CHAPTER 26

To Market, To Market—2010

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OVERVIEW

Approvals of new molecular entities (NMEs) were somewhat lower in 2010 than in previous years. For example, 21 new drugs were approved in the United States in 2010, compared with 25 in 2009 and 24 in 2008 [1]. Seven of the 21 U.S. approved NMEs had previously been approved outside of the United States. Approvals continue to include first-in-class agents, along with drugs for established targets that offer significant new benefits. This year's To-Market-To-Market chapter provides summaries for 24 NMEs that have been approved for the first time worldwide, of which 19 are small molecules. Twelve of the summaries are for NMEs that were first approved in the United States and seven are for NMEs first approved in the European Union. The remaining NMEs are from Canada, Japan, and Russia. Treatments for cancer dominate the list, with five drug approvals for small molecules and approval of the first vaccine for hormone-refractory prostate cancer. The infectious disease and cardiovascular disease areas are next in number of new drug approvals, with three each. Two new drugs were approved for treatment of multiple sclerosis (MS) and associated symptoms. Other therapeutic categories saw approval of one to two new drugs each. For completeness, a few marketed drugs that were approved in 2009 and were not covered in Volume 45 of *ARMC* are summarized in this chapter. The following overview is organized by therapeutic area, starting with drugs that are covered in the detailed summaries and followed by approvals that are not covered in the detail but are of significant interest, including new combinations, new indications for previously approved drugs, new vaccines, and new enzymes.

In the anticancer area, five new small molecules were approved along with a novel therapeutic vaccine for the treatment of hormone-refractory prostate cancer. Of the small molecules, four are related to natural products and one is a cyclic peptide. Jevtana® (cabazitaxel), a microtubule inhibitor, is a semisynthetic analog of the natural product taxol® that was approved by the Food and Drug Administration (FDA) in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients who were previously treated with a docetaxel-containing regimen for late-stage disease. Prostate cancer usually occurs in older men and is the second most common cancer among men in the United States, behind skin cancer. Cabazitaxel is dosed

intravenously at 25 mg/m^2 over 1 h every 3 weeks along with 10 mg of oral prednisone administered daily throughout cabazitaxel treatment. The median overall survival rate for patients on cabazitaxel treatment was ~2.4 months longer than current alternatives. Halaven™ (eribulin), another microtubule inhibitor, is a synthetic analog of the marine natural product halichondrin B that was approved for the treatment of metastatic breast cancer (MBC) in patients who previously received at least two chemotherapeutic regimens for late-stage disease. Breast cancer is the second leading cause of cancer-related deaths among women in the United States after lung cancer, according to the National Cancer Institute. Eribulin mesylate is dosed intravenously at 1.4 mg/m^2 over 2–5 min on days 1 and 8 of a 21-day cycle. The median overall survival rate for patients on eribulin mesylate treatment was found to be ~2.5 months longer than current alternatives. Eribulin has 19 stereocenters, and the commercial route to its synthesis is purported to involve 62 steps. Junovan® (mifamurtide) is a liposomal formulation of muramyl tripeptide phosphatidylethanolamine that has been approved by the European Commission (EC) for the treatment of osteosarcoma. Phase III results with mifamurtide clearly demonstrated ~30% decrease in the risk for death, with ~78% of patients surviving through the sixth year of treatment. Mifamurtide is thought to act by stimulating the innate immune system to release proinflammatory cytokines, leading to tumoricidal activity. Mifamurtide is dosed intravenously at 2 mg/m^2 administered as adjuvant therapy over 1 h twice weekly for an initial 12 weeks. Istodax® (romidepsin) is a natural product isolated from *Chromobacterium violaceum* that was approved by the FDA as a single-agent therapy for the treatment of cutaneous T cell lymphoma (CTCL) in patients who previously received at least one systemic therapy. Romidepsin is a cyclic peptide derivative and is an inhibitor of histone deacetylases (HDACs) with modest selectivity for class I HDACs. Romidepsin is dosed intravenously at 14 mg/m^2 over 4 h on days 1, 8, and 15 of a 28-day cycle. In clinical trials, the overall objective disease response (ODR) and complete response (CR) rates were found to be ~34% and 6%, respectively. Javlor® (vinflunine) is a fluorinated, semisynthetic analog of the natural *vinca* alkaloids vinblastine and vincristine that has been approved by EMEA for the treatment of bladder cancer for patients who were previously treated with a first-line platinum-containing regimen. The recommended dose of vinflunine ditartrate is 320 mg/m^2 administered intravenously over 20 min once every 3 weeks. In a Phase III study, vinflunine treated patients showed improvement in the median overall survival of 6.9 months compared to 4.3 months for patients who were treated with best supportive care (BSC). Provenge® (sipuleucel-T) is an autologous vaccine for the treatment of asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer. The vaccine is made from individual

