_{max} of free aflibercept in plasma was 0.02 μg/mL, with a T_{max} of 1–3 days.[20] Aflibercept was undetectable in the plasma after 2 weeks. The safety and efficacy of aflibercept in patients with wet AMD were evaluated in two 52-week randomized, double-masked, active-controlled studies (VIEW-1 and VIEW-2 trials).[20,21] The primary endpoint was the proportion of patients who maintained vision, as defined by losing fewer than 15 letters on the best corrected visual acuity (BVCA) scale. A secondary endpoint was the change in BVCA from baseline as measured by a letter score. Aflibercept was dosed intravitreally in one of three regimens: 2 mg every 4 weeks followed by 2 mg every 8 weeks, 2 mg every 4 weeks, or 0.5 mg every 4 weeks. The active control ranibizumab was given at 0.5 mg every 4 weeks. Efficacy results for either 2 mg dose regimen of aflibercept were equivalent to ranibizumab in both the primary and secondary endpoints. The proportions of patients that maintained visual acuity were 94% in VIEW-1 and 95% in VIEW2 for aflibercept at 2 mg every 4 weeks followed by 2 mg every 8 weeks; the same response rate was seen with ranibizumab at 0.5 mg every week. The most common adverse events ($\geq 5\%$) for aflibercept were similar to those for ranibizumab and included conjunctival hemorrhage (25%), eye pain (9%), cataract (7%), vitreous detachment (6%), vitreous floaters (6%), and increased ocular pressure (5%). The incidence of immunoreactivity to aflibercept was similar before and after treatment for 52 weeks (1–3%). The recommended dose for aflibercept is 2 mg administered by intravitreal injection every 4 weeks for the first 3 months, and then every 8 weeks thereafter. Aflibercept is also undergoing extensive evaluation as an anticancer agent.[22]

3. APIXABAN (ANTITHROMBOTIC)[23–37]

Class:	Factor Xa inhibitor
Country of origin:	United States
Originator:	Bristol Myers Squibb Company
First introduction:	European Union
Introduced by:	Bristol-Myers Squibb Company and Pfizer Inc.
Trade name:	Eliquis®
CAS registry no:	503612-47-3
Molecular weight:	459.5



Eliquis® (apixaban), a direct inhibitor of factor Xa (FXa), was approved by the European Commission on May 18, 2011 for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. VTE, a condition characterized by clot formation in a vein, is a potentially lethal and debilitating cardiovascular condition. VTE is the third most common cardiovascular disease after stroke and acute coronary syndrome (ACS) and can result from hereditary conditions, acquired risk factors, and surgery. Both deep vein thrombosis (DVT) and pulmonary embolism (PE) are disease conditions of VTE. DVT describes clot formation in the veins of the legs and pelvis. PE results when a dislodged clot migrates to the veins in the lungs. Hip or knee replacement surgery greatly increases the risk of DVT by 40–60% with the risk of VTE persisting 3 months post surgery.[23–25] Anticoagulant prophylaxis after surgery reduces the risk of VTE, with studies showing the duration of prophylaxis treatment as an important factor to reducing the incidence and severity of DVT.[25,26] Warfarin, low-molecular-weight heparins (LMWH), and fondaparinux are approved agents used for the prophylaxis of VTE, but these drugs have some limitations. Warfarin has

a narrow therapeutic window resulting in the need for frequent monitoring and dose adjustments and requires careful diet control. LMWHs require injection with the timing of administration being important to reduce surgical bleeding complications.[27] FXa is a blood coagulation cascade serine protease that converts prothrombin to thrombin, setting in motion the formation of fibrin which is then cross-linked to form a fibrin rich clot. After vascular injury, the extrinsic pathway of blood coagulation is initiated by tissue factor binding to FVII to generate FVIIa. The resultant tissue factor–FVIIa complex cleaves a single amino acid from the heavy chain of FX to produce FXa. The assembly of FVa, FXa, and calcium ions on a phospholipid membrane (the tenase complex) then converts prothrombin to thrombin. This initially generated thrombin amplifies the coagulation cascade by converting FV to FVa, FXIII to FXIIIa, and FXI to FXIa. The activation of FXIa initiates the intrinsic pathway which leads to increased concentration of FXa, thrombin, and FIXa. The resulting increase in thrombin production accelerates the formation of fibrin.[28–31] With the central role of FXa in producing thrombin by both the intrinsic and extrinsic pathways of blood coagulation established and with the favorable results from pharmacological studies using selective peptide inhibitors isolated from bats, ticks, and snakes, efforts to identify drug inhibitors of FXa were initiated.[32] The discovery of apixaban was the culmination of a succession of novel and innovative medicinal chemistry discoveries starting with the identification of nonpeptide leads, rational drug design using computer-aided and X-ray crystallographic information, and the building of drug-like properties through the systematic replacement of basic groups with neutral moieties. One remarkable finding was the discovery of exquisitely potent picomolar inhibitors with high selectivity over other serine proteases in the blood coagulation cascade.[33] Apixaban arose from modifications to razaxaban by constraining a pyrazole amide to form a bicyclic pyrazolo-pyridinone scaffold. Optimization of the P1 group resulted in the identification of the nonbasic methoxy phenyl group, while a P4 piperidinone improved the balance of potency and pharmacokinetics with low Vdss. The synthesis of apixaban begins with the generation of a hydrazone of 4-methoxyaniline which is then used in a 3 + 2 cycloaddition with a dihydropiperidinone to form a bicyclic pyrazolo-pyridinone scaffold. The distal piperidinone group is installed using an Ullmann coupling reaction followed by aminolysis of an ethyl ester on the pyrazole ring to complete the synthesis of apixaban.

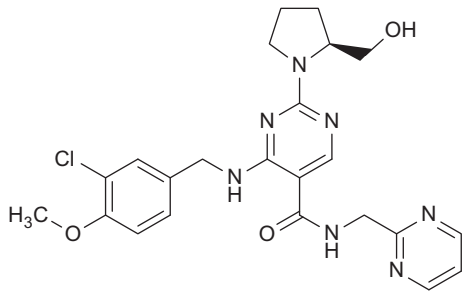
Apixaban inhibits human FXa with a $K_i = 80$ pM. After oral administration in a dog PK study, apixaban was shown to be 58% bioavailable with a slow clearance rate (0.02 L/Kg/h), low volume of distribution (0.2 L/kg), and a half-life of 5.8 h.[33] In the rabbit arteriovenous (A/V) shunt model, apixaban inhibited thrombus formation in a dose-dependent manner with an IC_{50} value of 329 nM.[34]

Oral administration of apixaban in a single-dose study in male healthy volunteers showed rapid absorption reaching T_{max} in 1 h (0.50–2.00) with an average terminal half-life of 12.7 h ± 8.55.[35] A study of the metabolism and drug disposition of [^{14}C]-apixaban showed excretion in the feces (56% of recovered dose) and urine (24.5–28.8% of recovered dose). The parent drug is the major component in plasma, urine, and feces. The major metabolite of apixaban, the sulfate of *O*-desmethyl-apixaban, is inactive. Apixaban has been studied in nine Phase III studies assessing its role in preventing VTE in patients undergoing total knee replacement (TKR) and total hip replacement (THR). Apixaban has also been studied in the secondary prevention of cardiovascular events in ACS and in the prevention of stroke in patients with atrial fibrillation. In the apixaban versus acetylsalicylic acid to prevent strokes trial, 5600 patients with atrial fibrillation who were not eligible for warfarin were given either 5 mg of apixaban bid or aspirin (81 or 324 mg) for 36 months or until end of study. The trial was stopped early due to the significant benefit found in the apixaban dosing group. Apixaban was found to reduce the risk of stroke or systemic embolic events 54%, was superior to aspirin, and showed no increased risk of major bleeding. In the 18,000 patient Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial, apixaban 5 mg twice daily was compared to warfarin in patients with atrial fibrillation. In the ARISTOTLE trial, apixaban showed superiority to warfarin in preventing stroke or systemic embolism. In comparison to warfarin, apixaban was found to cause less bleeding and resulted in lower mortality.[36] Four clinical trials have been conducted in patients undergoing major orthopedic surgery. The Phase II APROPOS (apixaban prophylaxis in patients undergoing total knee replacement) study compared apixaban (qd and bid doses) to warfarin and enoxaparin. In this study, apixaban dose dependently decreased the incidence of VTE. The Phase III studies ADVANCE-1 and ADVANCE-2 assessed apixaban in TKR patients, while the ADVANCE-3 study assessed apixaban in THR patients. The ADVANCE trials all used an oral dose of 2.5 mg bid apixaban. In the ADVANCE-2 trial, apixaban was shown to be superior to enoxaparin in the composite end-point of DVT, PE, and

all-cause mortality, with the major bleeding rates being comparable between the two drugs. ADVANCE-3 also demonstrated apixaban to be superior to enoxaparin with similar bleeding risk.[27,37] These studies formed the basis for the approval by the European Commission of Eliquis® 2.5 mg (apixaban) on May 18, 2011 for prevention of venous thromboembolism after elective hip or knee replacement surgery. Eliquis® is an oral, direct inhibitor of FXa and is codeveloped by Bristol-Myers Squibb and Company and Pfizer Inc.

4. AVANAFIL (MALE SEXUAL DYSFUNCTION)[38–45]

Class:	PDE5 inhibitor
Country of origin:	Japan
Originator:	Mitsubishi Tanabe Pharma Corporation
First introduction:	South Korea
Introduced by:	JW Choongwae Pharmaceutical Corp, Vivus, Inc., Mitsubishi Pharma Corporation
Trade name:	Zepeed
CAS registry no:	330784-47-9
Molecular weight:	483.95

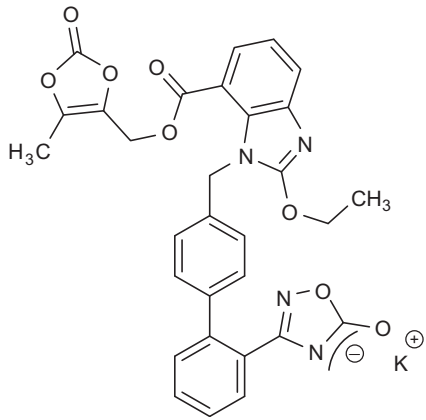


Avanafil (Zepeed) was approved by the Korean Health Ministry for the treatment of erectile dysfunction (ED) in August 2011.[38] Avanafil is a highly selective type 5 phosphodiesterase (PDE5) inhibitor. Other PDE5 inhibitors on the market are Pfizer's Viagra® (sildenafil), Eli Lilly & Co.'s Cialis® (tadalafil), Bayer's Levitra® (vardenafil), and Dong-A Pharmaceutical Co.'s Zydena® (udenafil). PDE5 inhibitors have revolutionized the treatment of ED by providing an efficacious, convenient, and safe treatment option to patients. The physiological event for stimulation and

maintenance of an erection is governed by vascular pressure changes in the corpora caverona through the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway. Increase in the release of NO causes the relaxation of smooth muscle cells which increases blood flow in the penis.[39] Inhibition of PDE5 prevents the cleavage of cGMP thus prolonging NO production. Of the five PDE5 inhibitors on the market, there are differences with regard to selectivity. Sildenafil, vardenafil, and avanafil show some PDE6 activity, while tadalafil shows some inhibition of PDE11. PDE6 is located in retinal photoreceptors and a side effect of PDE6 inhibition seen in some patients is color vision abnormalities. PDE11 is located in the testes and prostrate, but no side effects have been ascribed to inhibition of this enzyme. Avanafil is reported to be the most selective PDE5 inhibitor on the market. The onset of T_{max} and half-life also varies among the marketed PDE5 inhibitors. Sildenafil has a T_{max} at 1 h and a half-life of 3–5 h. Vardenafil is somewhat similar with a T_{max} of 0.6 h and a half-life of 4–6 h. Tadalafil has the longest half-life among the marketed drugs with a half-life of 17 h. Avanafil has a fast onset of action reaching T_{max} in 0.6 h with a half-life of 1.2 h.[40] A synthesis of avanafil (TA-1790) is described in the patent literature.[41] The pharmacokinetic profile of avanafil was studied in two trials, a single dose (200 mg) study and a repeat bid dosing study over 7 days. From these studies, the T_{max} for avanafil was found to be 0.5–0.7 h, with a mean half-life of 1.1–1.2 h. Metabolism studies showed that avanafil is metabolized by CYPs with no metabolite being more potent or having a longer half-life than avanafil.[42,43] The main elimination route of avanafil is through the bile and feces. Avanafil was also found to be reabsorbed through enterohepatic recirculation. In a 16-week Phase III study (390 patients), avanafil at 100 and 200 mg doses showed positive results on erectile function in men with both diabetes and ED. The effectiveness rate rose from 32% to 54% with the 100 mg dose, and from 42% to 63% with the 200 mg dose, versus an increase of 36% to 42% in the placebo group.[44] In another Phase III trial studying 646 subjects over 12 weeks at 50, 100, and 200 mg doses, all avanafil doses were shown to be more effective than placebo. Successful intercourse was demonstrated >6 h post dose in the avanafil dose group (59–83% success) versus placebo (25% success).[45] Avanafil (Zepeed) was approved by the Korean Health Ministry in August 2011 at doses of 100 and 200 mg for the treatment of ED and is being comarketed by JW Choongwae Pharmaceutical Corp, Vivus, Inc., and Mitsubishi Pharma Corporation.

5. AZILSARTAN MEDOXOMIL (ANTIHYPERTENSIVE)[46–52]

Class:	Angiotensin II receptor blocker
Country of origin:	United States
Originator:	Takeda
First introduction:	United States
Introduced by:	Takeda
Trade name:	Edarbi®
CAS registry no:	863031-21-4 (free acid)
	863031-24-7 (salt)
Molecular weight:	568.53 (free acid)
	607.63 (salt)



Azilsartan medoxomil (Edarbi®), an angiotensin II receptor antagonist, was approved by the U.S. FDA in February 2011 for the treatment of hypertension in adults. Hypertension is a major risk factor for cardiovascular disease and stroke. A report from the CDC on hypertension trends in the United States over 1999–2008 showed that the prevalence of hypertension remains at 30% of the population (74.5 million individuals).[46] Some of the treatment options available for patients are drugs that act on the renin–angiotensin system (RAS). The RAS modulates both blood pressure (BP) and fluid homeostasis. Stimulation of the angiotensin II type I receptor (AT_1), a G-protein coupled receptor (GPCR) located on the

vasculature, by the endogenous octapeptide angiotensin II (Ang-II) causes vasoconstriction. Ang-II also interacts with AT_1 receptors in the kidney causing modulation of sodium and water reabsorption. The formation of Ang-II results from the cleavage of Ang-I by angiotensin converting enzyme, which, in turn, is formed as the cleavage product of angiotensinogen by renin. Antagonists of the AT_1 receptor limit the vasoconstrictive effects set in motion by Ang-II.[47] There are eight approved angiotensin receptor blockers (ARB) on the market. The discovery of azilsartan was the result of a medicinal chemistry effort to identify an ARB with a different carboxylic acid isostere than the ones found in the marketed ARBs. Several of the marketed ARBs use a tetrazole group as a carboxylic acid isostere. The medicinal chemistry approach that led to azilsartan involved the replacement of this commonly used tetrazole with a 5-oxo-1,2,4-oxadiazole group. Azilsartan can be synthesized by Suzuki coupling of *p*-tolyl boronic acid to 2-bromobenzonitrile, followed by bromination of the methyl group. The bromide is displaced to introduce a protected 2-ethoxy-1H-benzo[d] imidazole-7-carboxylate. The cyano group is converted to a hydroxylamidine, followed by reaction with an alkyl-chloroformate and intramolecular cyclization to form the 5-oxo-1,2,4-oxadiazole ring.[48] The acid is then deprotected and converted to a prodrug. The parent, azilsartan has been extensively characterized *in vitro* and compared with other marketed AT_1 antagonists olmesartan, valsartan, telmisartan, irbesartan, and candesartan. Azilsartan was found to be a potent ($IC_{50} = 2.6$ nM), selective, inverse agonist of the AT_1 receptor. From washout experiments, azilsartan was found have slow dissociation from the receptor and thus is characterized as an insurmountable antagonist.[49] This feature is proposed to provide the long acting clinical efficacy that has been observed in Phase III trials.

In human studies, azilsartan medoxomil was found to be rapidly hydrolyzed to azilsartan. The pharmacokinetic profile from Phase I studies showed a 12-h half-life and 60% bioavailability. Azilsartan medoxomil is metabolized by CYP2C9. A Phase III trial with 1291 patients having a baseline 24-h mean systolic BP of 145 mm Hg evaluated azilsartan medoxomil at 40 and 80 mg doses in comparison to valsartan (320 mg) and olmesartan medoxomil (40 mg). The primary endpoints of this study were improvement in ambulatory BP and clinical BP as measured by a change from baseline in 24-h mean systolic BP. In this study, azilsartan medoxomil (80 mg) was found to be superior to valsartan (320 mg) and

olmesartan (40 mg) in lowering 24-h systolic BP.[50,51] Another Phase III trial compared azilsartan medoxomil (20, 40, and 80 mg) to olmesartan medoxomil (40 mg) in patients ($n = 1275$) with primary hypertension and baseline 24-h mean ambulatory systolic pressure between 130 and 170 mm Hg over 6 weeks of treatment. In this study, azilsartan medoxomil (80 mg) was found to be superior to olmesartan medoxomil (40 mg) by showing an additional 2.1 mm Hg drop in systolic BP. In both of these studies, azilsartan medoxomil was safe and well tolerated.[52] The results from the Phase III studies suggest that within the ARB class of drugs, azilsartan medoxomil could provide higher efficacy in lowering hypertension. Azilsartan medoxomil (Edarbi®) 40 and 80 mg once daily was approved by the U.S. FDA in February 2011 for the treatment of hypertension in adults. The 40 mg dose is recommended for patients who are being treated with high-dose diuretics to reduce salt in the body.

6. BELATACEPT (IMMUNOSUPRESSIVE)[53–61]

Class:	Recombinant fusion protein
Country of origin:	United States
Originator:	Bristol-Myers Squibb
First introduction:	United States
Introduced by:	Bristol-Myers Squibb
Molecular weight:	~90 kDa
Trade name:	Nulojix®
Expression system:	Rodent CHO-cell line
CAS registry no:	706808-37-9

Belatacept is an immunosuppressive that was approved by the U.S. FDA for prophylactic prevention of rejection in kidney transplant recipients. Approximately 16,000 kidney transplants are performed each year in the United States, and graft rejection is typically prevented through post-transplant induction of immunosuppression with antithymocyte globulin or interleukin 2 receptor antagonists (basilixumab), a calcineurin inhibitor (tacrolimus or cyclosporine A), and concomitant agents such as mycophenolate mofetil and corticosteroids.[53,54] Belatacept, which selectively blocks T cell costimulation, provides an alternative to the

calcineurin inhibitors, which are associated with adverse effects on renal function as well as cardiovascular and metabolic parameters. T-cell activation by antigen-presenting cells (APCs) requires a costimulatory signal in addition to the signal mediated by interaction of the T-cell receptor and MHC-bound peptide antigen. Belatacept can block that second signal by binding to APC costimulatory surface proteins CD80 and CD86 to inhibit their interaction with the T-cell signaling molecule CD28. Belatacept is a recombinant protein comprising a hinge-region modified (to reduce Fc receptor binding) carboxyl-terminal human IgG1 Fc domain fused to a modified extracellular domain of human CTLA-4 that includes two amino acid substitutions in the ligand-binding site.[55] As a result of this modification, belatacept binds more tightly to CD80 and CD86 than the parent molecule abatacept (Orencia®, FDA approved for treatment of adult RA and juvenile idiopathic arthritis), from which its structure is derived. CTLA-4 is a T-cell negative signaling molecule that is structurally related to CD28 and shares its two ligands. While belatacept incorporates CTLA-4 sequences to bind CD80 and CD86, the immunosuppressive activity of the drug suggests that its principal mechanism of action is blockade of CD28-mediated T-cell activation.