patient's blood cells that have been cultured with a recombinant fusion protein comprising the prostate tumor antigen human prostatic acid phosphatase fused to granulocyte macrophage colony-stimulating factor (GM-CSF). It is administered as three separate infusions given at 2-week intervals. Sipuleucel-T improved median survival by 4.5 months. In addition to new single-agent approvals, several new indications for previously approved drugs for anticancer treatments are noteworthy. Two oral kinase inhibitors received extended approval for the treatment of a rare type of leukemia. Tasigna® (nilotinib) from Novartis and Sprycel® (dasatinib) from Bristol-Myers Squibb both received approval for the additional indication of treatment of Philadelphia chromosome positive chronic phase chronic myeloid leukemia (Ph+ CP-CML), a slowly progressing blood and bone marrow disease linked to a genetic abnormality. Tasigna® was previously approved for treatment of chronic myeloid leukemia. Sprycel® was previously approved for treatment of chronic myelocytic leukemia and acute lymphocytic leukemia. The FDA extended the indications for the monoclonal antibody Rituxan® (rituximab) with its approval for treatment of chronic lymphocytic leukemia (CLL), a slowly progressing blood and bone marrow cancer. Rituxan® is being developed by Biogen Idec and Genentech (Roche) and is intended for patients with CLL who are beginning chemotherapy for the first time and for those who have not responded to other cancer drugs for CLL. Rituxan® was previously approved for treatment of B cell lymphoma and rheumatoid arthritis. Herceptin® (trastuzumab), a monoclonal antibody from Genentech that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2), was approved for treatment of gastric cancer. Herceptin® is specifically indicated in combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease. Herceptin® was previously approved for treatment of HER2 overexpressing breast cancer.

The area of infectious disease treatments saw approvals for one antibacterial drug and two anti-influenza drugs, along with two new vaccines. Teflaro® (ceftaroline fosamil), a novel cephalosporin prodrug, was approved as an injectable antibiotic to treat adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI), including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Infections due to drug-resistant gram-positive bacteria, particularly MRSA, are a continuing concern worldwide. Four Phase III trials were used to demonstrate the efficacy of ceftaroline fosamil in ABSSSI and CABP. In ABSSSI, clinical cure rates were similar and high ($>90\%$) for both the ceftaroline and vancomycin plus aztreonam-treated groups. In CABP, clinical cure rates

were higher for ceftaroline fosamil than for ceftriaxone for gram-positive organisms and were similar for gram-negative organisms. Like most cephalosporins, ceftaroline fosamil was safe and well tolerated. Two new neuraminidase (NA) inhibitors, Inavir® (laninamivir octanoate) and Rapiacta (peramivir), were approved in Japan in 2010 for treatment of influenza infection, joining previously approved NA inhibitors Relenza® (zanamivir) and Tamiflu® (oseltamivir). Influenza is a global health concern, with both seasonal epidemics and unpredictable pandemics resulting in significant morbidity and mortality, particularly for patients at high risk for influenza-associated complications. Laninamivir octanoate, an ester prodrug form of the active drug laninamivir, is given by intranasal administration at a 20 or 40 mg dose. Laninamivir octanoate has a long half-life in humans such that efficacy can be achieved after only a single dose. Peramivir is the only NA inhibitor available for intravenous (IV) use. Peramivir is given as a single 300 mg IV dose for adult and pediatric uncomplicated seasonal influenza infection, and as single and multiple 600 mg IV doses for patients at high risk for complications associated with influenza virus infection. Two vaccines were approved in the infectious diseases arena. Prevnar 13® from Pfizer is a pneumococcal 13-valent conjugate vaccine that was approved in the United States for infants and young children ages 6 weeks through 5 years for the prevention of invasive disease caused by 13 different serotypes of the bacterium *Streptococcus pneumoniae*. It is also approved for the prevention of otitis media caused by the seven serotypes shared with a previously approved vaccine, Prevnar®. *S. pneumoniae* can cause pneumonia as well as infections of the blood, middle ear, and the covering of the brain and spinal cord. Prevnar 13 will be the successor to Prevnar®, extending protection to six additional types of disease-causing bacteria. Menveo® from Novartis was approved as a vaccine to prevent meningococcal disease. Meningococcal disease is a leading cause of bacterial meningitis, an infection of the membrane around the brain and spinal cord, and sepsis, an often life-threatening blood infection. The vaccine is indicated for the active immunization of people between 2 and 55 years old in the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135.

Within the cardiovascular disease arena, three new agents were approved, along with several new drug combinations. Kalbitor® (ecallantide) is an analog of tissue factor pathway inhibitor (TFPI) and is a first-in-class drug that potently inhibits plasma kallikrein and effectively treats the symptoms and frequency of hereditary angioedema (HAE), an autosomal disease that affects between 1:10,000 and 1:50,000 people. Patients with HAE go through a cycle of flare-ups with symptoms of pain and swelling of cutaneous and mucosal tissues. The disease results from a genetic deficiency of the C1-esterase inhibitor protein, which in turn leads

to the excessive formation of bradykinin resulting in edema. In Phase III trials, ecallantide was found to be effective in relieving HAE symptoms and reducing the frequency and duration of HAE attacks. The drug was effective in moderate and severe HAE patients and was found to have a 24-h duration of action. Ecallantide is given as three 10 mg subcutaneous doses. Brilique™ (ticagrelor), an antagonist of the $P2Y_{12}$ receptor that effectively blocks platelet aggregation, was approved for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS). It is the first reversible $P2Y_{12}$ receptor antagonist to be approved. ACS and related events are the leading cause of mortality in the United States. The rupture of an atherosclerosis plaque in coronary arteries initiates a series of biochemical events that leads to platelet aggregation and thrombus formation with serious medical consequences. Stimulation of the $P2Y_{12}$ receptor is a powerful initiation step in the GPIIb/IIIa pathway of platelet activation and aggregation. As a $P2Y_{12}$ antagonist, ticagrelor is effective in treatment of events associated with ACS, including myocardial infarction, stroke, death from vascular complications, ischemia, and stent thrombosis. Brinavess™ (vernakalant) has been approved as an IV agent for the treatment of patients experiencing short duration or recent onset atrial fibrillation (AF), a condition in which signals from the atria of the heart are discoordinated with the ventricle signals, resulting in irregular heart beat. Episodes can last from a few minutes to days to weeks and years. The symptoms include chest pains, palpitations, and weakness. The condition is associated with congestive heart failure (CHF). Vernakalant is a selective class III antiarrhythmic that has more of its effects in atrial tissues than ventricular tissues. It has activity for cardiac Na+ and K+ channels and also for the atrial-selective Kv1.5 channel. Two cardiovascular drugs that were previously approved outside the U.S. received FDA approval in 2010: Pradaxa® (dabigatran) for prevention of stroke and Lumizyme® (alglucosidase alfa) for treatment of Pompe disease, a rare, inherited and often fatal disorder that disables the heart and muscles. These were reviewed in To-Market-To-Market in previous years. For combination agents, there were three new approvals for the treatment of hypertension. It is estimated that about one billion people globally have high blood pressure, and many of these remain either untreated, or even if treated, are not at their ideal blood pressure target. Tekamlo® from Novartis is a single-pill combination of the renin inhibitor Tekturna® (aliskiren) and the calcium-channel blocker, amlodipine. The FDA approval of Tekamlo® for high blood pressure was based on clinical trial data involving more than 5000 patients with mild-to-moderate high blood pressure. Tekamlo® gave greater reductions in systolic and diastolic blood pressure compared with either agent alone. The aliskiren component of Tekamlo® inhibits the activity of the renin angiotensin aldosterone system (RAAS), an important regulator of blood