Belatacept is formulated as a lyophilized powder for intravenous infusion. It is dosed at 10 mg/kg on the day of transplantation and again on days 5, 14, 28, 56, and 84. It is then dosed at 5 mg/kg every 4 weeks beginning 16 weeks after transplantation. At the 10 mg/kg dose, the peak concentration of the drug is 247 ± 68 μg/mL and the terminal half-life is 9.8 ± 3.2 days. At the 5 mg/kg dose, the peak concentration of the drug is 139 ± 28 μg/mL and the terminal half-life is 8.2 ± 2.4 days. Belatacept reactive antibodies were detected in approximately 8% of 372 patients tested prior to treatment, and in another 2% post treatment. Development of antidrug antibodies was not associated with altered clearance. Belatacept was tested in two randomized, controlled Phase III trials. One of these trials randomized 686 patients receiving a kidney transplant from living or standard criteria deceased donors (the BENEFIT study[56–59]), and the second randomized 578 patients receiving extended criteria donor kidneys (the BENEFIT-EXT study[58–61]). Patients receiving extended criteria donor kidneys have a lower probability of allograft survival over time due to the more marginal quality of these organs. For both studies, patients were randomized 1:1:1 to 3 arms. One cohort received cyclosporine

A, and the other two cohorts received belatacept under two different dosing regimens: the prescribed dosing regimen and a more intense regimen that included more frequent and higher doses of drug over the first 6 months. Overall efficacy outcomes were similar for the two different belatacept dosing regimens. Acute rejection episodes were reported more frequently in belatacept-treated patients than cyclosporine-treated patients. In the BENEFIT study, acute rejection episodes at 3 years were reported in 19.9% of patients receiving the recommended dose of belatacept compared to 10.4% of patients receiving cyclosporine A, while graft loss frequencies were 2.2% and 3.6%, respectively. Ninety-one percent of patients receiving the recommended dose of belatacept were alive with functioning grafts at 3 years, compared to 86.9% of the cyclosporine A-treated patients. In the BENEFIT-EXT study, acute rejection episodes at 3 years were reported in 24% of prescribed-dose belatacept-treated patients compared to 22.8% of cyclosporine A-treated patients, while graft loss frequencies were 12% and 12.5%, respectively; and 81.7% of prescribed-dose belatacept-treated patients were alive with functioning grafts at 3 years, compared to 77.7% of the cyclosporine A-treated patients. Overall kidney graft function, as assessed by glomerular filtration rate, was better at 3 years in patients receiving the recommended belatacept regimen (65.8 and 42.2 mL/min/1.73 m^2 for BENEFIT and BENEFIT-EXT, respectively) versus cyclosporine A-treated patients (44.4 and 31.5 mL /min/1.73 m^2 for BENEFIT and BENEFIT-EXT, respectively). As with all immunosuppressive therapies, malignancies and infections are a clinical concern. The principle safety concerns associated with belatacept are posttransplant lymphoproliferative disorder (PTLD), of which the predominant site of presentation was the central nervous system, and serious infections, including progressive multifocal leukoencephalopathy (PML). At 3 years of follow-up, 1.2% of patients receiving the recommended belatacept regimen had developed PTLD versus 0.2% of patients receiving cyclosporine A. Lack of immunity to Epstein–Barr virus was identified as the greatest risk factor for development of PTLD with belatacept, and therefore, use in such patients is contraindicated. Two cases of fatal PML have been reported in clinical studies in patients receiving the more intensive belatacept dosing regimen. No cases of PML have been reported in patients receiving the recommended dosing regimen.

7. BELIMUMAB (IMMUNOSUPPRESSIVE, LUPUS)[62–68]

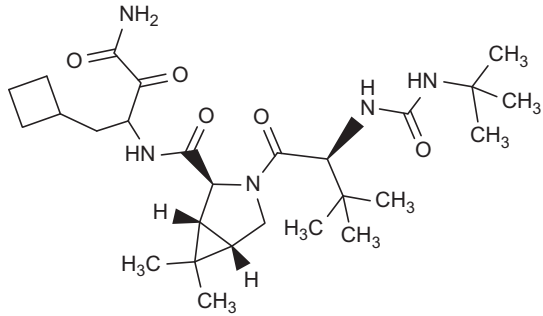
Class:	Recombinant monoclonal antibody
Country of origin:	United States
Originator:	Human Genome Sciences
First introduction:	United States
Type:	Human IgG1λ, anti-BLys
Introduced by:	Human Genome Sciences
Molecular weight:	~147 kDa
Trade name:	Benlysta®
Expression system:	Mammalian cell line
CAS registry no:	356547-88-1

Belimumab was approved by the U.S. FDA in March 2011 for treatment of patients with active, autoantibody-positive, systemic lupus erythematosus (SLE). SLE is a serious, and sometimes fatal, autoimmune disease that can affect multiple organs. Prevalence estimates for SLE vary widely across populations. It was reported to be the underlying cause of over 1400 U.S. deaths in 1998.[62] Existing treatment options include broad-based immunosuppressive drugs such as corticosteroids, hydroxychloroquine, cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate. Prior to belimumab, no new drugs have been approved for SLE in the past 50 years.[63] Belimumab is a human sequence monoclonal antibody that binds to human B lymphocyte stimulator protein (BLys; also known as BAFF, THANK, TALL-1, TNFSF13B, and zTNF4), which is overexpressed in SLE patients. BLys is expressed on the cell surface of monocytes, macrophages, and monocyte-derived dendritic cells and is cleaved to form a soluble cytokine that stimulates cell proliferation and antibody secretion in B lineage cells that express the BLys receptor BAFF-R (also known as BR-3). The precise function of two additional BLys receptors, TACI and BCMA, is less clear. Belimumab inhibits BLys interaction with these three receptors leading to measurable reductions in autoantibodies, such as anti-dsDNA, and specific circulating B cell lineage compartments including antibody producing plasma cells.[64] Belimumab was discovered by screening molecules from a phage display library of human single-chain Fv sequences for BLys binding and functional blocking, followed by optimization of the lead through the introduction of variant residues in V_H CDR3.[65]

Belimumab is formulated as a lyophilizate for intravenous infusion and is administered as a 1-h infusion at 10 mg/kg every 2 weeks for the first three doses, followed by a maintenance regimen of 10 mg/kg every 4 weeks. At this dose and schedule, the mean C_{max} was 313 μg/mL and the observed terminal half-life was 19.4 days. The single-dose C_{max} and terminal half-life at 10 mg/kg were reported to be 192.4 ± 34.9 μg/mL and 10.63 ± 2.89 days, respectively.[66] Antidrug antibodies were detected at a frequency of 0.7%; however, high drug levels could have interfered with the assay as the antidrug antibody frequency was higher (4.8%) in patients treated at a lower dose (1 mg/kg). Two placebo-controlled, randomized Phase III trials of belimumab have been reported. Both trials enrolled autoantibody-positive (antinuclear or anti-dsDNA) patients with active disease (SELENA-SLEDAI score ≥6) and included three different dosing arms, randomized 1:1:1, to receive placebo, 1 mg/kg, or 10 mg/kg belimumab on days 0, 14, and 28, and then every 28 days. Patients with severe active lupus nephritis or CNS disease were excluded. The two trials differed in length, with patients dosed either through week 52 (867 patients, BLISS-52 trial[67]) or through week 72 (819 patients, BLISS-76 trial[68]). The primary endpoint for both trials was the response rate at week 52 as measured by the systemic lupus erythematosus responder index, which is based on improvement in disease activity without worsening of the overall disorder or development of substantial disease activity in new organ systems. The response rates for the 10 mg/kg belimumab-treated cohorts in both trials were significantly greater than reported for the placebo-treated groups (58% vs. 44%, $p = 0.0129$; and 43.2% vs. 33.5%, $p = 0.017$). The response rate at 76 weeks was measured in the BLISS-76 trial and was reported to be 38.5% in the belimumab 10 mg/kg cohort compared to 32.4% ($p = 0.13$) in the placebo group. The incidence of severe SLE flares over 76 weeks in the belimumab cohort was 20.5% compared to 26.5% ($p = 0.13$) in the placebo group. In the BLISS-52 trial, the incidence of severe flares over 52 weeks was 14% in the belimumab 10 mg/kg cohort compared to 23% ($p = 0.0055$) for the placebo group. For both trials, the rates of adverse events, laboratory abnormalities, and infections were similar for the belimumab 10 mg/kg and placebo groups. There were no malignancies in any of the cohorts for the BLISS-52 trial, and 7 in the BLISS-76 trial (2 and 1 in the belimumab 10 mg/kg and placebo groups respectively). Rates of serious infections (grade 3 or 4) for the belimumab 10 mg/kg groups in the two trials were 2% and 2.6%, compared with 3% and 4% for the placebo groups. The death rate for both groups was 1% in the BLISS-52 trial. There were no reported deaths in the placebo group in the BLISS-76 trial, and 1 death in the belimumab 10 mg/kg group.

8. BOCEPREVIR (ANTIVIRAL)[69–77]

Class:	Hepatitis C virus NS3-4A protease inhibitor
Country of origin:	United States
Originator:	Merck/Schering
First introduction:	United States
Introduced by:	Merck
Trade name:	Victrelis®
CAS registry no:	394730-60-0
Molecular weight:	519.68



In May 2011, the U.S. FDA approved boceprevir (SCH-503034), to be given in combination with peginterferon alfa plus ribavirin, for the treatment of patients with chronic hepatitis C genotype 1 viral infection.[69] Boceprevir and telaprevir (*vide infra*) are the first hepatitis C virus (HCV) protease inhibitors to be approved for the treatment of HCV infection.[70] More than 170 million people are chronically infected with HCV worldwide, with >350,000 people dying each year from HCV-related liver diseases.[71] Chronic HCV infection causes inflammation of the liver and can lead to diminished liver function, liver failure, and liver cancer. While no HCV vaccine is available, HCV infection can be cured in some patients by treatment with a combination of peginterferon and ribavirin (PR). However, HCV genotype 1, which is the most prevalent subtype in the United States, Europe, and Japan, is the least responsive to PR therapy with rates of sustained virologic response (SVR) of less than 50%. Boceprevir is an inhibitor of HCV NS3-4A protease, an essential enzyme required by HCV for posttranslational processing of viral proteins into their mature forms. Boceprevir binds covalently, but reversibly, to the active site serine by addition of the hydroxyl group to the keto-amide functionality. Boceprevir

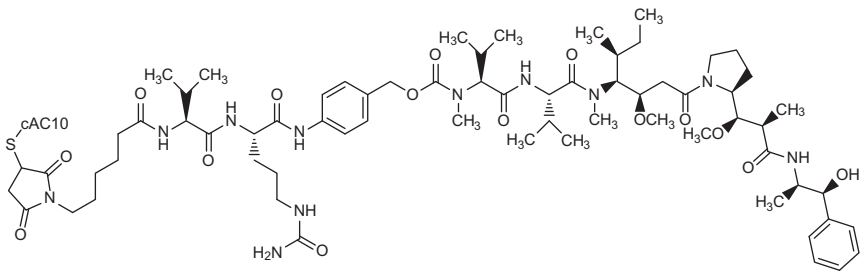
inhibits HCV NS3-4A protease with a K_i of 14 nM. In cell culture, the EC_{50} of boceprevir was 200 nM for an HCV replicon constructed from genotype 1b. Boceprevir was two- to threefold less potent against HCV replicon from genotypes 1a, 2, and 3. The potency of boceprevir decreased threefold in the presence of human serum. Boceprevir was discovered through a series of systematic truncations and modifications of a keto-amide undecapeptide lead molecule.[72] Structure-based drug design and crystallography were used extensively in the design process, particularly in optimization of the P1 (cyclobutylalanine) and P2 (dimethylcyclopropylproline) moieties to impart potency and selectivity, and introduction of the keto-amide moiety to improve potency.[73] Boceprevir is synthesized by coupling of 3-amino-4-cyclobutyl-2-hydroxybutyramide or the related oxobutyramide with a cyclopropyl-pyrrolidine carboxylic acid intermediate. The pyrrolidine derivative can be prepared via cyclopropanation of a bicyclic lactam derivative or by conversion of 3,3-dimethylcyclopropane-1,2-dicarboxylic acid to the pyrrolidine in a multistep route.[74] Boceprevir is a 1:1 mixture of diastereomers at the readily epimerizable position α to the keto group. Boceprevir showed 26% oral bioavailability in rats and a liver/plasma ratio of ~30.

The pharmacokinetics of boceprevir were evaluated in a number of Phase I clinical studies at doses of 50–800 mg.[75] Pharmacokinetic profiles were similar between healthy, HCV-infected, and renally-impaired subjects. Boceprevir was rapidly absorbed with a mean T_{max} of 1–2.25 h and a mean terminal phase half-life of 7–15 h across the dosing range. Food enhanced absorption by up to 65% at the 800 mg dose. The C_{max} of boceprevir given at 800 mg three times a day alone was ~1900 ng/mL. The volume of distribution (V_d/F) was 772 L at steady state, which was achieved after 1 day of three times daily dosing. Boceprevir is 75% protein bound in human plasma. The major route of metabolism is reduction by aldoketoreductase to give an inactive ketone-reduced metabolite. Metabolism by CYP-mediated oxidation occurs to a lesser extent. Boceprevir itself is an inhibitor of CYP3A4 and P-glycoprotein. Dosing of ^{14}C-boceprevir showed that the compound is eliminated primarily by the liver, with 79% of radioactivity being recovered in feces and 9% in urine. Boceprevir was evaluated in two Phase III studies in 1500 adult patients who were previously untreated (SPRINT-2)[76] or who had inadequate response on previous PR therapy (RESPOND-2).[77] The key outcome measure was SVR as defined by undetectable plasma levels of HCV-RNA at follow-up week 24. In SPRINT-2, the addition of boceprevir to a PR regimen gave SVR rates of 63–66% for the boceprevir/PR arms compared with 38% SVR for PR alone. The results were similar with 24 and

44 weeks of boceprevir. In RESPOND-2, SVR rates were 59–66% for the boceprevir/PR arms compared with 23% SVR for PR alone. Serious adverse events occurred in ~10% of treated patients. Fatigue, headache, and nausea were the most common clinical adverse events in all treatment groups, with no significant differences between subjects receiving boceprevir and PR or PR alone. Dysgeusia (altered taste) was more than twice as common in boceprevir-treated patients. Anemia was also more common in boceprevir-treated patients than in control subjects, with 42% of boceprevir-treated patients receiving erythropoietin compared with 24% on PR alone. The approved dose of boceprevir (Victrelis®) is 800 mg (four 200 mg capsules) given orally three times daily along with the PR regimen.

9. BRENTUXIMAB VERDOTIN (ANTICANCER)[78–83]

Country of origin:	United States
Class:	Antibody–drug conjugate
Originator:	Seattle Genetics
First introduction:	United States
Type:	Chimeric IgG1κ (anti-CD30), tubulin inhibitor conjugate
Introduced by:	Seattle Genetics
Molecular weight:	~153 kDa
Trade name:	Adcetris™
Expression system (antibody component):	Rodent CHO-cell line
CAS registry no:	914088-09-8



cAC10 = Monoclonal antibody

Brentuximab verdotin was approved by the U.S. FDA in August 2011 for treatment of Hodgkin's lymphoma (HL) in patients who have failed autologous stem cell transplant (ASCT) or ASCT ineligible patients who have

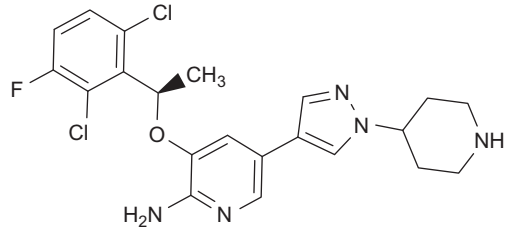
failed at least two prior chemotherapy regimens, and for second line treatment of systemic anaplastic large cell leukemia (ALCL). The cell surface target of brentuximab verdotin is the lymphocyte activation marker CD30, a TNF receptor family protein that is abundantly expressed on both HL and ALCL cells. HL and ALCL are rare malignancies. HL is the more common of the two, with an estimated incidence of approximately 9000 new cases in the United States in 2012.[78,79] The majority of patients with either of these cancers achieve durable complete remissions in the front-line setting with conventional combination chemotherapy and radiation. However, a fraction of the patients relapse and are then treated with salvage chemotherapy regimens that can include consolidation with ASCT. Patients who fail this second-line treatment are considered incurable: there are estimated to be over 1000 HL deaths annually in the United States.[78,79] Brentuximab verdotin is a chimeric (mouse V region/human C region) CD30 binding monoclonal antibody (cAC10) that is conjugated via cysteine residues to a small molecule comprising a cysteine reactive dipeptide linker moiety and the microtubule polymerization inhibitor monomethyl auristatin E(MMAE).[80] The antibody component of the drug binds to CD30 expressing tumor cells, and the active cytotoxic component, MMAE, is released by proteolytic cleavage of the dipeptide linker moiety.

The drug is formulated as a lyophilizate for intravenous infusion. It is dosed at 1.8 mg/kg (for patients over 100 kg, the dose is calculated using 100 kg) given as a 30-min infusion every 3 weeks for up to 16 cycles, or until disease progression or unacceptable toxicity. In a Phase I study using this dosing regimen, the observed C_{max} for the intact antibody–drug conjugate was 32 μg/mL (coefficient of variation of the geometric mean = 29%), and the terminal half-life was 4.4 days (coefficient of variation of the geometric mean = 38%).[81] In two Phase II studies using the same dosing regimen, approximately 7% and 30% of the treated patients developed either persistent or transient antibody responses to the chimeric antibody portion of the drug, respectively. Approximately 60% of the antibody-positive samples tested comprised neutralizing antibodies. These two open-label, single-arm, Phase II studies, in HL and ALCL, formed the basis of brentuximab verdotin's regulatory approval.[82,83] The HL Phase II trial enrolled 102 relapsed or refractory, post-ASCT patients. The overall objective response rate was 73%, including 32% CR and 40% PR. The median duration of the responses was 6.7 months, with a 20.5 and 3.5 month median duration for the CRs and PRs, respectively. The ALCL

Phase II trial enrolled 58 relapsed or refractory patients, including 42 patients in the more difficult to treat ALK-negative category. The overall objective response rate was 86%, including 57% CR and 29% PR. The median duration of the responses was 12.6 months, with a 13.2 and 2.1 month median duration for the CRs and PRs, respectively. Pooling data from the 160 patients in these two trials, the most common serious adverse events (grades 3 or 4), were neutropenia (21%), thrombocytopenia (9%), anemia (7%), peripheral sensory (9%), and motor neuropathy (4%).

10. CRIZOTINIB (ANTICANCER)[84–89]

Class:	ALK/c-MET multitargeted receptor tyrosine kinase inhibitor
Country of origin:	United States
Originator:	Pfizer
First introduction:	United States
Introduced by:	Pfizer
Trade name:	Xalkori®
CAS registry no:	877399-52-5
Molecular weight:	450.34



In August 2011, the United States FDA approved crizotinib (PF-02341066) for the treatment of anaplastic lymphoma kinase (ALK) rearranged non-small-cell lung cancer (NSCLC). Lung cancer is the second most common form of cancer in men (after prostate cancer) and in women (after breast cancer). The National Cancer Institute estimates ~220,000 new cases and ~157,000 deaths resulting from lung cancer in 2011.[84] NSCLC accounts for nearly 85% of lung cancer, with 15% as small-cell lung cancer. Chemotherapeutic options include platinum-based therapy with a median survival rate of less than a year. Other treatment options for NSCLC include the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib for patients with EGFR mutations. Crizotinib is

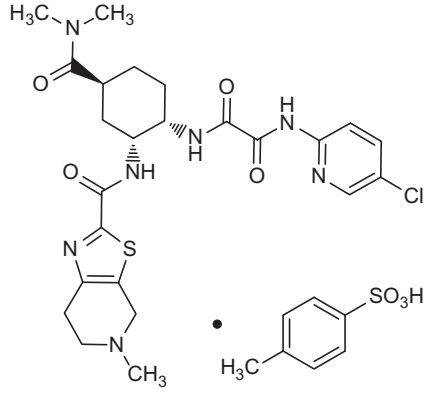
recommended for NSCLC that are driven by the ALK oncogene, which is activated by a breakage in chromosome 2 and a refusion of the two fragment genes in the opposite direction. Crizotinib is a dual ATP competitive inhibitor of tyrosine kinases c-MET (Mesenchymal-Epithelial Transition Factor) kinase (cellular $IC_{50} = 8$ nM) and ALK (cellular $IC_{50} = 20$ nM), both of which are important targets for cancer chemotherapy.[85] When crizotinib was tested for selectivity versus other kinases it was found to have enzyme $IC_{50's}$ within 100-fold multiples of c-MET for 13 of the 120 kinases tested. In cellular assays, crizotinib was found to inhibit RON (recepteur d'origine nantais) kinase with a 10-fold selectivity window over c-MET.[85] In preclinical studies, crizotinib regressed tumor growth within 15 days when administered to severe combined immunodeficient–beige mice bearing Karpas299 anaplastic large cell lymphoma tumor xenografts, at 100 mg/kg/day (oral dosing).[86] A process route to crizotinib has been described recently.[87] Key steps include chemoselective reduction of a nitropyridine group in the presence of halogens using sponge-nickel catalysts in methanol and a selective Suzuki reaction of an advanced 3-bromopyridine intermediate with a pyrazole-based pinacol boronate.

In an open-label, multicenter, Phase I trial involving 167 patients, peak plasma concentrations (C_{max}) were reached 4 h after oral administration of a single dose of 250 mg of crizotinib.[88] The mean absolute bioavailability was determined to be 43%. Increasing pH and a high-fat meal appeared to lower the bioavailability of crizotinib. The half-life of crizotinib was 43–51 h. Crizotinib is a substrate of P-gp and CYP 3A4 and a moderate inhibitor of CYP 3A4. The safety and efficacy of crizotinib (250 mg, BID, oral dosing) was assessed in two multicenter, single-arm studies labeled Study A and Study B.[89] The 136 patients in study A with ALK-positive NSCLC were identified using the Vysis ALK Break-Apart fluorescence *in situ* hybridization probe kit (Abbott Laboratories). The 119 ALK-positive patients in study B were identified using various local clinical trial assays. Except for 15 patients in Study B, all patients were on prior systemic therapy. The primary end point in both trials was overall response rate (ORR), defined as complete responses and partial responses. The ORR in study A was 50% with one complete response. In study B, the ORR was 61% with two complete responses. In a retrospective analysis on overall survival in patients with advanced NSCLC harboring ALK gene rearrangement, the 1-year survival was 77% for crizotinib-treated patients compared with 73% in historical controls, whereas the 2-year survival was 64% versus 33%, respectively. The most common serious adverse events (> 25%) for crizotinib were vision disorder, nausea, diarrhea, vomiting, edema, and constipation observed in

both studies. The recommended dose of crizotinib is 250 mg administered orally twice daily for the treatment of patients with locally advanced or metastatic NSCLC, as detected by an FDA-approved diagnostic test designed to detect rearrangements of the ALK gene.

11. EDOXABAN (ANTITHROMBOTIC)[24–27,32,90–96]

Class:	Factor Xa inhibitor
Country of origin:	Japan
Originator:	Daiichi Pharmaceutical
First introduction:	Japan
Introduced by:	Daiichi Sankyo Company
Trade name:	Lixiana®
CAS registry no:	480448-29-1 (free base) 480449-71-6 (salt)
Molecular weight:	548.06 (free base) 738.28 (salt)



Edoxaban (Lixiana®), a direct inhibitor of Factor Xa (FXa) was approved by the Minister of Health, Labor, and Welfare in Japan in April 2011 for the prevention of venous thromboembolism (VTE) after major orthopedic surgery.[90] VTE, a condition characterized by clot formation in a vein, can result from hereditary conditions, acquired risk factors, and surgery. In the United States, VTE is the third most common cardiovascular disease after stroke and ACS. Both deep vein thrombosis (DVT), a condition describing clot formation in the veins of the legs and pelvis, and pulmonary embolism (PE), a condition that arises from a dislodged clot migrating to the veins of the lung, are disease conditions of VTE. The risk of DVT is increased by 40–60% in patients undergoing hip or knee replacement surgery with the risk of VTE persisting 3 months

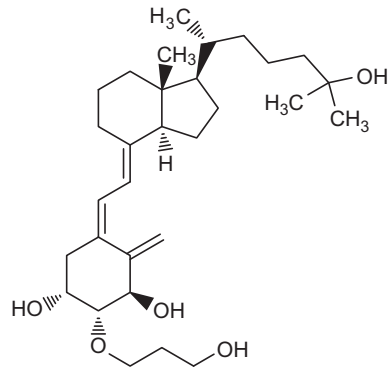
post surgery.[90,24,25] Anticoagulant prophylaxis after surgery reduces the risk of VTE, with studies showing the duration of prophylaxis treatment as an important factor in reducing the incidence and severity of DVT.[25,26] Drugs in other classes that are used for the postoperative treatment of VTE have some limitations. Warfarin has a narrow therapeutic window resulting in the need for frequent monitoring and dose adjustments and requires food restrictions and careful diet control. Low molecular weight heparins (LMWH) are intravenously administered drugs with the timing of administration important to reduce surgical bleeding complications.[27] The generation of FXa, a blood coagulation cascade serine protease, converts prothrombin to thrombin setting in motion clot formation through the generation of fibrin which when cross-linked forms fibrin rich clot. With central role of FXa in producing thrombin by both the intrinsic and extrinsic pathways of blood coagulation and the favorable results from pharmacological studies using selective peptide inhibitors, efforts to identify drug inhibitors of FXa were initiated.[32] The discovery of edoxaban resulted from the identification of a 1,2-*cis*-diaminocyclohexane template, the discovery of the novel 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine as an S4 binding element and systematic studies of novel and efficient P1 groups.[91–93] Edoxaban inhibits hFXa with a $K_i = 0.56$ nM. Edoxaban is a weak inhibitor of thrombin $K_i = 6000$ nM, has $>10{,}000$ fold selectivity over other serine proteases in the coagulation cascade, and demonstrates selectivity over trypsin and chymotrypsin. The synthesis of this class of FXa inhibitors begins with assembly of the diaminocyclohexane scaffold, *cis-t*-butyl ((1*R*,2*S*,5*S*)-2-amino-5-(dimethylcarbamoyl)cyclohexyl)carbamate. The free amine is coupled to the P1 group, 2-((5-chloropyridin-2-yl) amino)-2-oxoacetic acid. The Boc protecting group on the amine of the scaffold is removed and the resulting free amine is coupled to the P4 group, 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylic acid. In monkey studies, when dosed at 1 mg/kg orally, edoxaban showed a rapid onset of action and reached a C_{max} at 4 h with concentrations detectable at 24 h and a bioavailability of 60%. In rats and rabbits, edoxaban produced a dose-dependent reduction in thrombus formation.[94]

In a single ascending dose study in healthy male subjects at doses of 10, 30, 90, 120, and 150 mg, edoxaban was well tolerated with no adverse effects and showed dose proportional increases in exposure. The half-life in the dose ranges of 30–150 mg were 8.56–10.7 h. The range for the mean renal clearance was 34.7–38.8%. Edoxaban is a substrate for P-gp. There was no effect of food on pharmacokinetics.[95] Edoxaban has been studied in Phase III clinical trials for the prophylactic treatment and prevention of

VTE and for the prevention of stroke in patients with atrial fibrillation. Several Phase III trials assessing edoxaban for the prevention of VTE in TKR and THR have been completed. In the STARS E-3 trial (761 Japanese patients), edoxaban was given at a dose of 30 mg once daily and compared to 20 mg bid of enoxaparin. In this study, edoxaban was shown to be superior to enoxaparin on the primary endpoint of reducing symptomatic PE, and symptomatic and asymptomatic DVT in patients that had undergone total knee surgery. The STARS J-5 trial studied 610 Japanese patients that had undergone hip arthroplasty and used the same dosing regimen as the STARS E-3 trial, with 30 mg once daily of edoxaban and 20 mg bid of enoxaparin. STARS J-5 also demonstrated that edoxaban was superior to enoxaparin in reducing PE and symptomatic and asymptomatic DVT.[96] Edoxaban (Lixiana®) doses of 15 and 30 mg once daily were approved by the Ministry of Health, Labor, and Welfare in Japan on April 22, 2011 for the prevention of VTE after major orthopedic surgery. Lixiana® is being developed and marketed by Daiichi Sankyo Company Limited.

12. ELDECALCITOL (OSTEOPOROSIS)[97–102]

Class:	Vitamin D3 derivative
Country of origin:	Japan
Originator:	Chugai Pharmaceutical/Roche
First introduction:	United States
Introduced by:	Taisho Pharmaceutical Holdings and Chugai Pharmaceutical
Trade name:	Edirol®
CAS registry no:	104121-92-8
Molecular weight:	490.71



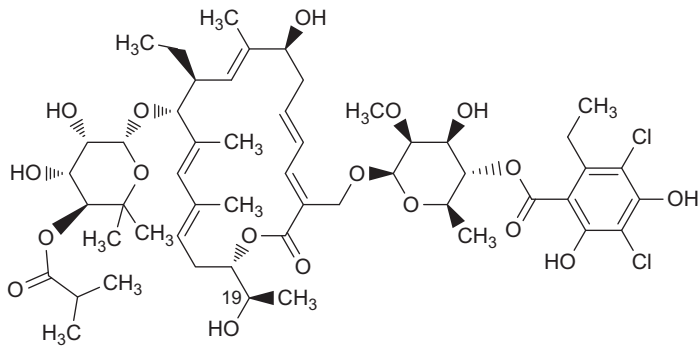
Eldecalcitol (Edirol®) was approved in January 2011 by the Japanese Ministry of Health, Labor, and Welfare for the treatment of osteoporosis. The prevalence of osteoporosis is increasing as the mean age of populations in Japan, Europe, United States, and several other countries increases. Japan, in particular, has one of the longest life expectancies in the world, with a mean age of 77 years for men and 84 years for women. In an aging population, the weakening of the bone matrix from osteoporosis increases the risk of severe fractures, such as spinal and hip fractures, thus creating a burden on quality of life and the health care system.[97] Some of the contributing risk factors are prior incidence of fracture, reduction of bone mineral density, and increasing age. Bone health is dependent on calcium homeostasis, which is maintained through the actions of vitamin D. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D, exerts its action through interactions with the calcitriol receptor, a nuclear hormone receptor that is responsible for calcium absorption and bone formation and depletion.[98] Because of vitamin D's central role in the bone health, vitamin D and analogs of vitamin D have been used to treat patients diagnosed with osteoporosis.[99] Eldecalcitol is an analog of the active form of vitamin D, calcitriol, in which the lower cyclohexane ring contains a hydroxypropyl group. The synthesis of eldecalcitol involves the assembly of two units, a fully protected (3*S*,4*S*,5*R*)-oct-1-en-7-yne-3,4,5-triol and a fused bicyclic system, (*R*)-6-((1*R*,3a*R*,7a*R*,*E*)-4-(bromomethylene)-7a-methyloctahydro-1*H*-inden-1-yl)-2-methylheptan-2-ol, through a Diels-Alder reaction to give fully protected eldecalcitol. The hydroxyl groups are then deprotected to give the parent molecule.[100] Eldecalcitol binds to the vitamin D receptor 2.7-fold more potently than calcitriol, while only weakly inhibiting serum parathyroid hormone. Eldecalcitol in animal studies (ovariectomized rats) showed improvements in bone mass while lowering bone resorption, thus demonstrating its effectiveness against osteoporosis in preclinical models.

In healthy male volunteers, eldecalcitol at oral doses from 0.1 to 1.0 μg once daily showed rapid absorption and linear PK with a long elimination half-life of 8 h reaching C_{max} in 3.4 h. Unlike vitamin D, eldecalcitol is not a substrate for CYP3A4. Eldecalcitol has been studied in two Phase III trials comparing its effectiveness in treating osteoporosis versus alpha-calcitriol. Biomarkers of osteoporosis, serum bone-specific alkaline phosphatase, and serum osteocalcin were significantly reduced in patients receiving eldecalcitol orally 1.0 μg once daily when compared to either placebo or alpha-calcitriol. In another Phase III study, eldecalcitol at a 0.75-μg dose once daily was found to be superior to alpha-calcitriol in reducing the

incidence of vertebrae fractions over 3 years. Eldecalcitol also was found to increase calcium levels and bone mineral density[101,102] over a 3-year period. Eldecalcitol (Edirol®) was approved in January 2011 by the Japanese Ministry of Health, Labour, and Welfare for the treatment of patients with osteoporosis (0.5 and 0.75 μg doses). Edirol® is being codeveloped by Chugai Pharmaceutical and Taisho Pharmaceutical Holdings.

13. FIDAXOMICIN (ANTIBACTERIAL)[103–108]

Class:	Bacterial RNA polymerase inhibitor
Country of origin:	United States
Originator:	Optimer Pharmaceuticals
First introduction:	United States
Introduced by:	Optimer Pharmaceuticals
Trade name:	Dificid®
CAS registry no:	873857-62-6
Molecular weight:	1058.04



Fidaxomicin (OPT-80) was approved by the U.S. FDA in May 2011 for the treatment of *Clostridium difficile*-associated diarrhea (CDAD), joining metronidazole and vancomycin as drugs recommended for treatment of *C. difficile* infections (CDI).[103,104] *C. difficile* is a gram-positive, anaerobic bacterium that is responsible for a variety of gastrointestinal (GI) infections. It is the causative agent in up to 25% of all antibiotic-associated diarrhea and 50–75% of antibiotic-associated colitis; severe cases of CDAD can result in death. Up to 2% of all hospitalized patients and up to 4% of intensive care patients are estimated to be infected with

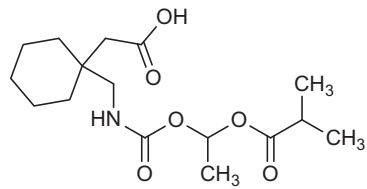
this pathogen, which has surpassed methicillin-resistant *Staphylococcus aureus* as the most common cause of hospital-acquired infections. Metronidazole is the preferred treatment for mild to moderate CDI, but is less effective than vancomycin for severe infections, including those caused by a hypervirulent strain of *C. difficile*. Vancomycin is effective in these cases but is also associated with selection of resistant bacteria. Fidaxomicin, also known as lipiarmycin and tiacumicin, is an 18-membered macrolide natural product that was first reported in mid-1970s[105] and is produced by fermentation.[106] Fidaxomicin and its primary metabolite OP-1118, which results from hydrolysis of the isobutyryl ester, are narrow-spectrum antibacterial agents with activity against gram-positive aerobic and anaerobic organisms, but not against gram-negative organisms. Fidaxomicin and OP-1118 exert their antibacterial activity by inhibiting bacterial RNA polymerase, thereby inhibiting bacterial protein synthesis. The MIC_{90} (minimum inhibitory concentration to kill 90% of bacteria) for fidaxomicin against *C. difficile* is 0.125–0.25 μg/mL; OP-1118 is 4- to 16-fold less potent than the parent compound. Fidaxomicin has been reported to spare native intestinal flora such as *Bacteroides* spp. and as such, may prevent selection of drug-resistant bacteria. Fidaxomicin is bactericidal to *C. difficile* and has a low propensity for resistance development with no cross-resistance to existing antibiotics.

Fidaxomicin shows minimal systemic absorption following oral administration in preclinical studies and humans.[107] Following single- and multiple-dosing regimens in healthy adults and CDI patients, plasma concentrations of fidaxomicin are negligible while fecal concentrations reach very high levels. In a Phase IIa study, fecal concentrations reached 1433 μg/g in subjects treated with 400 mg/day for 10 days, a concentration that is >5000 times higher than the MIC_{90} for *C. difficile*. The metabolite OP-1118 is found in feces at a $\sim$2:1 ratio of parent to metabolite. Fidaxomicin was evaluated in two Phase III randomized, multicenter, double-blinded trials designed to show noninferiority to vancomycin.[103] In a Phase III trial with 629 randomized patients having mild to severe CDI, 88.2% of patients treated with fidaxomicin (oral, 200 mg/day, twice a day, 10 days) achieved clinical cure compared with 85.8% of patients treated with vancomycin (oral, 125 mg/day, four times a day, 10 days). Patients receiving fidaxomicin had a statistically significant reduction in recurrence of CDI for all strains of *C. difficile* compared with vancomycin (15.4% vs. 25.3%). In a second Phase III trial, similar results were seen with

similar efficacy and lower rates of recurrence for fidaxomicin compared with vancomycin. Fidaxomicin was reported to be well tolerated in clinical studies. The major adverse events were similar to those for vancomycin and included nausea (11%), vomiting (7%), abdominal pain (6%), and GI hemorrhage (4%). Fidaxomicin (Dificid®) is available in the United States as a 200-mg tablet, with a recommended dose of 200 mg twice daily with or without food, for a treatment course of 10 days. The lower rate of recurrence of CDI with fidaxomicin makes it an attractive option for the treatment of CDI.[108]

14. GABAPENTIN ENACARBIL (RESTLESS LEG SYNDROME)[109–117]

Class:	Gamma aminobutyric acid analogue
Country of origin:	United States
Originator:	Xenoport
First introduction:	United States
Introduced by:	GlaxoSmithKline
Trade name:	Horizant®
CAS registry no:	478296-72-9
Molecular weight:	329.39



In April 2011, the U.S. FDA approved gabapentin enacarbil (XP-13512) for the treatment of moderate-to-severe Restless Legs Syndrome (RLS) in adults.[109] RLS is a neurological disorder that is characterized by an urge to move the legs, usually accompanied or caused by unpleasant sensations in the legs. Symptoms begin or worsen during periods of inactivity are relieved by movement (unlike leg cramps) and are typically worse in the evening. RLS results in significant sleep disturbances for patients and a reduction in daily function and quality of life. It is estimated that 2–3% of the United States population experience RLS symptoms that are severe enough to warrant pharmacological treatment. The underlying

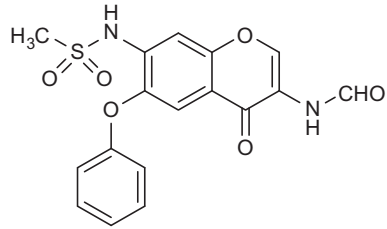
mechanism of RLS is not well understood. Two dopamine agonists, ropinirole and pramipexole, are currently approved in the U.S. for the treatment of RLS. While these agents provide relief for many RLS sufferers, they are not effective in all patients and can be associated with issues such as increased severity of symptoms and significant side effects. Gabapentin, which is approved in the United States for treatment of convulsions and for postherpetic neuralgia, has shown evidence of efficacy for RLS in clinical trials, although the mechanism of action is unclear. Gabapentin has variable and unpredictable bioavailability, which limits its utility as an oral agent. Gabapentin enacarbil is a novel prodrug of gabapentin that was designed to be recognized as a substrate for two high-capacity nutrient transports, monocarboxylate transporter type 1 and sodium-dependent multivitamin transporter, and to be efficiently cleaved after absorption to give gabapentin.[110] The separated enantiomers of gabapentin enacarbil have similar cleavage rates in human tissues. Preclinical studies showed that gabapentin enacarbil provides good systemic exposure of gabapentin in rats and monkeys.[111] Gabapentin enacarbil is prepared as a racemic mixture from gabapentin either by sequential coupling with 1-chloroethyl chloroformate in the presence of trimethylsilyl chloride and triethylamine followed by addition of isobutyric acid[110] or by direct coupling with an activated 1-(isobutyryloxy) ethyl carbonate.[112]

In healthy volunteers, gabapentin enacarbil was well absorbed and gave dose-proportional exposure of gabapentin with a T_{max} of 2.1–2.6 h and oral bioavailability based on urinary recovery of $>70\%$.[113] Oral bioavailability increased approximately twofold when taken with a meal. An extended release form gave a T_{max} of 7.3–9.8 h, with oral bioavailability of 82–86%. The efficacy of gabapentin enacarbil was demonstrated in two 12-week randomized, double-blinded, placebo-controlled clinical trials in adult RLS patient using endpoints based on the International Restless Legs Syndrome (IRLS) and Clinical Global Impression of Improvement (CGI-I) rating scales. In trial XP052, subjects with an initial IRLS score of ≥ 15 were treated with 1200 mg of gabapentin enacarbil or placebo, taken with food at 5 p.m. for 12 weeks.[114] Subjects who received gabapentin enacarbil showed a mean change in IRLS score of -13.2 and 76% responders based on the CGI-I scale, which was significantly improved compared to placebo controls (IRLS mean change of -8.8; 39% responders). The most commonly reported adverse events were somnolence (27% vs. 7% for placebo) and dizziness (20% vs. 5% for placebo). The XP053 12-week trial showed both 600

and 1200 mg of gabapentin enacarbil to significantly improve RLS symptoms and sleep disturbance compared with placebo.[115] Maintained improvements and long-term tolerability were demonstrated in a 9-month randomized, controlled study with 1200 mg of gabapentin enacarbil.[116] Gabapentin enacarbil (Horizant®) is supplied in an extended release tablet form, with the recommended dose of 600 mg once daily taken with food at about 5 p.m. Patients are warned not to drive until they have sufficient experience with Horizant® to assess whether it will impair their ability to drive.[117]

15. IGURATIMOD (ANTIARTHRITIC)[118–124]

Class:	Disease modifying antirheumatic drug
Country of origin:	Japan
Originator:	Toyama
First introduction:	China
Introduced by:	Simcere Pharmaceutical
Trade name:	Iremod
CAS registry no:	123663-49-0
Molecular weight:	374.37



In August 2011, China's State FDA approved Simcere Pharmaceutical Group's new drug application for iguratimod (T-614), a disease modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). The World Health Organization estimates the prevalence of RA to be 0.3–1% world-wide. RA is more common in women and developed countries. According to statistics from the Center for Disease Control and Prevention, ~1.5 million adults in the United States had RA in 2007. Prevalence of RA in mainland China ranges from 0.2% to 0.37% which is similar to most Asian countries.[118] While the exact pathophysiology of RA is not known, genetic predisposition along with environmental and hormonal

triggers contribute to the autoreactivity of the immune system. The pathogenesis of RA is multifactorial and includes synovial cell proliferation, fibrosis, pannus formation, and bone and cartilage erosion. The current paradigm for treating RA involves treatment with DMARD's such as methotrexate followed by injectable biologics such as etanercept, anakinra, tocilizumab, abatacept, rituximab, and others. Biochemical studies done at Toyama suggest that iguratimod inhibits PGE_2 production and COX-2 m-RNA expression in cultured fibroblasts suggesting a profile similar to selective COX-2 inhibitors.[119] Other mechanisms, such as suppression of NF-kB activation, have been proposed to explain the mechanism of action of iguratimod.[120] Preclinical *in vivo* studies indicated that iguratimod was effective in an established adjuvant-induced arthritis model ($ED_{40} = 3.6$ mg/kg) in rats and also efficacious in a type II collagen-induced arthritis model in DBA/1J mice at 30 mg and 100 mg/kg.[121] The key step in a four-step synthesis of iguratimod starting from readily available materials involves a pyrone-ring annulation with *N*,*N*-dimethylformamide dimethylacetal.[121]

In a controlled, randomized, double blind, parallel group Phase III study in 376 patients using American College of Rheumatology (ACR)20 response scores, iguratimod (25 mg for the first 4 weeks and 50 mg for the subsequent 24 weeks, oral dosing, daily) was superior to placebo (53.8% vs. 17.2%, $P < 0.001$) and was not inferior when compared to another DMARD salazosulfapyridine (63.1% vs. 57.7%).[122] A transient increase in hepatic enzyme levels, dermatological disorder (low frequency), abdominal pain, anemia, and symptoms related to gastrointestinal tract disorders were noted in this study. The long-term safety of iguratimod was assessed in a 52-week clinical study in 394 Japanese RA patients.[123] Increases in alanine aminotransferase and aspartate aminotransferase (19.4% and 18.3%, respectively) were noted in this study. ACR20 response rates were 46.9% at week 28 and 41.0% at week 52. A randomized, placebo-controlled, 24-week Phase II clinical study in 280 patients was conducted in China.[124] Ninety-five patients were assigned to the placebo group, while iguratimod was given to the remaining patients at daily oral doses of 50 mg ($n = 93$) or 25 mg ($n = 92$). After 24 weeks, the ACR20 scores for the 25 mg, 50 mg, and placebo groups were 39.13%, 61.29%, and 24.21%, respectively, while the ACR50 scores were 23.91%, 31.18%, and 7.37%, respectively. Adverse events noted in the 25 and 50 mg groups were upper abdominal discomfort, leucopenia, elevated serum alanine aminotransferase, skin rash, and/or pruritus. Simcere Pharmaceutical Group has conducted clinical trials comparing iguratimod

with methotrexate in RA patients, but results are not available. Iguratimod is taken orally at 25 mg twice daily.