pressure, while the calcium-channel blocker, amlodipine, lowers blood pressure by relaxing the blood vessel walls through the inhibition of calcium influx. Amturnide™ is a single oral tablet from Novartis combining Tekturna® and amlodipine with the diuretic hydrochlorothiazide (HCTZ). Approval of Amturnide™ was based on a double-blind, active-controlled study in 1181 patients with moderately or severely elevated blood pressure. Both patient populations achieved greater systolic and diastolic blood pressure reductions with Amturnide™ compared to the dual combinations. Amturnide™ is indicated for the treatment of hypertension in patients not adequately controlled with any two of the following: aliskiren, dihydropyridine calcium-channel blockers, and thiazide diuretics. Tribenzor™ from Daiichi-Sankyo, a combination of three drugs (amlodipine, HCTZ, and an angiotensin II receptor antagonist olmesartan medoxomil), was approved as an oral agent for the treatment of hypertension. The FDA approval of Tribenzor™ was based on a double-blind, active-controlled study in 2492 hypertensive patients, with subjects receiving Tribenzor™ or one of three dual therapies. After 8 weeks of treatment, the triple combination therapy produced greater reductions in both systolic and diastolic blood pressures compared to each of the three dual combination therapies. Tribenzor™ is the second three-drug combination pill approved by the FDA, with Exforge HCT® (Novartis; amlodipine/valsartan/HCTZ) receiving approval in 2009.

Approvals for endocrine disease therapeutics included drugs for treating diabetes, agents for infertility and contraception, and a combination drug for treating benign prostatic hyperplasia. Diabetes is a disease with increasing worldwide prevalence that has a significant impact on human mortality and the cost of healthcare. Nesina® (alogliptin) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) that increases the concentration and half-life of the incretin GLP-1, a master regulator of glucose homeostasis. Alogliptin is the fourth DPP-4 inhibitor approved for the treatment of diabetes. Victoza® (liraglutide), a GLP-1 analog, was approved in the United States for diabetes treatment. This drug was previously approved in several countries outside the United States and was summarized in To-Market-To-Market in 2009. Kombiglyze XR™ from Bristol-Myers Squibb and Astra-Zeneca is a new combination tablet for the treatment of type 2 diabetes consisting of metformin and saxagliptin, a DPP-4 inhibitor. The FDA approved once-a-day Kombiglyze XR™ based on two Phase III clinical trials and bioequivalence studies. Kombiglyze XR™ offers strong glycemic control and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. In the area of reproductive health, one new drug was approved for infertility and a new combination was approved for contraception. Elonva® (corifollitropin alfa) is a long-acting follicle-stimulating hormone (FSH) analog that

was approved for increasing the success rate for conception. Corifollitropin alfa is first-in-class for sustained follicle stimulants (SFS). One injection of corifollitropin alfa replaces seven daily injections of recombinant FSH (rFSH) in a controlled ovarian stimulation cycle. Natazia® from Bayer Healthcare Pharmaceuticals is a combination hormonal tablet approved for use as an oral contraceptive. Natazia® contains two female hormones, an estrogen (estradiol valerate) and a progestin (dienogest), and is the first oral contraceptive marketed in the United States to vary the doses of progestin and estrogen four times throughout each 28-day treatment cycle. The safety and efficacy of Natazia® were evaluated in two multicenter Phase III clinical trials involving 1867 women and nearly 30,000 28-day treatment cycles. Natazia® was found to be effective as a hormonal contraceptive in both studies. The synthetic steroid ella® (ulipristal acetate) was approved in the United States for emergency contraception when taken orally within 120 h (5 days) after a contraceptive failure or unprotected intercourse. Ulipristal was previously approved in the European Union and was covered in *To-Market-To-Market* in 2009. Jalyn™ is a new combination drug from Glaxo that received approval for treatment of benign prostatic hyperplasia (BPH). BPH is one of the most common prostate disorders, affecting nearly half of all men 50 years of age or older in the United States. Jalyn™ combines the synthetic steroid dutasteride, a 5-alpha reductase inhibitor, with tamsulosin, an alpha1A adrenoreceptor blocker. Dutasteride reduces symptoms and shrinks the prostate and is already approved as a single agent (Avodart®) for treatment of BPH. Tamsulosin acts by relaxing the muscles in the bladder and prostate. Approval of the combination was based on 2-year results from the CombAT (Combination of Avodart® and Tamsulosin) study, one of the largest clinical trials to date of men with BPH.