16. IPILIMUMAB (ANTICANCER)[78,125–131]

Class:	Recombinant monoclonal antibody
Country of origin:	United States
Originator:	Bristol-Myers Squibb
First introduction:	United States
Type:	Human IgG1κ, anti-CTLA-4
Introduced by:	Bristol-Myers Squibb
Molecular weight:	~148 kDa
Trade name:	Yervoy®
Expression system:	Rodent CHO-cell line
CAS registry no:	477202-00-9

Ipilimumab is a CTLA-4 blocking antibody that was approved by the U.S. FDA in March 2011 for the treatment of unresectable or metastatic melanoma. Metastatic melanoma has a long-term remission rate of less than 10%, with over 9000 estimated U.S. deaths in 2012.[78,125] Ipilimumab was discovered by immunization of transgenic mice comprising human immunoglobulin genes to generate a human CTLA-4-specific human sequence monoclonal antibody.[126] CTLA-4 is a membrane-bound T-cell protein that delivers a negative signal on engagement of its ligands CD80 or CD86. Therefore, ipilimumab has an indirect effect on tumors that is mediated through blockade of CTLA-4 negative signaling and augmentation of T-cell activity. It is one of a handful of immunostimulatory drugs (e.g., aldesleukin and interferon alfa-2b) now approved for cancer therapy. The drug is formulated as a solution for intravenous infusion. The recommended dosage is 3 mg/kg administered intravenously over 90 min every 3 weeks for a total of four doses. With this dosing regimen, ipilimumab C_{min} at steady state was observed to be 21.8 mcg/mL (±11.2), and the terminal half-life was 14.7 days. Blood samples from 1024 ipilimumab-treated patients were tested for the presence of antidrug antibodies. Antibodies were detected in 1.1% of the patients; however, they were not neutralizing, and none of these patients experienced infusion reactions. Because T-cell activation from treatment

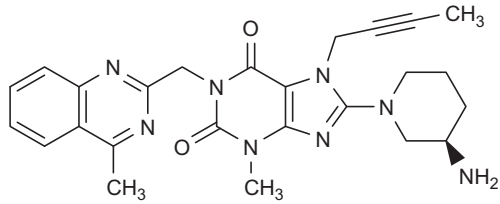
with ipilimumab can result in severe, and even fatal, immune-related reactions, the prescribing information includes specific warnings and precautions on the management of events such as enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and ocular inflammatory diseases. These include recommendations on discontinuation of ipilimumab treatment and on the use of corticosteroids to treat these reactions. Corticosteroid treatment of immune-related reactions does not appear to abrogate the efficacy of ipilimumab.[127]

Ipilimumab has been tested in two Phase III trials: one enrolling previously treated metastatic melanoma patients and the second in previously untreated patients. The first of these was a 3-arm (ipilimumab plus peptide vaccine, ipilimumab alone, vaccine alone; randomized 3:1:1) trial that enrolled 676 stage III or IV metastatic melanoma patients, whose disease had progressed while on a prior therapy.[128] Median survival for the ipilimumab plus vaccine arm was 10 months. For the ipilimumab alone and the vaccine alone arms, median survival was 10.1 and 6.4 months, respectively. This was the first Phase III, randomized, controlled trial to report a survival advantage for a therapeutic agent in metastatic melanoma patients. Consistent with the immunostimulatory mechanism of action of the drug, immune-related adverse events, such as rash, pruritis, vitiligo, diarrhea, colitis, hypothyroidism, hypopituitarism, hypohysitis, and adrenal insufficiency, were reported in approximately 60% of the ipilimumab-treated patients. The percentage of patients experiencing grade 3 immune-related adverse events was 9.7% and 12.2% in the two ipilimumab arms and 3% in the vaccine alone arm. Grade 4 immune-related events occurred at 0.5% and 2.3% in the ipilimumab arms. Fourteen deaths (2.1%) were reported to be related to study drug: eight in the combination arm, four in the ipilimumab alone arm, and two in the vaccine alone arm. Immune-related adverse events were managed by close patient follow-up and the administration of high-dose systemic corticosteroids as necessary for grade 3 and 4 events. The median time to resolution of grade 2 or higher diarrhea (the most common immune-related adverse event) was 2.0 and 2.3 weeks in the ipilimumab treatment arms. Four patients with diarrhea or colitis were treated with infliximab. Because the peptide vaccine used in two of the trial arms had been optimized for a single human leukocyte antigen (HLA) subtype, enrollment in the trial was restricted to patients positive for that subtype (HLA-A*0201). However, in a retrospective analysis of data from four different Phase II trials, no HLA

subtype-associated differences in survival or safety were observed.[129] Although the Phase III trial did not include a placebo arm, survival in the vaccine alone arm was consistent with historical data for other experimental agents in metastatic melanoma. A meta-analysis of data from 42 different Phase II trials of experimental agents involving 2100 metastatic melanoma patients between 1977 and 2005 found a 1-year survival rate 25.5%.[130] The vaccine alone arm of the ipilimumab Phase III showed 25.3% survival at 1 year, compared to 43.6% and 45.6% survival for the ipilimumab treatment arms. In the second Phase III clinical trial, a combination of ipilimumab therapy together with the cytotoxic drug dacarbazine was tested against dacarbazine alone in previously untreated metastatic melanoma patients.[131] The dose and schedule of ipilimumab in this trial was different from that used in the first Phase III (which was used to define the recommended dosage). Ipilimumab was given at 10 mg/kg instead of 3 mg/kg, and after four doses, some patients received additional doses. The 502 enrolled patients were randomized 1:1 to two treatment arms. Patients received 10 mg/kg ipilimumab, or a placebo, and 850 mg/m^2 dacarbazine on weeks 1, 4, 7, and 10, followed by 850 mg/m^2 dacarbazine every 3 weeks through week 22. Patients with stable disease or an objective response, and no dose-limiting toxicities, were subsequently dosed with 10 mg/kg ipilimumab, or placebo, every 12 weeks. Median survival was 11.2 months in the combination arm and 9.1 months in the dacarbazine alone arm. Survival rates at 1, 2, and 3 years were also higher in the ipilimumab-treated arm (47.3%, 28.5%, and 20.8% vs. 36.3%, 17.9%, and 12.2%). Grade 3 adverse events occurred in 40.1% of the ipilimumab patients, compared to 17.9% of the patients treated with dacarbazine alone. Rates of grade 4 events were 16.2% and 9.6% in the ipilimumab and dacarbazine alone arms, respectively. There were no reported drug-related deaths in the ipilimumab-treated patients. As in the previous Phase III trial, immune-related adverse events were the most common study drug-related events. However, the combination with dacarbazine appeared to result in a different spectrum of observed immune-related adverse events. In contrast to the previous trial, where diarrhea was the most commonly reported serious immune-related adverse event, elevated liver-function values were the most common immune-related adverse event when ipilimumab was combined with cytotoxic therapy. Grade 3 or 4 immune-related hepatitis was reported in 31.6% of the ipilimumab-treated patients compared to 2.4% of the patients in the dacarbazine alone arm.

17. LINAGLIPTIN (ANTIDIABETIC)[132–140]

Class:	Dipeptidyl peptidase-4 (DPP-4) inhibitor
Country of origin:	United States
Originator:	Boehringer Ingelheim
First introduction:	United States
Introduced by:	Boehringer Ingelheim and Eli Lilly and Company
Trade name:	Tradjenta®
CAS registry no:	668270-12-0
Molecular weight:	472.54



Linagliptin (trade names Tradjenta® and Trajetna®) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) that was approved by the U.S. FDA in May 2011 for the treatment of Type 2 diabetes along with diet and exercise. Type 2 diabetes is a disease in which insulin resistance and beta-cell dysfunction lead to hyperglycemia. According to the American Diabetic Association, diabetes is the seventh leading cause of death and increases the risk of heart disease and stroke by two to four times. Macro- and microvascular complications result from the progression of the severity of diabetes. The prevalence of diabetes continues to increase world-wide with an estimated 370 million people projected to be affected by 2030. The current number of cases in the United States (8% of the population) is predicted to double by 2050. In the United States, the economic impact of diabetes was estimated at $176 billion in 2007, with $116 billion attributed medical expenditures.[132,133] The progression of diabetes is attributed to several factors. Patients in a hyperglycemic state exhibit increases in free fatty acids, cytokines, adipokines, and associated metabolites leading to the loss of beta-cell function and beta-cell mass in islets.[134] As islet function is lost, the severity of insulin resistance increases. The introduction of dipeptidyl-peptidase IV inhibitors (DPP-4 inhibitors) has brought a novel class of insulinotropic agents into the treatment options available to type 2 diabetic patients. Glucagon-like peptide-1 (GLP-1), an endogenous 30-amino acid peptide that plays a central role in glucose homeostasis, is inactivated by cleavage of the N-terminal dipeptide sequence (His-Ala) through the

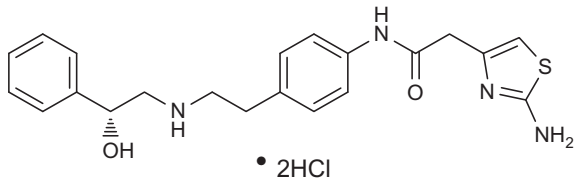
peptidase action of DPP-4. This inactivation occurs rapidly, with the half-life of circulating GLP-1 being <2 min. DPP-4 has several other substrates including another beneficial incretin peptide, gastric inhibitory peptide (GIP). Inhibitors of DPP-4 have been shown in man to increase GLP-1 and GIP levels two- to threefold. Because insulin secretion via the actions of GLP-1 occurs only in response to rising glucose levels, the risk of hypoglycemia is low, resulting in the wide acceptance of DPP-4 inhibitors into clinical practice. DPP-4 inhibitors are primarily once a day, weight neutral drugs with a favorable adverse-effect profile. As shown by animal studies, the class can decrease beta-cell apoptosis and increase beta-cell survival. In animal models, DPP-4 inhibitors increase the number of insulin positive beta-cells in islets. Islet insulin content is found to be increased, and glucose-stimulated insulin secretion in isolated islets is improved.[132–135] Linagliptin (BI-1356) has been described as a potent highly selective, slow-off rate and long acting inhibitor of DPP-4. Linagliptin arose from optimization efforts of xanthine-based DPP-4 inhibitors with the initial lead identified from an HTS campaign. After optimizing the activity of the initial micromolar lead, two issues that needed to be addressed were activity for hERG and muscarinic receptor M_1. Introduction of a butynyl group at the N7 position of the xanthine ring gave much reduced M_1 affinity with no measureable hERG activity. Linagliptin inhibits DPP-4 with an $IC_{50} = 1$ nM and is highly selective (>10,000-fold) against DPP-8 and DPP-9. Linagliptin shows no interactions with CYPs up to 50 μM. The described synthesis of linagliptin starts with 8-bromoxanthine, which is alkylated at the N-7 position to introduce the butyne group, followed by alkylation of the N-1 group to introduce the methyl-quinazoline group. Displacement of the bromide with (*R*)-Boc-3-amino-piperidine followed by deprotection gives linagliptin.[136] When administered to *db/db* mice orally, linagliptin dose dependently reduced glucose excursion from 0.1 mg/kg (15% inhibition) to 1 mg/kg (66% inhibition). Linagliptin was reported to have a longer *in vivo* duration of action on glucose tolerance when compared to other DPP-4 inhibitors.[137]

The initial Phase I PK studies in male type 2 diabetic patients studied doses of linagliptin at 1, 2.5, 5, and 10 mg once daily for 12 days. Linagliptin showed a less than dose proportional increase in exposure, a short accumulation half-life (8.6–23.9 h), and a rapid achievement of steady-state concentrations (2–5 days). Linagliptin showed a long terminal half-life of 113–131 h.[138] Linagliptin is eliminated primarily intact, with the primary route of excretion being fecal (84.7%) and renal excretion being a minor pathway (5.4%). With the low renal clearance, no dose adjustment is needed for patients with renal impairment. The most abundant metabolite, CD-1790, results from replacement of the

3-(*R*)-amino group of the piperidine by a 3-(*S*)-hydroxyl group. CD-1790 is formed at low levels (< 10% of parent drug concentrations)[139] via CYP3A4-mediated conversion of the amino group to a ketone, followed by reduction to the alcohol primarily by aldo-keto reductases. A comprehensive meta-analysis of the nine clinical trials of linagliptin as either monotherapy or in combination with metformin, sulfonylureas, or piaglitazone has been reported.[140] Linagliptin as monotherapy or in combination therapy gives a statistically significant reduction in fasting plasma glucose and HbA1C levels. Linagliptin was shown to be safe and well tolerated. Adverse events were minimal and not statistically different from placebo. In the eight Phase III trials, linagliptin did not increase cardiovascular events relative to placebo. The 6000 patient CARO-LINA study, comparing the effects of 5 mg linagliptin to glimeride on cardiovascular events, is ongoing. Linagliptin (Tradjenta®), a highly selective, long acting DPP-4 inhibitor for the treatment of type 2 diabetes, received regulatory approval from the U.S. FDA in May 2011 as monotherapy at a 5-mg dose taken once daily and as combination therapy as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Tradjenta® is the fifth marketed inhibitor of DPP-4 and is comarketed by Boehringer Ingelheim and Eli Lilly and Company.

18. MIRABEGRON (URINARY TRACT/BLADDER DISORDERS)[141–144]

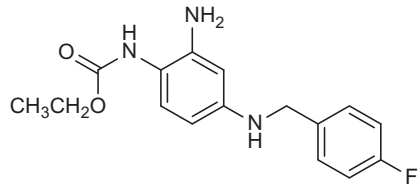
Class:	β_3-Adrenoceptor agonist
Country of origin:	Japan
Originator:	Astellas Pharma Inc.
First introduction:	Japan
Introduced by:	Astellas Pharma Inc.
Trade name:	Betanis®
CAS registry no:	223673-61-8 (free base) 223672-18-2 (salt)
Molecular weight:	396.51 (free base) 469.43 (salt)



Betanis® (Mirabegron) was approved in July 2011 by the Japanese Ministry of Health, Labour, and Welfare for the treatment of urgency, urinary frequency, and urinary urge urinary incontinence associated with overactive bladder (OAB). A study to determine the incidence of OAB in Japan found 14% of men and 11% of women had the condition with prevalence increasing with age.[141] Mirabegron activates the β_3-adrenergic receptor (β3-AR), which is located on the bladder and involved in bladder smooth muscle relaxation. Mirabegron is synthesized by coupling 4-nitrophenethyl amine to (*R*)-2-hydroxy-2-phenylacetic acid. The resulting amide is reduced to an amine. The nitro group is then reduced and the resulting aniline is coupled to 2-(2-aminothiazol-4-yl) acetic acid to give mirabegron.[142] Mirabegron has an EC_{50} of 22 nM (intrinsic activity = 0.8) for β3-AR with no detectable activity for β_1- and β_2-AR ($EC_{50} > 10{,}000$ nM). In an anesthetized rat rhythmic bladder contraction model in which bladder contractions are induced by saline, mirabegron at 3 mg/kg iv decreased the frequency of rhythmic bladder contraction without suppressing contraction amplitude. These data suggest that the activation of β3-AR increases bladder capacity without influencing the frequency of bladder contraction. In Phase I clinical studies, mirabegron was found to be metabolized by CYP3A4 and CYP2D6. Genetic polymorphism of CYP2D6 causes variability in the metabolism of mirabegron in humans. In patients characterized as poor metabolizers (PM), the amount of mirabegron excreted in the urine is higher (15.4%) versus patients that are extensive metabolizers (EM) where the amount in the urine is lower (11.7%). The terminal half-life in PM patients was 25 h and in the EM patients 23 h.[143] In a randomized, double-blinded Phase III study with 1976 patients comparing mirabegron 50 and 100 mg once daily to tolterodine extended-release (ER) 4 mg over 4 weeks in OAB patients, the frequency of incontinence per 24 h was reduced in both mirabegron dosing groups relative to the tolterodine-treated group. In another Phase III trial, mirabegron at 50 and 100 mg qd was studied over a 12-week period in patients with OAB. This 1328 patient study showed improvement in the reduction of incontinence episodes per 24 h versus placebo (−1.13, −1.47, and −1.63 for placebo, mirabegron 50 mg, and mirabegron 100 mg, respectively; $p < 0.05$).[144] Mirabegron, 50 mg once daily, was approved in July 2011 by the Japanese Ministry of Health, Labour, and Welfare for the treatment of urgency, urinary frequency, and urinary urge urinary incontinence associated with OAB. Betanis® is being developed by Astellas Pharma Inc.

19. RETIGABINE (ANTICONVULSANT)[145–156]

Class:	Potassium channel opener
Country of origin:	Germany
Originator:	ASTA Medica group
First introduction:	European Union
Introduced by:	Valeant/Glaxo Smith Kline
Trade name:	Trobalt (European Union), Potiga™ (United States)
CAS registry no:	150812-12-7
Molecular weight:	303.33



Retigabine was approved in March 2011 by the European Commission for the adjunctive treatment of partial-onset seizures in adults who have epilepsy; in June 2011, the U.S. FDA approved the same drug, known in the United States as ezogabine.[145–147] Epilepsy is a neurological disorder characterized by a predisposition to recurrent unprovoked seizures. Seizures are caused by abnormal electrical disturbances in the brain, with partial-onset seizures being localized to a limited area of the brain and generalized seizures affecting the whole brain. Epilepsy is estimated to affect more than 50 million people world-wide, with partial seizures occurring in ~60% of patients with epilepsy.[146] More than 20 antiepileptic drugs are available, however, 30–40% of patients continue to experience seizures on treatment with existing drugs.[148] Retigabine differs from all currently approved antiepileptic drugs in that it acts as a selective positive allosteric modulator (opener) of KCNQ2-5 potassium channels, which are key regulators of neuronal excitability.[149] The discovery of retigabine was based on modification of an analgesic agent flupirtine that had serendipitously shown potent anticonvulsant activity in animal models of epilepsy. Changing a central 2,3,6-triaminopyridine to a 1,2,4-triaminobenzene decreased analgesic activity while enhancing antiepileptic activity.[150] Retigabine (D-23129) was shown to be a broad spectrum anticonvulsant with oral activity in a variety of animal models. The mechanism of action of retigabine was discovered well after its

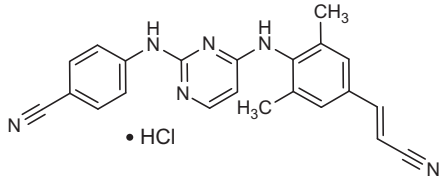
in vivo activity was recognized.[151] Retigabine can be prepared by reductive amination of 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene with 4-fluorobenzaldehyde, followed by hydrogenation in the presence of Raney nickel.[152]

The oral pharmacokinetic profile of retigabine was determined in healthy volunteers at doses of 25–600 mg and in patients at doses up to 1200 mg/day.[146] Retigabine is rapidly absorbed with T_{max} occurring between 0.5 and 2 h, and its absolute bioavailability relative to an intravenous dose is 60%. Retigabine undergoes extensive metabolism and is eliminated primarily by renal excretion as shown by administration of radiolabeled retigabine where 84% of the dose was eliminated in urine and 14% in feces. Parent drug was 36% of the dose in the urine, with 18% of the *N*-acetyl metabolite, and 24% of the *N*-glucuronide metabolite. Plasma protein binding of retigabine is ~80% and the volume of distribution is 2–3 L/kg at steady state. The plasma half-life of retigabine is 6–10 h, with an elimination half-life of 7–11 h. Coadministration of retigabine had no clinically significant effect on trough concentrations of various antiepileptic drugs. However, the clearance of retigabine was increased when dosed with carbamazepine or phenytoin. Retigabine is neither a substrate nor an inhibitor of CYP enzymes. In mutagenesis assays,[153] retigabine was negative in the *in vitro* Ames assay, the *in vitro* CHO *Hprt* gene mutation assay, and the *in vivo* mouse micronucleus assay. It was positive in the *in vitro* chromosomal aberration assay in human lymphocytes. The efficacy of retigabine was established in three randomized, double-blind, placebo-controlled studies in >1200 adult patients at oral doses of 600, 900, or 1200 mg/day tid. Enrolled patients had a diagnosis of localization-related epilepsy which was refractory to 1–3 antiepileptic drugs. The primary endpoint was change in seizure frequency from baseline; the secondary endpoint was responder rate defined as the percentage of patients with ≥50% reduction in total partial seizure frequency. In all three trials, patients had a forced titration period, wherein retigabine was initially given at 300 mg/day tid with an increase at 1-week intervals of 150 mg/day to the targeted dose, followed by a maintenance period of 8–12 weeks. In the first trial, decreases in seizures were 600 mg/day, −23%; 900 mg/day, −29%; 1200 mg/day, −35%; and placebo, −13%.[154] In the RESTORE-1 trial, 1200 mg/day tid of retigabine gave a 44% decrease in seizure frequency and a 44% responder rate (placebo: 17.5% decrease, 17.8% responder rate).[155] The RESTORE-2 trial showed significantly greater reductions in seizure frequency for retigabine at 600 mg/day (−28%) and 900 mg/day (−40%) compared with placebo (−16%).[156] Responder rates were also significantly improved. Across all trials, there were more study dropouts during the forced titration phase than during the maintenance phase. Adverse events noted in at least 10% of patients across

trials were primarily related to the central nervous system and included somnolence, dizziness, fatigue, and confusion. The recommended dose of retigabine (Trobalt/Potiga™) is 300 mg/day tid increasing by 150 mg/day tid in 1-week intervals to 600 mg/day tid to 1200 mg/day tid depending on tolerability.

20. RILPIVIRINE (ANTIVIRAL)[4,157–165]

Class:	HIV nonnucleoside reverse transcriptase inhibitor
Country of origin:	Belgium
Originator:	Janssen
First introduction:	United States
Introduced by:	Tibotec (a subsidiary of Johnson and Johnson)
Trade name:	Edurant®
CAS registry no:	500287-72-9 (free base) 700361-47-3 (salt)
Molecular weight:	366.42 (free base) 402.88 (salt)



In May 2011, the U.S. FDA approved rilpivirine in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) 1 infection in treatment-naïve adult patients. HIV infection results in destruction of host CD4+ T-cells, an essential part of the immune system, and can lead to acquired immune deficiency syndrome (AIDS), which is characterized by low T-cell count and the presence of opportunistic infections. In a joint UNAIDS/WHO report, it was estimated that in 2008, 33 million people worldwide were living with HIV infection and 2 million people died from AIDS-related deaths.[157] The U.S. CDC estimated in 2009 that 1.2 million people in the U.S. were living with HIV infection.[157] Drugs for treating HIV infection have been approved from several classes, including HIV reverse transcriptase (RT) inhibitors (nucleosides/nucleotides and nonnucleosides), HIV protease inhibitors, HIV fusion/entry inhibitors, HIV integrase inhibitors, and others.[158] Treatment of HIV infection was revolutionized in the mid-1990s with the recognition that combination therapy with multiple antiretroviral agents was highly effective in controlling HIV

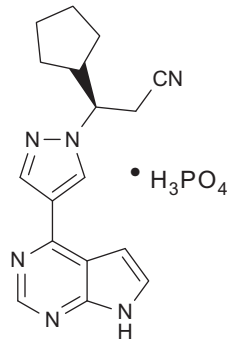
replication and inducing immune recovery. There remains a need for new HIV treatments that can be tolerated in long-term dosing with minimal side-effects, retained potency, and simplified dosing schedules. Rilpivirine is a member of the nonnucleoside reverse transcriptase inhibitor (NNRTI) class of anti-HIV agents. It is highly potent against a range of wild-type HIV strains ($EC_{50} = 0.07–1.0$ nM), ~10–20 times more potent than the NNRTI efavirenz (Sustiva®), and active against HIV strains resistant to other NNRTIs.[159,160] The discovery of rilpivirine was guided by molecular modeling and X-ray crystallography of HIV-1 RT complexed with inhibitors.[160,161] The synthesis of rilpivirine is accomplished by an efficient 6-step route in which the key step is coupling of 4-((4-chloropyrimidin-2-yl)amino)benzonitrile with (*E*)-3-(4-amino-3,5-dimethylphenyl)acrylonitrile.[159] In preclinical studies, the oral bioavailability of rilpivirine was 31% in dogs and 32% in rats.

When rilpivirine was given to HIV-seronegative male volunteers in a 7-day study with single daily doses ranging from 25 to 200 mg, T_{max} was 3–4 h, C_{max} was 2–3 times higher on day 7 than on day 1, and the terminal half-life was 34–55 h.[159,162,163] The C_{max} decreased by 45% when given under fasting conditions, indicating that rilpivirine should be given with food. Rilpivirine is highly protein bound (99.7%) and is a substrate but not an inhibitor of CYP3A4. Based on drug–drug interaction studies, rilpivirine should not be coadministered with drugs that cause CYP3A4 induction or gastric pH increase as these may lead to significant decreases in plasma concentrations. In studies with ^{14}C-labeled rilpivirine, 85% of radioactivity was recovered in feces and 6% in urine. Unchanged drug accounted for 25% of drug-related material in feces. Glutathione-dependent conjugative metabolism is the primary pathway of metabolism in hepatocytes from rodents and humans. The efficacy, safety, and tolerability of rilpivirine in comparison with efavirenz were assessed in two 48-week Phase III trials in patients not previously given antiretroviral therapy. A 25-mg dose of rilpivirine was selected based on having the best efficacy/side-effect profile in a 96-week Phase IIb trial extended to 192 weeks. In the ECHO trial,[164] rilpivirine (25 mg, once daily) and efavirenz (600 mg, once daily) were dosed in combination with tenofovir and emtricitabine; in the THRIVE[165] trial, rilpivirine was combined with an investigator-selected regimen of tenofovir/emtricitabine, zidovudine/lamivudine, or abacavir/lamivudine. Pooled results from the two trials showed that rilpivirine was equivalent to efavirenz in reducing viral load, with 83% of patients having undetectable virus levels in the rilpivirine combination regimen compared with 80% for the efavirenz

combination regimen. Patients with higher initial viral load were more likely to not respond to rilpivirine than efavirenz; patients who failed rilpivirine therapy had more drug resistance than those who failed on efavirenz. Compared with efavirenz, rilpivirine showed a lower incidence of CNS effects, rash, and serum lipid disturbances. Rilpivirine (Edurant®) was approved as a 25-mg oral tablet to be taken once daily with a meal in combination with other antiretroviral drugs for the treatment of HIV1 infection. In August 2011, the FDA approved the specific three-drug combination Complera®, a fixed dose combination of rilpivirine (25 mg) with emtricitabine (200 mg), and tenofovir (300 mg) to be given once daily taken orally with meals.[4]

21. RUXOLITINIB (ANTICANCER)[166–171]

Class:	Janus kinase 1 and 2 inhibitor
Country of origin:	United States
Originator:	Incyte Corporation
First introduction:	United States
Introduced by:	Incyte Corporation
Trade name:	Jakafi®
CAS registry no:	941678-49-5 (free base) 1092939-17-7 (salt)
Molecular weight:	306.37 (free base) 404.36 (salt)



In November 2011, the U.S. FDA approved ruxolitinib (INCB018424) for the treatment of patients with intermediate or high-risk myelofibrosis. The annual incidence rate of primary myelofibrosis in European, Australian, and North American populations is estimated to range from 0.3 to 1.5 cases per 100,000 persons.[166] Treatment options for myelofibrosis include

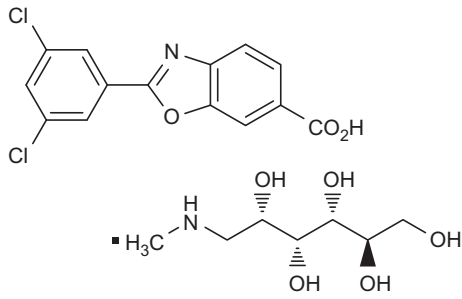
allogeneic hematopoietic stem cell transplantation (allo-HSCT) although this is more appropriate for younger, sufficiently healthy patients with high-risk myelofibrosis for whom a suitable donor is available. Other options include (a) treatment with hydroxyurea or low dose thalidomide and prednisone mainly to alleviate organomegaly and cytopenia (b) splenectomy, and (c) spleen irradiation. Myelofibrosis is associated with dysregulated Janus-associated kinases (JAKs) JAK1 and JAK2. Ruxolitinib is an ATP-competitive inhibitor of JAK1 and JAK2 ($IC_{50's}$ of 3.3 ± 1.2 nM and 2.8 ± 1.2 nM, respectively) and inhibition occurs regardless of the $JAK2^{V617F}$ mutational status. Ruxolitinib is a moderately potent inhibitor of the related JAK, TYK2 ($IC_{50} = 19 \pm 3.2$ nM) but is selective versus JAK3 ($IC_{50} = 428 \pm 243$ nM). It was also selective versus a panel of 26 other kinases at concentrations approximately 100-fold the IC_{50} of JAK1 and JAK2.[167] Inhibition of JAK1 and JAK2 downregulates the JAK-signal transducer and activator of transcription (STAT) pathway, inhibiting myeloproliferation, inducing apoptosis, and reducing numerous cytokine plasma levels. Consistent with this hypothesis, ruxolitinib inhibited IL-6 and thrombopoietin induced STAT-3 phosphorylation in an *in vitro* human whole blood assay with $IC_{50's}$ of 282 ± 54 nM and 281 ± 62 nM, respectively.[167] In a mouse model of myeloproliferative neoplasms, ruxolitinib dosed orally reduced enlargement of the spleen; eliminated neoplastic cells from the spleen, liver, and bone marrow; normalized histology of affected organs; and prolonged survival. In addition, significant suppression of IL-6 levels was seen and TNF-α levels were normalized.[167] An enantiospecific synthesis of ruxolitinib employing an organocatalytic asymmetric aza-Michael addition of pyrazoles to (*E*)-3-cyclopentylacrylaldehyde with diarylprolinol silyl ether as the catalyst has been described.[168]

The pharmacokinetics and pharmacodynamics of ruxolitinib were evaluated in single and multiple ascending dosing studies in healthy volunteers.[169] In the single ascending dose studies (5, 10, 25, 50, 100, and 200 mg), ruxolinitib was rapidly absorbed with a mean T_{max} of < 2 h and a mean terminal half-life of <5 h. Clearance was low (~ 20 L/h) and the apparent volume of distribution at the terminal phase was moderate (79–97 L). The apparent volume of distribution of ruxolitinib in myelofibrosis patients, at steady-state, was 53–65 L. Ruxolinitib is a substrate for CYP3A4 and is significantly protein bound ($\sim 97\%$). The safety and efficacy of ruxolinitib were assessed in two Phase III trials in patients with myelofibrosis. Study 1 (COMFORT-I)[170] was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for

available therapy. The ongoing Study 2 (COMFORT-II)[171] is an open-label, randomized study in 219 patients who were randomized 2:1 to ruxolinitib versus best available therapy. The primary efficacy endpoint was the proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at week 24 (for Study 1) or week 48 (for Study 2) as measured by MRI or CT. In Study 1, efficacy analysis of primary endpoints indicated that the response rate was 41.9% among recipients of ruxolitinib at a starting dosage of 15 or 20 mg twice daily (depending on baseline platelet count) and then optimized during treatment, compared with 0.7% for placebo ($p < 0.0001$). In the ongoing Study 2, a response rate of 28.5% has been reported. The most common hematologic adverse reactions (incidence >20%) are thrombocytopenia and anemia. The most common nonhematologic adverse reactions (incidence >10%) are bruising, dizziness, and headache. The recommended dose of ruxolitinib is 20 mg administered orally twice daily.

22. TAFAMIDIS MEGLUMINE (NEURODEGENERATION)[172–176]

Class:	Transthyretin stabilizer
Country of origin:	United States
Originator:	Scripps Research Institute
First introduction:	European Union
Introduced by:	Pfizer
Trade name:	Vyndaqel®
CAS registry no:	951395-08-7 (salt) 594839-88-0 (free acid)
Molecular weight:	503.33 (salt) 308.12 (free acid)



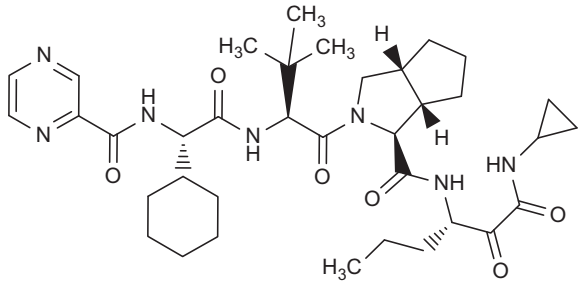
In November 2011, the European Commission approved tafamidis meglumine (Fx-1006A, PF-06291826) for the treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in adult patients with stage 1 symptomatic polyneuropathy. TTR-FAP is a rare, progressive, and fatal disorder which presents itself phenotypically in the form of neuropathy, cardiomyopathy, renal failure, and blindness. TTR-FAP affects approximately 8000–10,000 patients worldwide.[172] Since transthyretin (TTR) is primarily synthesized in the liver, liver transplantation is an option for younger patients with the common Val30Met (V30M) mutation but is of little benefit for older patients or those with other mutations (*vide infra*). TTR is a 55-kDa homotetramer (each monomer is comprised of 127 amino acids) that transports thyroxine and retinol. The dissociation of the TTR tetramer into monomers is thought to be the rate-limiting step in the pathogenesis of TTR-FAP. The monomers, which are rich in beta sheet structures, undergo partial denaturation resulting in amyloid deposits. The hereditary form of the disease is caused by autosomal dominant mutations in the TTR gene. Tafamidis stabilizes both the wild type and mutant forms of TTR tetramer and prevents tetramer dissociation[173] by noncooperatively binding to the two thyroxine binding sites. Tafamidis is the first approved medicine for TTR-FAP. The K_d values for tafamidis for the two thyroxine binding sites on TTR, as determined by isothermal titration calorimetry, were 3 nM and 278 nM, respectively. In another *in vitro* study using wild type TTR, V30M mutant TTR, and V122I mutant TTR, it was shown that tafamidis inhibited fibril formation in a concentration-dependent manner reaching EC_{50} at a tafamidis:TTR stoichiometry of <1 (EC_{50} was in the range of 2.7–3.2 μM, corresponding to a tafamidis:TTR stoichiometry range of 0.75–0.9).[174] Tafamidis has been synthesized by coupling 4-amino-3-hydroxybenzoic acid with 3,5-dichlorobenzoyl chloride followed by dehydration using *p*-toluenesulfonic acid.[174] A recent publication describes the use of a nickel-catalyzed C-H arylation employing 1,3-dichloro-5-iodobenzene and a benzoxazole amide.[175]

In Phase I clinical trials in healthy volunteers, it was shown that tafamidis (20 mg, oral dosing) was rapidly absorbed with a T_{max} of 0.5 h and mean C_{max} of 1431 ng/mL. The mean $AUC_{0-\infty}$ derived from plasma concentration profile for tafamidis was 47,864.31 ng.h/ml, the mean apparent total clearance was 0.44 L/h, and the mean half-life of the terminal elimination phase was 54 h. Volume of distribution of the central compartment (V_c/F) and volume of distribution of the peripheral compartment (V_p/F) estimates were 0.48 L and 18.9 L, respectively.[176]

Tafamidis is highly protein bound (>99.5%). Following the completion of a pivotal Phase II/III trial, a 1-year open-label extension study was conducted to evaluate long-term safety and efficacy of tafamidis in which patients who completed the 18-month pivotal study were eligible to enroll. Of the 86 patients enrolled in the study, 45 were previously on tafamidis and 41 were previously on placebo. Patients treated with tafamidis for 30 months had less neurologic deterioration than patients who began tafamidis 18 months later (the placebo-tafamidis group), showing a 55.9% preservation of function as measured by the Neuropathy Impairment Score-Lower Limb (NIS-LL, primary endpoint). In addition, the secondary endpoints demonstrated that patients treated with tafamidis over 30 months showed preservation in large (66% preservation) and small nerve fiber function (45.5%). Despite having more severe disease (i.e., those patients initiating treatment 18 months later), initiation of tafamidis in patients previously on placebo resulted in slowing of disease progression.[176] Most common adverse drug reactions reported included diarrhea, upper abdominal pain, urinary tract infection, and vaginal infection. The recommended dose of tafamidis is 20 mg orally once daily.

23. TELAPREVIR (ANTIVIRAL)[69,70,177–183]

Class:	Hepatitis C virus NS3-4A Protease inhibitor
Country of origin:	United States
Originator:	Eli Lilly
First introduction:	United States
Introduced by:	Vertex Pharmaceuticals
Trade name:	Incivek®
CAS registry no:	402957-28-2
Molecular weight:	679.85



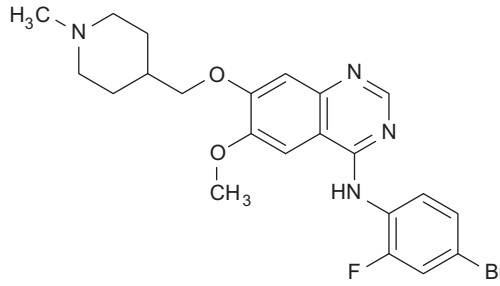
The hepatitis C virus (HCV) protease inhibitor telaprevir (VX-950, MP-424, LY-570310) was approved by the U.S. FDA in May 2011 for the treatment of genotype 1 chronic HCV infection in adult patients in combination with peginterferon alfa and ribavirin (PR).[69,177] Telaprevir and boceprevir (*vide supra*) are the first two HCV protease inhibitors to be approved for treatment of HCV infection. The World Health Organization estimates that 3% of the world population (170 million people) is infected with HCV and that 3–4 million new cases occur each year.[70] HCV is an RNA virus that causes acute and chronic liver disease. Infected individuals may remain asymptomatic for years, but >70% of people chronically infected with HCV progress to serious illness, including cirrhosis and hepatocellular carcinoma. Before the introduction of HCV protease inhibitors, the standard of care for treating HCV infection was a combination of PR. Some patients are cured of HCV infection with this regimen, as defined by a sustained virologic response (SVR) without detectable HCV RNA for 6 months after completion of therapy. However, with HCV genotype 1, which is the most prevalent subtype in the United States, Europe, and Japan, only 40–50% of patients achieve viral cure with PR therapy. In addition, the PR regimen has many adverse side effects, making it difficult for patients to tolerate the 48-week treatment duration. Telaprevir is a HCV NS3-4A protease inhibitor that exerts its antiviral effect by blocking the release of nonstructural viral proteins from a polyprotein precursor. Telaprevir is a potent inhibitor of the protease ($IC_{50}=10$ nM) and is active in cell culture (HCV 1b replicon assay, $EC_{50}=354$ nM).[177] Telaprevir was identified from efforts to truncate a decamer peptide inhibitor derived from the natural substrate NS5A-5B and was guided by structure-based design. The keto-amide group of telaprevir forms a covalent, reversible bond with the active site serine hydroxyl of the protease and compensates for the loss of affinity resulting from truncation of the peptide. Despite the presence of the reactive keto-amide group, telaprevir is >500-fold less potent against other serine proteases. Synthesis of the key octahydrocyclopenta[*c*]pyrrole-1-carboxylic acid fragment of telaprevir is achieved by α-deprotonation of Boc-protected 3-azabicyclo[3.3.0]nonane followed by reaction with CO_2 and resolution of the racemic acid.[178,179] Alternatively, deprotonation is carried out in the presence of a chiral amine to give the enantiomerically enriched acid.

Initial evaluation of telaprevir in healthy volunteers at doses up to 1250 mg every 8 h for 5 days showed the drug to be well tolerated.[180] Telaprevir was next evaluated in a Phase Ib study as a single agent in HCV-infected patients at doses of 450, 750, or 1250 mg, three times daily

for 14 days. While a profound and rapid reduction in plasma HCV RNA was noted, viral breakthrough due to selection of variants with decreased sensitivity was observed in some patients, indicating that telaprevir should not be used as monotherapy. The 750-mg dose gave the most consistent antiviral activity and lowest viral breakthrough and was chosen as the clinical dose.[180] Exposures are higher in combination with PR than when given alone and exposure is 330% higher when given with a high fat meal. Telaprevir reaches T_{max} 4–5 h after dosing and has an elimination half-life of 4–5 h. The major metabolites are the (*R*)-isomer at the position α to the keto-amide (30 times less potent than the (*S*)-isomer), pyrazinoic acid, and the inactive-reduced ketoamide. Dosing of ^{14}C-telaprevir gave 90% recovery of radioactivity, with 82% in the feces and 1% in urine. Telaprevir is a substrate and inhibitor for CYP3A4 and a substrate for P-glycoprotein. It is 59–76% bound to plasma proteins. The efficacy of telaprevir in combination with PR was established in three Phase III clinical trials with the primary endpoint of SVR, defined as undetectable HCV RNA 24 weeks after the end of treatment. The ADVANCE trial was a randomized, double-blind, placebo-controlled study in treatment naïve patients.[181] SVR was 75% in patients given telaprevir/PR for 12 weeks followed by PR to week 24 or week 48 versus 44% SVR on PR alone. The patients with the shorter duration of PR follow-on therapy were those who had achieved an extended rapid viral response (eRVR), defined as undetectable HCV RNA at weeks 4 and 12. The SVR rate was 92% in this subset of subjects. The ILLUMINATE trial[182] was a randomized, open-label trial in treatment-naive subjects given PR plus 750 mg of telaprevir three times a day for 12 weeks followed by PR. The SVR rate in patients with eRVR was 92% in patients receiving 12 weeks of follow-up on PR versus 90% in patients receiving 36 weeks of PR follow-up, indicating noninferiority of the shorter follow-up duration. The REALIZE trial[183] enrolled patients who were previously treated with PR and either had poor responses or relapsed following treatment. SVR rates were significantly higher in the telaprevir/PR patients compared with PR alone: 86% versus 22% in relapsers, 59% versus 15% in partial responders, and 32% versus 5% in non-responders. The most common adverse events with telaprevir/PR combination therapy were rash, fatigue, pruritis, nausea, anemia, and diarrhea. The largest differences in adverse reactions compared with PR alone were with rash (56%), pruritis (47%), and anemia (36%). Adverse events were reversible after discontinuation of drug. The recommended dosage of telaprevir (Incivek®) is 750 mg taken three times a day with food, and in combination with peginterferon alfa and ribavirin.