Approvals in the metabolic disease category include drugs for osteoporosis, lipid disorders, and gout. Osteoporosis is a disease in which the bones become weak and are more likely to break. The vast majority of people with osteoporosis are women; one of every two women over age 50 will break a bone in their lifetime due to osteoporosis. Prolia®/Xgeva® (denosumab) is a fully human monoclonal antibody that inhibits bone resorption by blocking the ligand for the osteoclast receptor RANK. It was approved in two different dosage forms for treatment of postmenopausal women with osteoporosis at high risk for fracture, and for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Denosumab is given as a 60-mg subcutaneous injection every 6 months for osteoporosis and 120 mg every 4 weeks for patients with bone metastases. For osteoporosis patients, the drug provided an approximately threefold reduction in fractures over placebo; for cancer patients, bone mineral density, progression free survival, overall survival, and adverse events were comparable to bisphosphonate therapy. In the area

of lipid disorders, Egrifta™ (tesamorelin) is the first FDA-approved treatment for HIV patients with lipodystrophy, a condition in which excess fat develops in different areas of the body, most notably around the liver, stomach, and other abdominal organs. The use of antiretroviral agents for the treatment of HIV infection has been widespread since the mid-1990s because of their effectiveness in improving the symptoms and halting progression of the virus. One of the side effects observed with antiretroviral treatment (ART) is the accumulation of fat in some patients. Tesamorelin is a growth hormone-releasing factor (GRF) drug that is administered in a once-daily injection. VPRIV® (velaglucerase alfa) from Shire Human Genetic Therapies has been approved as a long-term, injectable enzyme replacement therapy for the treatment of pediatric and adult patients with type 1 Gaucher disease, a rare genetic disorder in which lipid accumulates in cells and certain organs due to a hereditary deficiency of the enzyme glucocerebrosidase. About 1:50,000 to 1:100,000 people in the general population have Gaucher disease. The safety and effectiveness of VPRIV® was assessed in three clinical studies involving 82 patients with type 1 Gaucher disease ages 4 years and older. The studies included patients who switched to VPRIV® after being treated with Cerezyme, a previously approved enzyme replacement therapy. The primary endpoint, hemoglobin concentration, either improved or stabilized upon treatment with VPRIV®. Krystexxa® (pegloticase) from Savient Pharmaceuticals is a polyethylene glycol conjugate of a recombinant mammalian uricase enzyme that was approved for IV treatment of chronic gout in adult patients refractory to conventional therapy. Gout occurs due to buildup of uric acid, which is eventually deposited as needle-like crystals in the joints or in soft tissue and causes the severe pain associated with the disease. Krystexxa® catalyzes the oxidation of uric acid to allantoin, a water-soluble metabolite that is readily eliminated, thereby lowering uric acid levels. Approval of Krystexxa® was based on two replicate, multicenter, randomized, double-blind, placebo-controlled 6-month studies in 212 patients. The difference between Krystexxa® and placebo was statistically significant for an every 2-week dosing regimen, but not for an every 4-week dosing regimen. Carbaglu® (carglumic acid) was approved in the United States for treatment of hyperammonemia due to *N*-acetylglutamate synthase (NAGS) deficiency, an extremely rare, genetic disorder that results in too much ammonia in the blood. Hyperammonemia can be fatal if it is not detected and treated early. Carbaglu® was previously approved in Europe in 2003.

For diseases of the central nervous system (CNS), new agents were approved for the treatment of schizophrenia and for multiple sclerosis (MS). The atypical antipsychotic Latuda® (lurasidone hydrochloride) was approved as a once-daily, oral agent for the treatment of patients with schizophrenia. Schizophrenia is a debilitating mental disorder that affects

1% of the population worldwide. Like other atypical antipsychotic agents, lurasidone has potent antagonist activity at D_2 and 5-HT_{2A} receptors. It is also a 5-HT_{1A} receptor partial agonist and a potent 5-HT_7 receptor antagonist. The efficacy of lurasidone for the treatment of schizophrenia was established in four 6-week, placebo-controlled studies in adult patients. The recommended starting dose for lurasidone is 40 mg/day. Unlike many atypical antipsychotics, lurasidone has a neutral effect on weight gain. Two new small molecule drugs were approved for people with MS, a chronic and disabling disease that affects the brain, spinal cord, and optic nerves. According to the National Multiple Sclerosis Society, there are about 400,000 people in the United States and 2.1 million people worldwide with MS. Ampyra® (dalfampridine) is a voltage-gated potassium channel blocker that is the first oral therapy approved by the FDA to improve walking in MS patients with existing gait impairment. The extended release formulation of dalfampridine improves pharmacokinetic parameters and minimizes the side effects of dalfampridine. A drug with a similar structure and mechanism of action, Firdapse™ (amifampridine) from BioMarin Pharmaceuticals, was approved in 2009 for the treatment of Lambert-Eaton myasthenic syndrome, a rare disorder of neuromuscular transmission. Gilenya® (fingolimod), a sphingosine-1-receptor agonist, is the first approved oral therapy for the relapsing–remitting form of multiple sclerosis (RRMS). Fingolimod is a prodrug and is converted *in vivo* to the active drug, (*S*)-fingolimod phosphate, primarily by sphingosine kinase-2. (*S*)-Fingolimod phosphate acts on sphingosine 1-phosphate receptors and blocks lymphocyte egress from lymph nodes and prevents their recirculation and entry into the CNS. The U.S. FDA approved fingolimod for RRMS at a dose of 0.5 mg once daily.

Two new drugs were approved for treatment of ophthalmologic diseases. Diquas (diquafosol) was approved in Japan in 2010 as a 3% ophthalmic solution for treatment of dry eye disease. Diquafosol is a $P2Y_2$ purinergic receptor agonist with the ability to activate the receptor on the ocular surface and stimulate water, lipid, and mucin secretion. The 3% solution was reported to improve dry eye symptoms by promoting secretion of mucin and water, thereby bringing the tear film closer to a normal state. Lastacaft™ (alcaftadine) was approved as a once-daily, 0.25% ophthalmic solution for the prevention of itching and redness associated with allergic conjunctivitis. Alcaftadine blocks histamine receptors and thus prevents the inflammatory effects of histamine.

In the respiratory diseases area, two new drugs were approved in 2010. Daxas® (roflumilast) is a selective, orally active phosphodiesterase (PDE) 4 inhibitor that was approved as an add-on to bronchodilator treatment for maintenance therapy of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in adult patients with a history of frequent exacerbations. COPD is a chronic inflammatory

disease and is the sixth most common cause of death worldwide and a major cause of morbidity. Roflumilast is a potent and competitive inhibitor of PDE4 and is equipotent against PDE4A, 4B, and 4D but is inactive against PDE4C and other members of the PDE family. Despite its inhibition of PDE4D, roflumilast shows the lowest incidence of nausea (3–5%) of the PDE4 inhibitors investigated to date. In clinical trials, patients with COPD having more severe airway obstruction showed a significant reduction in exacerbation frequency with roflumilast. In patients with chronic bronchitis, a 500-μg daily oral dose of roflumilast also gave a significant improvement in forced expiratory volume in 1 s (FEV_1) and a reduction in exacerbation rate. Bilaxten™ (bilastine) is an orally bioavailable, selective inhibitor of the histamine H_1 receptor that has a rapid biological onset and long duration of action. A total of 28 clinical trials were run with bilastine in 5000 patients. Bilastine effectively treats allergic rhinitis, shows no effect on cardiovascular parameters, and has no sedation side effects.