24. VANDETANIB (ANTICANCER)[184–189]

Class:	EGFR family, VEGF, RET inhibitor
Country of origin:	United Kingdom
Originator:	Astra Zeneca
First introduction:	United States
Introduced by:	AstraZeneca
Trade name:	Caprelsa®
CAS registry no:	443913-73-3
Molecular weight:	475.36

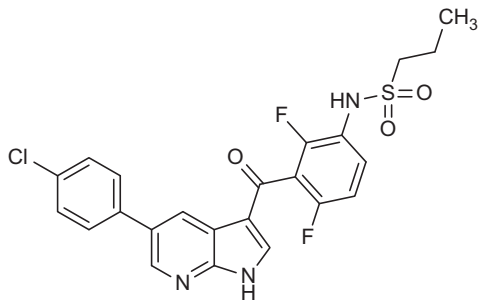


In April 2011, the U.S. FDA approved vandetanib (ZD6474) for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in adult patients with inoperable advanced or metastatic disease. According to statistics from the National Cancer Institute, there are 56,000 new cases of thyroid cancer each year in the United States.[184] Of the four types of thyroid cancer (papillary, follicular, medullary, and anaplastic), the incidence of MTC is 4%. The prognosis for MTC is poor. Surgery and radiotherapy are commonly employed to remove the primary tumor, but the treatment of metastatic disease remains a challenge with 5-year survival rates of ~40%. Twenty-five percent of MTC cases are primarily associated with the RET (REarranged during Transfection) oncogene. Vandetanib inhibits KDR/VEGFR2, VEGFR3, EGFR, and RET kinases with $IC_{50's}$ of 40, 110, 500, and <100 nM, respectively.[185] In athymic mice bearing MTC tumors, a 14.5-fold reduction of tumor volume was observed after 45 days of treatment with vandetanib at 50 mg/kg/day. The decrease in tumor volume was accompanied by decreases in mitotic index (Ki67) and tumor angiogenesis in treated xenografts. Key steps in the synthesis of vandetanib include the displacement of the chlorine atom from 7-benzyloxy-4-chloro-6-methoxyquinazoline with 4-bromo-2-fluoroaniline under acidic conditions in a protic solvent and a Mitsunobu reaction of a *N*-protected piperidine alcohol with a phenol.[186,187]

In a study conducted on 231 patients with MTC, oral administration of vandetanib at 300 mg/day had a mean clearance of approximately 13.2 L/h, a mean volume of distribution of approximately 7450 L, a median T_{max} of 6 h, and a median plasma half-life of 19 days. The *in vitro* protein binding for vandetanib was ~90%.[188] The efficacy of vandetanib was assessed in a single, double-blind, placebo-controlled study involving 331 patients with unresectable locally advanced or metastatic MTC.[189] Of the 331 patients enrolled in the study, 231 were randomized to vandetanib (300 g) and 100 were randomized to placebo. Progression free survival (PFS), which was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), was used as the efficacy end point. Statistically significant improvements in PFS were observed in patients randomly assigned to vandetanib compared to placebo after a median follow-up period of 24 months. Patients with the most common activating gene mutation in MTCs, *RET* Met918Thr, had better response rates and more prolonged PFS than patients without this mutation. Most common adverse events for vandetanib versus placebo included diarrhea, rash, acne, nausea, hypertension, headache, fatigue, decreased appetite, abdominal pain, and QTc prolongation. The recommended dose of vandetanib is 300 mg administered orally once daily.

25. VEMURAFENIB (ANTICANCER)[190–195]

Class:	Kinase inhibitor
Country of origin:	United States
Originator:	Plexxikon
First introduction:	United States
Introduced by:	Hoffman-La Roche.
Trade name:	Zelboraf®
CAS registry no:	918504-65-1
Molecular weight:	489.9



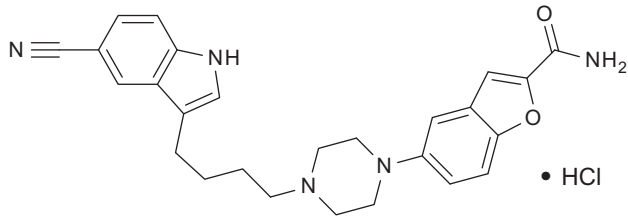
In August 2011, the United States FDA approved vemurafenib (PLX-4032, RO-5185426) for the treatment of patients with metastatic melanoma with the $BRAF^{V600E}$ mutation. Statistics from the National Cancer Institute indicate ~76,250 new cases of melanoma will be diagnosed in 2012.[190] Immunotherapeutic options include treatment with IL-2 and more recently with ipilimumab. Chemotherapeutic options include treatment with dacarbazine. However, overall survival (OS) rates with either IL-2 or dacarbazine treatment are not high. Vemurafenib has been developed as a targeted therapy for patients with the BRAF gene mutation since oncogenic B-raf signaling is implicated in approximately 50% of melanomas. A mutation in the kinase domain at nucleotide 1799 of the BRAF gene results in the substitution of valine to glutamic acid leading to the constitutive activation of B-raf kinase. This results in excessive cell proliferation due to dysregulated downstream signaling and gene expression. Vemurafenib was identified based on an initial high-throughput screen followed by the extensive use of structure-based drug design.[191,192] Vemurafenib is a potent inhibitor of $B\text{-}Raf^{V600E}$ kinase ($IC_{50} = 13$ nM) compared to its potency against wild-type B-raf ($IC_{50} = 160$ nM) and is fairly selective versus a panel of 200 kinases.[192] It does inhibit other kinases (RAF1, SRMS, ACK1, MAP4K5, and FGR) and mutant B-raf kinases ($BRAF^{V600K}$, $BRAF^{V600D}$, and $BRAF^{V600R}$) with enzyme $IC_{50's}$ of < 100 nM.[193] Vemurafenib was tested against a panel of 17 melanoma cell lines and was a potent inhibitor in cell lines expressing the $B\text{-}Raf^{V600E}$ mutant. In a murine LOX melanoma xenograft model, vemurafenib significantly inhibited tumor growth and induced tumor regression when dosed at 12.5, 25, and 75 mg/kg BID.[193] Efficacy was also seen in the A-375, COLO 829, and C8161 melanoma models. Key steps in the synthesis of vemurafenib[194] are a Friedel-Crafts reaction of 5-bromopyrrolo[2,3-*b*] pyridine with 2,6-difluoro-3-(propylsulfonamido)benzoyl chloride followed by Suzuki coupling with 4-chlorophenylboronic acid.

Pooled data from 458 patients with BRAF mutation-positive metastatic melanoma dosed with vemurafenib at 960 mg (BID) indicated a median T_{max} of ~3 h with a mean C_{max} and AUC_{0-12} of 62 ± 17 μg/mL and 601 ± 170 μg h/mL, respectively. Apparent volume of distribution and clearance are estimated to be 106 L and 31 L/day, respectively, and the half-life is estimated to be 57 h. The safety and efficacy of vemurafenib was assessed in a randomized, open label trial involving 675 patients.[195] Of these, 337 patients were assigned to vemurafenib, 960 mg orally twice daily, and the rest were assigned to dacarbazine at 1000 mg/m^2 administered intravenously once every 3 weeks. Efficacy measures included OS and investigator-assessed

progression-free-survival (PFS). Interim analysis of the trial after 6 months indicated that the OS was 6.2 months for patients treated with vemurafenib and 4.5 months for patients treated with dacarbazine. The median PFS was 5.3 months for patients receiving vemurafenib and 1.6 months for patients receiving dacarbazine. In a second, single-arm trial involving 132 patients with $BRAF^{V600E}$ mutation and who had received at least one systemic therapy, the median duration of response was 6.5 months when vemurafenib was administered at 960 mg orally twice daily.[195] Most common adverse events (>30%) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma. Cutaneous squamous cell carcinoma occurred in ~24% of patients treated with vemurafenib. The recommended dose of vemurafenib is 960 mg administered orally twice daily for the treatment of patients with metastatic melanoma, as detected by the cobas 4800 BRAF V600 mutation Test (Roche Molecular Systems, Inc.).

26. VILAZODONE HYDROCHLORIDE (ANTIDEPRESSANT)[196–204]

Class:	Dual serotonin reuptake inhibitor and 5-HT1A partial agonist
Country of origin:	Germany
Originator:	Merck KGaA
First introduction:	United States
Introduced by:	Forest Laboratories
Trade name:	Viibryd®
CAS registry no:	163521-12-8 (free base) 163521-08-2 (salt)
Molecular weight:	441.52 (free base) 477.99 (salt)



In January 2011, the U.S. FDA approved vilazodone for the treatment of major depressive disorder (MDD).[196,197] MDD is a serious medical condition that is characterized by persistent low mood, sadness, loss of interest in previously enjoyed activities, feelings of guilt or worthlessness, and thoughts of death or suicide. It is estimated that ~15% of the United

States population will experience MDD in their lifetime, with rates being higher in women than men. Treatments for MDD include antidepressant medications, psychotherapy, and electroconvulsive therapy. Among antidepressant treatments, the selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications. Although these agents are generally safe and effective, fewer than 50% of all patients with depression show full remission with optimized SSRI treatment.[198] In addition, SSRIs must typically be dosed for 1–2 weeks before clinical benefit is seen. SSRIs act by blocking the serotonin (5-hydroytryptamine, 5-HT) transporter, which leads to increased levels of extracellular 5-HT and acute stimulation of presynaptic 5-HT1A autoreceptors with an initial reduction of 5-HT cell firing and 5-HT release. Repeated dosing of SSRIs is thought to lead to desensitization of 5-HT1A autoreceptors, thereby increasing 5-HT levels and augmenting serotonergic neurotransmission. Combination of SSRI activity with 5-HT1A partial agonism or antagonism is an approach to improving the onset of antidepressant efficacy by blunting the initial activation of the 5-HT1A receptor. Vilazodone is a novel antidepressant agent that combines potent serotonin reuptake inhibition ($IC_{50} = 0.2$ nM) with high affinity for 5-HT1A receptors ($IC_{50} = 0.5$ nM) and partial 5-HT1A receptor agonist functional activity. Vilazodone has good selectivity over other monoamine receptors and is efficacious in preclinical models of depression in rats and mice.[199] Vilazodone is an indolylbutylpiperazine derivative that has been prepared by coupling of an indolylbutyl chloride or tosylate with 5-(piperazin-1-yl)benzofuran-2-carboxamide or the corresponding ester.[200] The cyanoindole portion of vilazodone is important for conferring high affinity for both the serotonin transporter and the 5-HT1A receptor. Para-substitution on the phenyl group attached to the piperidine moiety reduces affinity for dopamine receptors, while the carboxamide group provides improved pharmacokinetic properties.[200]

In humans, vilazodone shows dose proportional increases in exposure at doses ranging from 5 to 80 mg.[196] Doses higher than 40 mg were poorly tolerated. Steady state is achieved after 3 days, with a plasma accumulation factor of 1.8. Vilazodone is 96–99% protein bound and has a high volume of distribution. Studies with radiolabeled vilazodone gave 85% recovery of radioactivity, with 65% in feces and 20% in urine. Only 3% was recovered as unchanged drug. Vilazodone is primarily metabolized by CYP3A4 to an inactive 6-hydroxylindole derivative.[201,202] When given with food, the C_{max} for vilazodone increases 147–160%, the AUC increases 64–85%, T_{max} is 4–5 h, and bioavailability is 72%. The efficacy of vilazodone was

demonstrated in two Phase III short term (8-week), randomized, double-blind, placebo-controlled trials with ~900 subjects.[203] In these studies, vilazodone was given at a 10-mg dose for 7 days, a 20-mg dose for the next 7 days, and a 40-mg daily dose thereafter. The primary endpoint was the mean change in the Montgomery-Asberg Depression Rating Scale (MADRS), with the secondary endpoints including the change in the 17-item Hamilton Rating Score for Depression (HAM-D-17). After 8 weeks, there was a significant reduction from baseline in the MADRS (−12.9 for vilazodone treatment vs. −9.6 for placebo) and HAM-D-17 scores (−13.3 for vilazodone treatment vs. −10.3 for placebo). Data from a 52-week, open-label trial in ~600 subjects were used for evaluation of efficacy, safety, and tolerability.[204] Patients were titrated to a 40-mg dose and showed a significant improvement in MADRS total score (29.9 at baseline to 7.1 at week 52) and in other measures of efficacy. Common adverse events were diarrhea and nausea in both the 8- and 52-week trials and were considered mild to moderate. In the 8-week trials, there was a lower incidence of weight gain and sexual dysfunction compared with placebo. As with all approved antidepressant drugs in the United States, vilazodone has a black box warning describing the increased risk of suicidal thinking and behavior in children, adolescents, and young adults. The recommended dose of vilazodone is 40 mg once daily following titration from 10 mg for 7 days to 20 mg for 7 days. Vilazodone should be taken with food and the dose of vilazodone should be decreased to 20 mg if given in combination with a CYP3A4 inhibitor. Because there were no active comparators in clinical trials with vilazodone, differentiation from other antidepressants remains to be established.

Note: The authors are employees of Bristol-Myers Squibb and own stock in the company.

REFERENCES

(1) The collection of new therapeutic entities first launched in 2011 originated from the following sources: Prous Integrity Database; Thomson-Reuters Pipeline Database; The Pink Sheet; Drugs@FDA Website; FDA News Releases; IMS R&D Focus; Adis Business Intelligence R&D Insight; Pharmaprojects.
(2) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm285554.htm.
(3) http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280525.htm.
(4) http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm267592.htm.
(5) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202331lbl.pdf.
(6) http://www.merck.com/product/usa/pi_circulars/j/juvisync/juvisync_pi.pdf.
(7) http://seer.cancer.gov/statfacts/html/prost.html.

(8) O'Donnell, A.; Judson, I.; Dowsett, M.; Raynaud, F.; Dearnaley, D.; Mason, M.; Harland, S.; Robbins, A.; Halbert, G.; Nutley, B.; Jarman, M. *Br. J. Cancer* **2004**, *90*, 2317.
(9) Potter, G.A.; Barrie, S.E.; Jarman, M.; Rowlands, M.G. *J. Med. Chem.* **1995**, *38*, 2463.
(10) Jarman, M.; Barrie, S.E.; Llera, J.M. *J. Med. Chem.* **1998**, *41*, 5375.
(11) Potter, G.A.; Hardcastle, I.R.; Jarman, M. *Org. Prep. Proc. Int.* **1997**, *29*, 123.
(12) Barrie, S.E.; Potter, G.A.; Goddard, P.M.; Haynes, B.P.; Dowsett, M.; Jarman, M. *J. Steroid Biochem. Mol. Biol.* **1994**, *50*, 267.
(13) de Bono, J.S.; Logothetis, C.J.; Molina, A.; Fizazi, K.; North, S.; Chu, L.; Chi, K.N.; Jones, R.J.; Goodman, O.B., Jr.; Saad, F.; Staffurth, J.N.; Mainwaring, P.; Harland, S.; Flaig, T.W.; Hutson, T.E.; Cheng, T.; Patterson, H.; Hainsworth, J.D.; Ryan, C.J.; Sternberg, C.N.; Ellard, S.L.; Fléchon, A.; Saleh, M.; Scholz, M.; Efstathiou, E.; Zivi, A.; Bianchini, D.; Loriot, Y.; Chieffo, N.; Kheoh, T.; Haqq, C.M.; Scher, H.I. *N. Engl. J. Med.* **2011**, *364*, 1995.
(14) Sonpavde, G.; Attard, G.; Bellmunt, J.; Mason, M.D.; Malavaud, B.; Tombal, B.; Sternberg, C.N. *Eur. Urol.* **2011**, *60*, 270.
(15) Stewart, M.W.; Grippon, S.; Kirkpatrick, P. *Nat. Rev. Drug Discov.* **2012**, *11*, 269.
(16) http://www.nei.nih.gov/health/maculardegen/armd_facts.asp.
(17) Stewart, M.W. *Mayo Clin. Proc.* **2012**, *87*, 77.
(18) Holash, J.; Davis, S.; Papadopoulos, N.; Croll, S.D.; Ho, L.; Russell, M.; Boland, P.; Leidich, R.; Hylton, D.; Burova, E.; Ioffe, E.; Huang, T.; Radziejewski, C.; Bailey, K.; Fandl, J.P.; Daly, T.; Wiegand, S.J.; Yancopoulos, G.D.; Rudge, J.S. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 11393.
(19) Papadopoulos, N.; Martin, J.; Ruan, Q.; Rafique, A.; Rosconi, M.P.; Shi, E.; Pyles, E.A.; Yancopoulos, G.D.; Stahl, N.; Weigand, S.J. *Angiogenesis* **2012**, *15*, 171.
(20) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf.
(21) Ohr, M.; Kaiser, P.K. *Expert Opin. Pharmacother.* **2012**, *13*, 585.
(22) Gaya, A.; Tse, V. *Cancer Treat. Rev.* **2012**, *38*, 484.
(23) Kim, E.S.H.; Bartholomew, J.R. Cleveland Clinic, August 1, 2010. Available at www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/venous-thromboembolism/.
(24) White, R.H. *Circulation* **2003**, *107*, 1.
(25) Quinlan, D.J.; Eikelboom, J.W.; Dahl, O.E.; Eriksson, B.I.; Sidhu, P.S.; Hirsh, J. *J. Thromb. Haemost.* **2007**, *5*, 1438.
(26) Kearon, C. *Chest* **2003**, *124*, 386S.
(27) Martin, M.T.; Nutescu, E.A. *Curr. Med. Res. Opin.* **2011**, *27*, 2123.
(28) Mann, K.G.; Nesheim, M.E.; Church, W.R.; Haley, P.; Krishnaswamy, S. *Blood* **1990**, *76*, 1.
(29) Davie, E.W. *Thromb. Haemost.* **1995**, *74*, 1.
(30) Davie, E.W. *J. Biol. Chem.* **2003**, *278*, 50819.
(31) Graham, J.B. *J. Thromb. Haemost.* **2003**, *1*, 871.
(32) Keiser, B. *Drugs Fut.* **1998**, *23*, 423.
(33) Pinto, D.J.P.; Orwat, M.J.; Koch, S.; Rossi, K.A.; Alexander, R.S.; Smallwood, A.; Wong, P.C.; Rendina, A.R.; Luettgen, J.M.; Knabb, R.M.; He, K.; Xin, B.; Wexler, R.R.; Lam, P.Y.S. *J. Med. Chem.* **2007**, *50*, 5339.
(34) Wong, P.C.; Crain, E.J.; Xin, B.; Wexler, R.R.; Lam, P.Y.S.; Pinto, D.J.; Luettgen, J.M.; Knabb, R.M. *J. Thromb. Haemost.* **2008**, *6*, 820.
(35) Raghavan, N.; Frost, C.E.; Yu, Z.; He, K.; Zhang, H.; Humphreys, W.G.; Pinto, D.; Chen, S.; Bonacorsi, S.; Wong, P.C.; Zhang, D. *Drug Metab. Dispos.* **2009**, *37*, 74.
(36) Granger, C.B.; Alexander, J.H.; McMurray, J.J.; Lopes, R.D.; Hylek, E.M.; Hanna, M.; Al-Khalidi, H.R.; Ansell, J.; Atar, D.; Avezum, A.; Bahit, M.C.;

Diaz, R.; Easton, J.D.; Ezekowitz, J.A.; Flaker, G.; Garcia, D.; Geraldes, M.; Gersh, B.J.; Golitsyn, S.; Goto, S.; Hermosillo, A.G.; Hohnloser, S.H.; Horowitz, J.; Mohan, P.; Jansky, P.; Lewis, B.S.; Lopez-Sendon, J.L.; Pais, P.; Parkhomenko, A.; Verheugt, F.W.; Zhu, J.; Wallentin, L. *N. Engl. J. Med.* **2011**, *365*, 981.

(37) Prom, R.; Spinler, S.A. *Ann. Pharmacother.* **2011**, *45*, 1262.

(38) PharmAsia News Oct 21st, 2011 http://www.elsevierbi.com/publications/pharmasia-news?issue=Oct-21-2011.

(39) Alwaal, A.; Al-Mannie, R.; Carrier, S. *Drug Des. Devel. Ther.* **2011**, *5*, 435.

(40) Limin, M.; Johnsen, N.; Hellstrom, W.J.G. *Expert Opin. Invest. Drugs* **2010**, *19*, 1427.

(41) Yamada, K.; Matsuki, K.; Omori, K.; Kikkawa, K. Patent Application US 2004/0142930, **2004**.

(42) Peterson, C.; Swearingen, D. *J. Sex. Med.* **2006**, *3*, 253.

(43) Jung, J.; Choi, S.; Cho, S.H.; Ghim, J.-L.; Hwang, A.; Kim, U.; Kim, B.S.; Koguchi, A.; Miyoshi, S.; Okabe, H.; Bae, K.-S.; Lim, H.-S. *Clin. Ther.* **2010**, *32*, 1178.

(44) VIVUS Announces Positive Results From Avanafil Phase 3 Study in Diabetics Presented at the 47th EASD Annual Meeting. 13 September **2011**. Available from: http://ir.vivus.com/releasedetail.cfm?ReleaseID=604819.

(45) Goldstein, I.; McCullough, A.R.; Jones, L.A.; Hellstrom, W.J.; Bowden, C.H.; DiDonato, K.; Trask, B.; Day, W.W. *J. Sex. Med.* **2012**, *9*, 1122.

(46) Yoon, S.S.; Ostchega, Y.; Louis, T. NCHS Data Brief, **2010**, *48*. http://www.cdc.gov/nchs/data/databriefs/db48.pdf.

(47) Lavoie, J.L.; Sigmund, C.D. *Endocrinology* **2003**, *144*, 2179.

(48) Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228.

(49) Ojima, M.; Igata, H.; Tanaka, M.; Sakamoto, H.; Kuroita, T.; Kohara, Y.; Kubo, K.; Fuse, H.; Imura, Y.; Kusumoto, K.; Nagaya, H. *J. Pharmacol. Exp. Ther.* **2011**, *336*, 801.

(50) *Azilsartan Medoxomil (TAK 491) Investigator's Brochure*. 3rd ed. Deerfield, IL: Takeda Global Research & Development Center, Inc; 2007.

(51) White, W.B.; Weber, M.A.; Sica, D.; Bakris, G.L.; Perez, A.; Cao, C.; Kupfer, S. *Hypertension* **2011**, *57*, 413.

(52) Bakris, G.L.; Sica, D.; Weber, M.; White, W.B.; Roberts, A.; Perez, A.; Cao, C.; Kupfer, S. *J. Clin. Hypertens.* **2011**, *13*, 81.

(53) Knoll, G. *Drugs* **2008**, *68*(Suppl. 1), 3.

(54) Bia, M.; Adey, D.B.; Bloom, R.D.; Chan, L.; Kulkarni, S.; Tomlanovich, S. *Am. J. Kidney Dis.* **2010**, *56*, 189.

(55) Larsen, C.P.; Pearson, T.C.; Adams, A.B.; Tso, P.; Shirasugi, N.; Strobert, E.; Anderson, D.; Cowan, S.; Price, K.; Naemura, J.; Emswiler, J.; Greene, J.; Turk, L.A.; Bajorath, J.; Townsend, R.; Hagerty, D.; Linsley, P.S.; Peach, R.J. *Am. J. Transplant.* **2005**, *5*, 443.

(56) Vincenti, F.; Charpentier, B.; Vanrenterghem, Y.; Rostaing, L.; Bresnahan, B.; Darji, P.; Massari, P.; Mondragon-Ramirez, G.A.; Agarwal, M.; Di Russo, G.; Lin, C.S.; Garg, P.; Larsen, C.P. *Am. J. Transplant.* **2010**, *10*, 535.

(57) Vincenti, F.; Larsen, C.P.; Alberu, J.; Bresnahan, B.; Garcia, V.D.; Kothari, J.; Lang, P.; Urrea, E.M.; Massari, P.; Mondragon-Ramirez, G.; Reyes-Acevedo, R.; Rice, K.; Rostaing, L.; Steinberg, S.; Xing, J.; Agarwal, M.; Harler, M.B.; Charpentier, B. *Am. J. Transplant.* **2012**, *12*, 210.

(58) Larsen, C.P.; Grinyó, J.; Medina-Pestana, J.; Vanrenterghem, Y.; Vincenti, F.; Breshahan, B.; Campistol, J.M.; Florman, S.; Rial Mdel, C.; Kamar, N.; Block, A.; Di Russo, G.; Lin, C.S.; Garg, P.; Charpentier, B. *Transplantation* **2010**, *90*, 1528.

(59) Vanrenterghem, Y.; Bresnahan, B.; Campistol, J.; Durrbach, A.; Grinyó, J.; Neumayer, H.H.; Lang, P.; Larsen, C.P.; Mancilla-Urrea, E.; Pestana, J.M.; Block, A.; Duan, T.; Glicklich, A.; Gujrathi, S.; Vincenti, F. *Transplantation* **2011**, *91*, 976.
(60) Durrbach, A.; Pestana, J.M.; Pearson, T.; Vincenti, F.; Garcia, V.D.; Campistol, J.; Rial Mdel, C.; Florman, S.; Block, A.; Di Russo, G.; Xing, J.; Garg, P.; Grinyó, J. *Am. J. Transplant.* **2010**, *10*, 547.
(61) Pestana, J.O.; Grinyo, J.M.; Vanrenterghem, Y.; Becker, T.; Campistol, J.M.; Florman, S.; Garcia, V.D.; Kamar, N.; Lang, P.; Manfro, R.C.; Massari, P.; Rial, M.D.; Schnitzler, M.A.; Vitko, S.; Duan, T.; Block, A.; Harler, M.B.; Durrbach, A. *Am. J. Transplant.* **2012**, *12*, 630.
(62) Centers for Disease Control, Prevention (CDC), *Morb. Mortal. Wkly. Rep.* **2002**, *51*, 371.
(63) Lo, M.S.; Tsokos, G.C. *Annu. N.Y. Acad. Sci.* **2012**, *1247*, 138.
(64) Stohl, W.; Hiepe, F.; Latinis, K.M.; Thomas, M.; Scheinberg, M.A.; Clarke, A.; Aranow, C.; Wellborne, F.R.; Abud-Mendoza, C.; Hough, D.R.; Pineda, L.; Migone, T.S.; Zhong, Z.J.; Freimuth, W.W.; Chatham, W.W.; on Behalf of the Bliss-52 and -76 Study Groups, *Arthritis Rheum.* **2012**, *64*, 2328.
(65) Baker, K.P.; Edwards, B.M.; Main, S.H.; Choi, G.H.; Wager, R.E.; Halpern, W.G.; Lappin, P.B.; Riccobene, T.; Abramian, D.; Sekut, L.; Sturm, B.; Poortman, C.; Minter, R.R.; Dobson, C.L.; Williams, E.; Carmen, S.; Smith, R.; Roschke, V.; Hilbert, D.M.; Vaughan, T.J.; Albert, V.R. *Arthritis Rheum.* **2003**, *48*, 3253.
(66) Furie, R.; Stohl, W.; Ginzler, E.M.; Becker, M.; Mishra, N.; Chatham, W.; Merrill, J.T.; Weinstein, A.; McCune, W.J.; Zhong, J.; Cai, W.; Freimuth, W.; the Belimumab Study Group, *Arthritis Res. Ther.* **2008**, *10*, R109.
(67) Navarra, S.V.; Guzmán, R.M.; Gallacher, A.E.; Hall, S.; Levy, R.A.; Jimenez, R.E.; Li, E.K.; Thomas, M.; Kim, H.Y.; León, M.G.; Tanasescu, C.; Nasonov, E.; Lan, J.L.; Pineda, L.; Zhong, Z.J.; Freimuth, W.; Petri, M.A.; the BLISS-52 Study Group, *Lancet* **2011**, *377*, 721.
(68) Furie, R.; Petri, M.; Zamani, O.; Cervera, R.; Wallace, D.J.; Tegzová, D.; Sanchez-Guerrero, J.; Schwarting, A.; Merrill, J.T.; Chatham, W.W.; Stohl, W.; Ginzler, E.M.; Hough, D.R.; Zhong, Z.J.; Freimuth, W.; van Vollenhoven, R.F.; the BLISS-76 Study Group, *Arthritis Rheum.* **2011**, *63*, 3918.
(69) Butt, A.A.; Kanwal, F. *Clin. Infect. Dis.* **2012**, *54*, 97.
(70) Asselah, T.; Marcellin, P. *Liver Int.* **2012**, *32*(s1), 88.
(71) World Health Organization, June 2011. http://www.who.int/mediacentre/factsheets/fs164/en.
(72) Venkatraman, S.; Bogen, S.L.; Arasappan, A.; Bennett, F.; Chen, K.; Jao, E.; Liu, Y.-T.; Lovey, R.; Hendrata, S.; Huang, Y.; Pan, W.; Parekh, T.; Pinto, P.; Popov, V.; Pike, R.; Ruan, S.; Santhanam, B.; Vibulbhan, B.; Wu, W.; Yang, W.; Kong, J.; Liang, X.; Wong, J.; Liu, R.; Butkiewicz, N.; Chase, R.; Hart, A.; Agrawal, S.; Ingravallo, P.; Pichardo, J.; Kong, R.; Baroudy, B.; Malcolm, B.; Guo, Z.; Prongay, A.; Madison, V.; Broske, L.; Cui, X.; Cheng, K.-C.; Hsieh, Y.; Brisson, J.-M.; Prelusky, D.; Korfmacher, W.; White, R.; Bogdanowich-Knipp, S.; Pavlovsky, A.; Bradley, P.; Saksena, A.K.; Ganguly, A.; Piwinski, J.; Girijavallabhan, V.; Njoroge, F.G. *J. Med. Chem.* **2006**, *49*, 6074.
(73) Prongay, A.J.; Guo, Z.; Yao, N.; Pichardo, J.; Fischmann, T.; Strickland, C.; Myers, J., Jr.; Weber, P.C.; Beyer, B.M.; Ingram, R.; Hong, Z.; Prosise, W.W.; Ramanathan, L.; Taremi, S.S.; Yarosh-Tomaine, T.; Zhang, R.; Senior, M.; Yang, R.-S.; Malcolm, B.; Arasappan, A.; Bennett, F.; Bogen, S.L.; Chen, K.; Jao, E.; Liu, Y.-T.; Lovey, R.G.; Saksena, A.K.; Venkatraman, S.; Girijavallabhan, V.; Njoroge, F.G.; Madison, V. *J. Med. Chem.* **2007**, *50*, 2310.
(74) Campas, C.; Pandian, R.; Bolos, J.; Castaner, R. *Drugs Fut.* **2009**, *34*, 697.
(75) Rizza, S.A.; Talwani, R.; Nehra, V.; Temesgen, Z. *Drugs Today* **2011**, *47*, 743.

(76) Poordad, F.; McCone, J., Jr.; Bacon, B.R.; Bruno, S.; Manns, M.P.; Sulkowski, M.S.; Jacobson, I.M.; Reddy, K.R.; Goodman, Z.D.; Boparai, N.; DiNubile, M.J.; Sniukiene, V.; Brass, C.A.; Albrecht, J.K.; J-P. Bronowicki for the SPRINT-2 Investigators, *N. Engl. J. Med.* **2011**, *364*, 1195.
(77) Bacon, B.R.; Gordon, S.C.; Lawitz, E.; Marcellin, P.; Vierling, J.M.; Zeuzem, S.; Poordad, F.; Goodman, Z.D.; Sings, H.L.; Boparai, N.; Burroughs, M.; Brass, C.A.; Albrecht, J.K.; Esteban, R.; for the RESPOND-2 Investigators, *N. Engl. J. Med.* **2011**, *364*, 1207.
(78) Siegel, R.; Naishadham, D.; Jemal, A. *CA Cancer J. Clin.* **2012**, *62*, 10.
(79) Younes, A.; Yasothan, U.; Kirkpatrick, P. *Nat. Rev. Drug Discov.* **2012**, *11*, 19.
(80) Francisco, J.A.; Cerveny, C.G.; Meyer, D.L.; Mixan, B.J.; Klussman, K.; Chace, D.F.; Rejniak, S.X.; Gordon, K.A.; DeBlanc, R.; Toki, B.E.; Law, C.L.; Doronina, S.O.; Siegall, C.B.; Senter, P.D.; Wahl, A.F. *Blood* **2003**, *102*, 1458.
(81) Younes, A.; Bartlett, N.L.; Leonard, J.P.; Kennedy, D.A.; Lynch, C.M.; Sievers, E.L.; Forero-Torres, A. *N. Engl. J. Med.* **2010**, *363*, 1812.
(82) Chen, R.; Gopal, A.K.; Smith, S.E.; Ansell, S.M.; Rosenblatt, J.D.; Klasa, R.; Connors, J.M.; Engert, A.; Larsen, E.K.; Kennedy, D.A.; Sievers, E.L.; Anas Younes, *Blood,* 2010, *116*, ASH Annual Meeting Abstracts # 283.
(83) Shustov, A.R.; Advani, R.; Brice, P.; Bartlett, N.L.; Rosenblatt, J.D.; Illidge, T.; Matous, J.; Ramchandren, R.; Fanale, M.A.; Connors, J.M.; Yang, Y.; Sievers, E.L.; Kennedy, D.A.; Pro, B. *Blood* **2010**, *116* ASH Annual Meeting Abstracts # 961.
(84) http://www.cancer.gov/cancertopics/types/lung.
(85) Cui, J.J.; Tran-Dube, M.; Shen, H.; Nambu, M.; Kung, P.-P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McTigue, M.; Grodsky, N.; Ryan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R.S.; Edwards, M.P. *J. Med. Chem.* **2011**, *54*, 6342.
(86) Christensen, J.G.; Zou, H.Y.; Arango, M.E.; Li, Q.; Lee, J.H.; McDonnell, S.R.; Yamazaki, S.; Alton, G.R.; Mroczkowski, B.; Los, G. *Mol. Cancer Ther.* **2007**, *6*, 3314.
(87) de Koning, P.D.; McAndrew, D.; Moore, R.; Moses, I.B.; Boyles, D.C.; Kissick, K.; Stanchina, C.L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P.R. *Org. Process Res. Dev.* **2011**, *15*, 1018.
(88) (a) Tan, W.; Wilner, K.D.; Bang, Y.; Kwak, E.L.; Maki, R.G.; Camidge, D.R.; Solomon, B.J.; Ou, S.I.; Salgia, R.; Clark, J.W. *J. Clin. Oncol.* **2010**, *28*(suppl; abstr 2596). (b) Li, C.; Alvey, C.; Bello, A.; Wilner, K.D.; Tan, W. *J. Clin. Oncol.* **2011**, *29* (suppl; abstr e13065).
(89) (a) Crinò, L.; Kim, D.; Riely, G.J.; Janne, P.A.; Blackhall, F.H.; Camidge, D.R.; Hirsh, V.; Mok, T.; Solomon, B.J.; Park, K.; Gadgeel, S.M.; Martins, R.; Han, J.; De Pas, T.M.; Bottomley, A.; Polli, A.; Petersen, J.; Tassell, V.R.; Shaw, A.T. *J. Clin. Oncol.* **2011**, *29*(suppl; abstr 7514). (b) Kwak, E.L.; Bang, Y.-J.; Camidge, D.R.; Shaw, A.T.; Solomon, B.; Maki, R.G.; Ou, S.-H.I.; Dezube, B.J.; Jänne, P.A.; Costa, D.B.; Varella-Garcia, M.; Kim, W.-H.; Lynch, T.J.; Fidias, P.; Stubbs, H.; Engelman, J.A.; Sequist, L.V.; Tan, W.; Gandhi, L.; Mino-Kenudson, M.; Wei, G.C.; Shreeve, S.M.; Ratain, M.J.; Settleman, J.; Christensen, J.G.; Haber, D.A.; Wilner, K.; Salgia, R.; Shapiro, G.I.; Clark, J.W.; Iafrate, A.J. *N. Engl. J. Med.* **2010**, *363*, 1693. (c) Camidge, D.R.; Bang, Y.; Kwak, E.L.; Shaw, A.T.; Iafrate, A.J.; Maki, R.G.; Solomon, B.J.; Ou, S.I.; Salgia, R.; Wilner, K.D.; Costa, D.B.; Shapiro, G.; LoRusso, P.; Stephenson, P.; Tang, Y.; Ruffner, K.; Clark, J.W. *J. Clin. Oncol.* **2011**, *29*(suppl; abstr 2501).
(90) http://www.daiichisankyo.com/news/20110422_305_E.pdf.

(91) Haginoya, N.; Kobayashi, S.; Komoriya, S.; Yoshino, T.; Suzuki, M.; Shimada, T.; Watanabe, K.; Hirokawa, Y.; Furugoori, T.; Nagahara, T. *J. Med. Chem.* **2004**, *47*, 5167.
(92) Yoshikawa, K.; Yokomizo, A.; Naito, H.; Haginoya, N.; Kobayashi, S.; Yoshino, T.; Nagata, T.; Mochizuki, A.; Osanai, K.; Watanabe, K.; Kanno, H.; Ohta, T. *Bioorg. Med. Chem.* **2009**, *17*, 8206.
(93) Yoshikawa, K.; Kobayashi, S.; Nakamoto, Y.; Haginoya, N.; Komoriya, S.; Yoshino, T.; Nagata, T.; Mochizuki, A.; Watanabe, K.; Suzuki, M.; Kanno, H.; Ohta, T. *Bioorg. Med. Chem.* **2009**, *17*, 8221.
(94) Furugohri, T.; Isobe, K.; Honda, Y.; Kamisato-Matsumoto, C.; Sugiyama, N.; Nagahara, T.; Morishima, Y.; Shibano, T. *J. Thromb. Haemost.* **2008**, *6*, 1542.
(95) Ogata, K.; Mendell-Harary, J.; Tachibana, M.; Masumoto, H.; Oguma, T.; Kojima, M.; Kunitada, S. *J. Clin. Pharm.* **2010**, *50*, 743.
(96) Camm, A.J.; Bounameaux, H. *Drugs* **2011**, *71*, 1503.
(97) Fujiwara, S. *J. Bone Miner. Metab.* **2005**, *23*, 83.
(98) Holick, M.F.; Siris, E.S.; Binkley, N.; Beard, M.K.; Khan, A.; Katzer, J.T.; Petruschke, R.A.; Chen, E.; de Papp, A.E. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 3215.
(99) Avenell, A.; Gillespie, W.J.; Gillespie, L.D.; O'Connell, D. *Cochrane Database of Systematic Reviews*, **2009**, Issue 2. Art. No.: CD000227. doi: http://dx.doi.org/10.1002/14651858. CD000227.pub3.
(100) Hatakeyama, S.; Yoshino, M.; Eto, K.; Takahashi, K.; Ishihara, J.; Ono, Y.; Saito, H.; Kubodera, N. *J. Steroid Biochem. Mol. Biol.* **2010**, *121*, 25.
(101) Sanford, M.; McCormack, P.L. *Drugs* **2011**, *71*, 1755.
(102) Ito, M.; Nakamura, T.; Fukunaga, M.; Shiraki, M.; Matsumoto, T. *Bone* **2011**, *49*, 328.
(103) Hardesty, J.S.; Juang, P. *Pharmacotherapy* **2011**, *31*, 877.
(104) Lancaster, J.W.; Matthews, S.J. *Clin. Ther.* **2012**, *34*, 1.
(105) Coronelli, C.; Parenti, F.; White, R.; Pagani, H. US Patent 3978211, 1976.
(106) Shue, Y.-K.; Hwang, C.-K.; Chiu, Y.-H.; Romero, A.; Babakhani, F.; Sears, P.; Okumu, F. US Patent Application 2008/0269145, **2008**.
(107) Miller, M. *Expert Opin. Pharmacother.* **2010**, *11*, 1569.
(108) Dolgin, E. *Nat. Med.* **2011**, *17*, 10.
(109) Burke, R.A.; Faulkner, M.A. *Expert Opin. Pharmacother.* **2011**, *12*, 2905.
(110) Cundy, K.C.; Branch, R.; Chernov-Rogan, T.; Dias, T.; Estrada, T.; Hold, K.; Koller, K.; Liu, X.; Mann, A.; Panuwat, M.; Raillard, S.P.; Upadhyay, S.; Wu, Q.Q.; Xiang, J.-N.; Yan, H.; Zerangue, N.; Zhou, C.X.; Barrett, R.W.; Gallop, M.A. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 315.
(111) Cundy, K.C.; Annamalai, T.; Bu, L.; De Vera, J.; Estrela, J.; Luo, W.; Shirsat, P.; Torneros, A.; Yao, F.; Zou, J.; Barrett, R.W.; Gallop, M.A. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 324.
(112) Revill, P.; Bolos, J.; Serradell, N.; Bayes, M. *Drugs Fut.* **2006**, *31*, 771.
(113) Cundy, K.C.; Sastry, S.; Luo, W.; Zou, J.; Moors, T.L.; Canafax, D.M. *J. Clin. Pharmacol.* **2008**, *48*, 1378.
(114) Kushida, C.A.; Becker, P.M.; Ellenbogen, A.L.; Canafax, D.M.; Barrett, R.W.; the XP052 Study Group, *Neurology* **2009**, *72*, 439.
(115) Lee, D.O.; Ziman, R.B.; Perkins, A.T.; Poceta, J.S.; Walters, A.S.; Barrett, R.W. *the XP053 Study Group. J. Clin. Sleep Med.* **2011**, *7*, 282.
(116) Bogan, R.K.; Cramer Bornemann, M.A.; Kushida, C.A.; Tran, P.V.; Barrett, R.W. *the XP060 Study Group. Mayo Clin. Proc.* **2010**, *85*, 512.
(117) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022399s000lbl.pdf.
(118) Zeng, Q.Y.; Chen, R.; Darmawan, J.; Xiao, Z.Y.; Chen, S.B.; Wigley, R.; Chen, S.L.; Zhang, N.Z. *Arthritis Res. Ther.* **2008**, *10*, R17.

(119) Tanaka, K.; Kawasaki, H.; Kurata, K.; Aikawa, Y.; Tsukamoto, Y.; Inaba, T. *Jpn. J. Pharmacol.* **1995**, *67*, 305.
(120) Tanaka, K. *Rheumatol. Rep.* **2009**, *1*, e4.
(121) Inaba, T.; Tanaka, K.; Takeno, R.; Nagaki, H.; Yoshida, C.; Takano, S. *Chem. Pharm. Bull.* **2000**, *48*, 131.
(122) Hara, M.; Abe, T.; Sugawara, S.; Mizushima, Y.; Hoshi, K.; Irimajiri, S.; Hashimoto, H.; Yoshino, S.; Matsui, N.; Nobunaga, M.; Nakano, S. *Mod. Rheumatol.* **2007**, *17*, 1.
(123) Hara, M.; Abe, T.; Sugawara, S.; Mizushima, Y.; Hoshi, K.; Irimajiri, S.; Hashimoto, H.; Yoshino, S.; Matsui, N.; Nobunaga, M. *Mod. Rheumatol.* **2007**, *17*, 10.
(124) Lu, L.-J.; Teng, J.-L.; Bao, C.-D.; Han, X.-H.; Sun, L.-Y.; Xu, J.-H.; Li, X.-F.; Wu, H.-X. *Chin. Med. J.* **2008**, *121*, 615.
(125) Agarwala, S.S. *Expert Rev. Anticancer Ther.* **2009**, *9*, 587.
(126) Keler, T.; Halk, E.; Vitale, L.; O'Neill, T.; Blanset, D.; Lee, S.; Srinivasan, M.; Graziano, R.F.; Davis, T.; Lonberg, N.; Korman, A. *J. Immunol.* **2003**, *171*, 6251.
(127) Harmankaya, K.; Erasim, C.; Koelblinger, C.; Ibrahim, R.; Hoos, A.; Pehamberger, H.; Binder, M. *Med. Oncol.* **2011**, *28*, 1140.
(128) Hodi, F.S.; O'Day, S.J.; McDermott, D.F.; Weber, R.W.; Sosman, J.A.; Haanen, J.B.; Gonzalez, R.; Robert, C.; Schadendorf, D.; Hassel, J.C.; Akerley, W.; van den Eertwegh, A.J.; Lutzky, J.; Lorigan, P.; Vaubel, J.M.; Linette, G.P.; Hogg, D.; Ottensmeier, C.H.; Lebbé, C.; Peschel, C.; Quirt, I.; Clark, J.I.; Wolchok, J.D.; Weber, J.S.; Tian, J.; Yellin, M.J.; Nichol, G.M.; Hoos, A.; Urba, W.J. *N. Engl. J. Med.* **2010**, *363*, 711 Erratum in: *N. Engl. J. Med.*, 2010 Sep 23;b(13):1290.
(129) Wolchok, J.D.; Weber, J.S.; Hamid, O.; Lebbé, C.; Maio, M.; Schadendorf, D.; de Pril, V.; Heller, K.; Chen, T.T.; Ibrahim, R.; Hoos, A.; O'Day, S.J. *Cancer Immun.* **2010**, *10*, 9.
(130) Korn, E.L.; Liu, P.Y.; Lee, S.J.; Chapman, J.A.; Niedzwiecki, D.; Suman, V.J.; Moon, J.; Sondak, V.K.; Atkins, M.B.; Eisenhauer, E.A.; Parulekar, W.; Markovic, S.N.; Saxman, S.; Kirkwood, J.M. *J. Clin. Oncol.* **2008**, *26*, 527.
(131) Robert, C.; Thomas, L.; Bondarenko, I.; O'Day, S.; Garbe, C.; Lebbe, C.; Baurain, J.F.; Testori, A.; Grob, J.J.; Davidson, N.; Richards, J.; Maio, M.; Hauschild, A.; Miller, W.H.; Gascon, P.; Lotem, M.; Harmankaya, K.; Ibrahim, R.; Francis, S.; Chen, T.T.; Humphrey, R.; Hoos, A.; Wolchok, J.D. *N. Engl. J. Med.* **2011**, *364*, 2517.
(132) Gallwitz, B.; Haering, H.-U. *Diabetes Obes. Metab.* **2010**, *12*, 1.
(133) Neumiller, J.J.; Wood, L.; Campbell, R.K. *Pharmacotherapy* **2010**, *30*, 463.
(134) Gerish, J. *Diabetes Res. Clin. Pract.* **2010**, *90*, 131.
(135) Zettl, H.; Schubert-Zsilavecz, M.; Steinhilber, D. *Chem. Med. Chem.* **2010**, *5*, 179.
(136) Eckhardt, M.; Langkopf, E.; Mark, M.; Tadayyon, M.; Thomas, L.; Nar, H.; Pfrengle, W.; Guth, B.; Lotz, R.; Sieger, P.; Fuchs, H.; Himmelsbach, F. *J. Med. Chem.* **2007**, *50*, 6450.
(137) Thomas, L.; Eckhardt, M.; Langkopf, E.; Tadayyon, M.; Himmelsbach, F.; Mark, M. *J. Pharmacol. Exp. Ther.* **2008**, *325*, 175.
(138) Heise, T.; Graefe-Mody, E.U.; Huttner, S.; Ring, A.; Trommeshauser, D.; Dugi, K.A. *Diabetes Obes. Metab.* **2009**, *11*, 786.
(139) Blech, S.; Ludwig-Schwellinger, E.; Grafe-Mody, E.U.; Withopf, B.; Wagner, K. *Drug Metab. Dispos.* **2010**, *38*, 667.
(140) Singh-Franco, D.; McLaughlin-Middlekauff, J.; Elrod, S.; Harrington, C. *Diabetes Obes. Metab.* **2012**, *14*, 694.
(141) Homma, Y.; Yamaguchi, O.; Hayashi, K. *Br. J. Urol.* **2005**, *96*, 1314.
(142) Maruyama, T.; Suzuki, T.; Onda, K.; Hayakawa, M.; Moritomo, H.; Kimizuka, T.; Matsui, T. Patent Application WO 9920607, **1999**.

(143) Takasu, T.; Ukai, M.; Sato, S.; Matsui, T.; Nagase, I.; Maruyama, T.; Sasamata, M.; Miyata, K.; Uchida, H.; Yamaguchi, O. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 646.
(144) Bhide, A.A.; Digesu, G.A.; Fernando, R.; Khullar, V. *Int. Urogynecol. J.* **2012**, (ahead of print). doi: 10.07/s00192-012-1724-0.
(145) Stafstrom, C.E.; Grippon, S.; Kirkpatrick, P. *Nat. Rev. Drug Discov.* **2011**, *10*, 729.
(146) Deeks, E.D. *CNS Drugs* **2011**, *25*, 887.
(147) Fattore, C.; Perucca, E. *Drugs* **2011**, *71*, 2151.
(148) Bialer, M.; White, H.S. *Nat, Rev. Drug Discov.* **2010**, *9*, 68.
(149) Gunthorpe, M.J.; Large, C.H.; Sankar, R. *Epilepsia* **2012**, *53*, 412.
(150) Rostock, A.; Tober, C.; Rundfeldt, C.; Bartsch, R.; Engel, J.; Polymeropoulos, E.E.; Kutscher, B.; Loscher, W.; Honack, D.; White, H.S.; Wolf, H.H. *Epilepsy Res.* **1996**, *23*, 211.
(151) Wickenden, A.D.; Yu, W.; Zou, A.; Jegla, T.; Wagoner, P.K. *Mol. Pharmacol.* **2000**, *58*, 591.
(152) Dieter, H.-R.; Engel, J.; Kutscher, B.; Polymeropoulos, E.; Szelenyi, S.; Nickel, B. US Patent 5384330, **1995**.
(153) http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022345s001lbl.pdf.
(154) Porter, R.J.; Partiot, A.; Sachdeo, R.; Nohria, V.; Alves, W.M. *Neurology* **2007**, *68*, 1197.
(155) French, J.A.; Abou-Khalil, B.W.; Leroy, R.F.; Yacubian, E.M.T.; Shin, P.; Hall, S.; Mansbach, H.; Nohria, V. *Neurology* **2011**, *76*, 1555.
(156) Brodie, M.J.; Lerche, H.; Gil-Nagel, A.; Elger, C.; Hall, S.; Shin, P.; Nohria, V.; Mansbach, H. *Neurology* **2010**, *75*, 1817.
(157) http://www.unaids.org/en/dataanalysis/epidemiology/; http://www.cdc.gov/hiv/topics/surveillance.
(158) Ghosh, R.K.; Ghosh, S.M.; Chawla, S. *Expert Opin. Pharmacother.* **2011**, *12*, 31.
(159) Guillemont, J.; Boven, K.; Crauwels, H.; de Bethune, M.-P. In *Antiviral Drugs: From Basic Discovery Through Clinical Trials*, 1st ed.; Kazmierski, W.M., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2011; p 59.
(160) Janssen, P.A.J.; Lewi, P.J.; Arnold, E.; Daeyaert, F.; de Jonge, M.; Heeres, J.; Koymans, L.; Vinkers, M.; Guillemont, J.; Pasquier, E.; Kukla, M.; Ludovici, D.; Andries, K.; de Bethune, M.-P.; Pauwels, R.; Das, K.; Clark, A.D., Jr.; Frenkel, Y.V.; Hughes, S.H.; Medaer, B.; De Knaep, F.; Bohets, H.; De Clerck, F.; Lampo, A.; Williams, P.; Stoffels, P. *J. Med. Chem.* **2005**, *48*, 1901.
(161) Guillemont, J.; Pasquier, E.; Palandjian, P.; Vernier, D.; Gaurrand, S.; Lewi, P.J.; Heeres, J.; de Jonge, M.R.; Koymans, L.M.H.; Daeyaert, F.F.D.; Vinkers, M.H.; Arnold, E.; Das, K.; Pauwels, R.; Andries, K.; de Bethune, M.-P.; Bettens, E.; Hertogs, K.; Wiegerinck, P.; Timmerman, P.; Janssen, P.A.J. *J. Med. Chem.* **2005**, *48*, 2072.
(162) Garvey, L.; Winston, A. *Expert Opin. Invest. Drugs* **2009**, *18*, 1035.
(163) US FDA http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf.
(164) Molina, J.-M.; Cahn, P.; Grinsztejn, B.; Lazzarin, A.; Mills, A.; Saag, M.; Supparatpinyo, K.; Walmsley, S.; Crauwels, H.; Rimsky, L.T.; Vanveggel, S.; Boven, K. on behalf of the ECHO study group. *Lancet* **2011**, *378*, 238.
(165) Cohen, C.; Andrade-Villanueva, J.; Clotet, B.; Fourie, J.; Johnson, M.A.; Ruxrungtham, K.; Wu, H.; Zorrilla, C.; Crauwels, H.; Rimsky, L.T.; Vanveggel, S.; Boven, K.; on behalf of the THRIVE study group, *Lancet* **2011**, *378*, 229.
(166) http://rarediseases.info.nih.gov/GARD/Condition/8618/QnA/22942/Myelofibrosis.aspx.
(167) Quintás-Cardama, A.; Vaddi, K.; Liu, P.; Manshouri, T.; Li, J.; Scherle, P.A.; Caulder, E.; Wen, X.; Li, Y.; Waeltz, P.; Rupar, M.; Burn, T.; Lo, Y.; Kelley, J.; Covington, M.; Shepard, S.; Rodgers, J.D.; Haley, P.; Kantarjian, H.; Fridman, J.S.; Verstovsek, S. *Blood* **2010**, *115*, 3109.

(168) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999.
(169) Shi, J.G.; Chen, X.; McGee, R.F.; Landman, R.R.; Emm, T.; Lo, Y.; Scherle, P.A.; Punwani, N.G.; Williams, W.V.; Yeleswaram, S. *J. Clin. Pharmacol.* **2011**, *51*, 1644.
(170) ClinicalTrials.gov, NCT00952289 (2011) http://clinicaltrials.gov.
(171) ClinicalTrials.gov, NCT00934544 (2011) http://clinicaltrials.gov.
(172) Saraiva, M.J.M. *Expert Rev. Mol. Med.* **2002**, *4*, 1.
(173) Hammarström, P.; Wiseman, R.L.; Powers, E.T.; Kelly, J.W. *Science* **2003**, *299*, 713.
(174) Razavi, H.; Palaninathan, S.K.; Powers, E.T.; Wiseman, R.L.; Purkey, H.E.; Mohamedmohaideen, N.N.; Deechongkit, S.; Chiang, K.P.; Dendle, M.T.A.; Sacchettini, J.C.; Kelly, J.W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2758.
(175) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem. Eur. J.* **2011**, *17*, 10113.
(176) European Medical Agency assessment report, Procedure No.: EMEA/H/C/002294, **2011**.
(177) Kwong, A.D.; Kauffman, R.S.; Hurter, P.; Mueller, P. *Nat. Biotechnol.* **2011**, *29*, 993.
(178) Revill, P.; Serradell, N.; Bolós, J.; Rosa, E. *Drugs Fut.* **2007**, *32*, 788.
(179) Tanoury, G. Patent Application WO 2011/153423, 2011; Tanoury, G.; Chen, M.; Cochran, J.E.; Looker, A. Patent Application WO 20101/126881, **2010**.
(180) Reesink, H.W.; Zuezem, S.; Weegink, C.J.; Forestier, N.; Van Vliet, A.; Van de Wetering de Rooij, J.; McNair, L.; Purdy, S.; Kauffman, R.; Alam, J.; Jansen, P.L.M. *Gastroenterology* **2006**, *131*, 997.
(181) Jacobson, I.M.; McHutchison, J.G.; Dusheiko, G.; Di Bisceglie, A.M.; Reddy, K.R.; Bzowej, N.H.; Marcellin, P.; Muir, A.J.; Ferenci, P.; Flisiak, R.; George, J.; Rizzetto, M.; Shouval, D.; Sola, R.; Terg, R.A.; Yoshida, E.M.; Adda, N.; Bengtsson, L.; Sankoh, A.J.; Kieffer, T.L.; George, S.; Kauffman, R.S.; Zeuzem, S.; for the ADVANCE Study Team, *N. Engl. J. Med.* **2011**, *365*, 2405.
(182) Sherman, K.E.; Flamm, S.L.; Afdhal, N.H.; Nelson, D.R.; Sulkowski, M.S.; Everson, G.T.; Fried, M.W.; Adler, M.; Reesink, H.W.; Martin, M.; Sankoh, A.J.; Adda, N.; Kauffman, R.S.; George, S.; Wright, C.I.; Poordad, F.; for the ILLUMINATE Study Team, *N. Engl. J. Med.* **2011**, *365*, 1014.
(183) Zeuzem, S.; Andreone, P.; Pol, S.; Lawitz, E.; Diago, M.; Roberts, S.; Focaccia, R.; Younossi, Z.; Foster, G.R.; Horban, A.; Ferenci, P.; Nevens, F.; Müllhaupt, B.; Pockros, P.; Terg, R.; Shouval, D.; van Hoek, B.; Weiland, O.; Van Heeswijk, R.; De Meyer, S.; Luo, D.; Boogaerts, G.; Polo, R.; Picchio, G.; Beumont, M. *N. Engl. J. Med.* **2011**, *365*, 2417.
(184) http://www.endocrineweb.com/conditions/thyroid-cancer/thyroid-cancer.
(185) Wedge, S.R.; Ogilvie, D.J.; Dukes, M.; Kendrew, J.; Chester, R.; Jackson, J.A.; Boffey, S.J.; Valentine, P.J.; Curwen, J.O.; Musgrove, H.L.; Graham, G.A.; Hughes, G.D.; Thomas, A.P.; Stokes, E.S.E.; Curry, B.; Richmond, G.H.P.; Wadsworth, P.F.; Bigley, A.L.; Hennequin, L.F. *Cancer Res.* **2002**, *62*, 4645.
(186) Hennequin, L.F.; Stokes, E.S.E.; Thomas, A.P.; Johnstone, C.; Ple´, P.A.; Ogilvie, D.J.; Dukes, M.; Wedge, S.R.; Kendrew, J.; Curwen, J.O. *J. Med. Chem.* **2002**, *45*, 1300.
(187) Hennequin, L.F.; Stokes, E.S.E.; Thomas, A.P. Patent Application WO 0132651, **2001**.
(188) Langmuir, P.B.; Yver, A. *Clin. Pharm. Ther.* **2012**, *91*, 71.
(189) Wells, S.A.; Robinson, B.G.; Gagel, R.F.; Dralle, H.; Fagin, J.A.; Santoro, M.; Baudin, E.; Vasselli, J.R.; Read, J.; Schlumberger, M. *J. Clin. Oncol.* **2010**, *28 (15s),* abstr. 5503.
(190) http://www.cancer.gov/cancertopics/types/melanoma.

(191) Tsai, J.; Lee, J.T.; Wang, W.; Zhang, J.; Cho, H.; Mamo, S.; Bremer, R.; Gillette, S.; Kong, J.; Haass, N.K.; Sproesser, K.; Li, L.; Smalley, K.S.M.; Fong, D.; Zhu, Y.-L.; Marimuthu, A.; Nguyen, H.; Lam, B.; Liu, J.; Cheung, I.; Rice, J.; Suzuki, Y.; Luu, C.; Settachatgul, C.; Shellooe, R.; Cantwell, J.; Kim, S.-H.; Schlessinger, J.; Zhang, K.Y.J.; West, B.L.; Powell, B.; Habets, G.; Zhang, C.; Ibrahim, P.N.; Hirth, P.; Artis, D.R.; Herlyn, M.; Bollag, G. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 3041.
(192) Bollag, G.; Hirth, P.; Tsai, J.; Zhang, J.; Ibrahim, P.N.; Cho, H.; Spevak, W.; Zhang, C.; Zhang, Y.; Habets, G.; Burton, E.A.; Wong, B.; Tsang, G.; West, B.L.; Powell, B.; Shellooe, R.; Marimuthu, A.; Nguyen, H.; Zhang, K.Y.J.; Artis, D.R.; Schlessinger, J.; Su, F.; Higgins, B.; Iyer, R.; D'Andrea, K.; Koehler, A.; Stumm, M.; Lin, P.S.; Lee, R.J.; Grippo, J.; Puzanov, I.; Kim, K.B.; Ribas, A.; McArthur, G.A.; Sosman, J.A.; Chapman, P.B.; Flaherty, K.T.; Xu, X.; Nathanson, K.L.; Nolop, K. *Nature* **2010**, *467*, 596.
(193) Puzanov, I.; Flaherty, K.T.; Sosman, J.A.; Grippo, J.F.; Su, F.; Nolop, K.; Leed, R.J.; Bollag, G. *Drugs Fut.* **2011**, *36*, 191.
(194) Ibrahim, P.N.; Artis, D.R.; Bremer, R.; Mamo, S.; Nespi, M.; Zhang, C.; Zhang, J.; Zhu, Y.-L.; Tsai, J.; Hirth, K.-P.; Bollag, G.; Spevak, W.; Cho, H.; Gillette, S.; Wu, G.; Zhu, H.; Shi, S. Patent Application WO07002325, **2007**.
(195) United States Food and Drug Administration. Labeling information Zelboraf. FDA website (2011) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429s000lbl.pdf.
(196) Frampton, J.E. *CNS Drugs* **2011**, *25*, 615.
(197) Laughren, T.P.; Gobburu, J.; Temple, R.J.; Unger, E.F.; Bhattaram, A.; Dinh, P.V.; Fossom, L.; Hung, H.M.; Kilmek, V.; Lee, J.E.; Levin, R.L.; Lindberg, C.Y.; Mathis, M.; Rosloff, B.N.; Wang, S.-J.; Wang, Y.; Yang, P.; Yu, B.; Zhang, H.; Zhang, L.; Zineh, I. *J. Clin. Psychiatry* **2011**, *72*, 1166.
(198) (a) Citrome, L. *Int. J. Clin. Practice* **2012**, *66*, 356. (b) Berton, O.; Nestler, E.J. *Nat. Rev. Neurosci.* **2006**, *7*, 137.
(199) Page, M.E.; Cryan, J.F.; Sullivan, A.; Dalvi, A.; Saucy, B.; Manning, D.R.; Lucki, I. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1220.
(200) Heinrich, T.; Bottcher, H.; Gericke, R.; Bartoszyk, G.D.; Anzali, S.; Seyfried, C.A.; Greiner, H.E.; van Amsterdam, C. *J. Med. Chem.* **2004**, *47*, 4684.
(201) Hewitt, N.J.; Hewitt, P. *Xenobiotica* **2004**, *34*, 243.
(202) Hewitt, N.J.; Buhring, K.-U.; Dasenbrock, J.; Haunschild, J.; Ladstetter, B.; Utesch, D. *Drug Metab. Dispos.* **2001**, *29*, 1042.
(203) Reed, C.R.; Kajdasz, D.K.; Whalen, H.; Athanasiou, M.C.; Gallipoli, S.; Thase, M.E. *Curr. Med. Res. Opin.* **2012**, *28*, 27.
(204) Robinson, D.; Kajdasz, D.K.; Gallipoli, S.; Whalen, H.; Wamil, A.; Reed, C.R. *J. Clin. Psychopharm.* **2011**, *31*, 643.