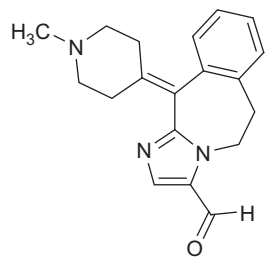
For treatment of pain, one new drug was approved in 2010. Civanex® (zucapsaicin) is a topical analgesic that was approved for use in conjunction with oral cyclooxygenase-2 (COX-2) inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve severe pain in adults with osteoarthritis of the knee. Zucapsaicin is the *cis*-isomer of the natural product capsaicin. Its analgesic action is mediated through the transient receptor potential vanilloid type 1 (TRPV1) channel, a ligand-gated ion channel that is expressed in the spinal cord and brain and is localized on neurons in sensory ganglia. Initial constant activation of TRPV1 is followed by desensitization to a variety of noxious stimuli. In clinical trials, 0.075% zucapsaicin cream was efficacious in patients experiencing severe pain. Application site burning sensation was the most frequently reported adverse event and was predominantly mild to moderate. A new indication was approved for Eli Lilly's Cymbalta® (duloxetine), namely for the treatment of chronic musculoskeletal pain, including discomfort from osteoarthritis and chronic lower back pain. Cymbalta® was first used to treat major depressive disorder. It has also been previously approved for the treatment of diabetic peripheral neuropathy, generalized anxiety disorder, maintenance treatment of major depression, and fibromyalgia. The efficacy of Cymbalta® in chronic low back pain and osteoarthritis was assessed in four double-blind, placebo-controlled, randomized clinical trials. At the end of the study period, patients taking Cymbalta had a significantly greater pain reduction compared with placebo.

Additional approvals in 2010 include an agent for the treatment of a debilitating hand disease and one for removal of varicose veins. Xiaflex® (collagenase clostridium histolyticum) from Auxilium Pharmaceuticals was approved in the United States for treatment of a hand disease known as Dupuytren's contracture, in which buildup of collagen in the

palm leads to formation of rope-like cords of tissue that prevent normal function of the fingers. Xiaflex® is a collagenase that acts by breaking down excessive collagen that builds up in the disease. In one 66-patient study, 44% of those injected with Xiaflex® were treated successfully, compared to 5% for patients who received a placebo. In a separate 306-patient study, 64% of patients given Xiaflex® were treated successfully, compared to only 7% of patients receiving the placebo. Asclera® (polidocanol) from Merz Aesthetics and Chemische Fabrik Kreussler was approved in the United States for removal of varicose veins. Polidocanol is a dodecyl ether derivative of a nine-unit polyethylene glycol. It works by damaging the cell lining of blood vessels, causing them to close and eventually be replaced by other types of tissue.

1. ALCAFTADINE (0.25%) (OPHTHALMOLOGIC, ALLERGIC CONJUNCTIVITIS) [2–6]

Class	Antihistamine
Country of origin	United States
Originator	Janssen Research Foundation
First introduction	United States
Introduced by	Vistakon Pharmaceuticals, LLC
Trade name	Lastacaft™
CAS registry no.	147084-10-4
Molecular weight	307.4



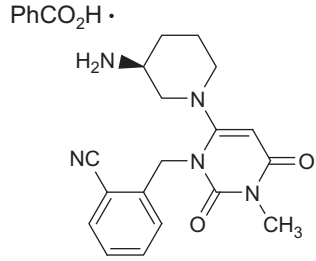
Alcaftadine, a histamine H_1/H_2 receptor antagonist, was approved in the United States in 2010 for the prevention of itching and redness associated with allergic conjunctivitis. Seasonal and perennial allergic conjunctivitis affects up to 40% of the population worldwide. There are numerous treatment options, with topical antihistamines being an effective therapy. Some of the primary symptoms and signs of allergic conjunctivitis are ocular itching and conjunctival redness. The pharmaceutical

market for conjunctivitis is substantial and steadily increasing. For example, the market for allergic conjunctivitis in the United States increased from $6 million in 1993 to $2 billion in 2008. The market in Europe has experienced similar growth. In a healthy eye, tight junctions form a barrier that prevents foreign agents from penetrating the conjunctival epithelium and allows for the paracellular passage of nutrients and water. The tight junctions comprise cell membrane protein complexes that provide stability and adhesion by linking the cytoskeleton of adjacent epithelial cells. In patients with seasonal allergic conjunctivitis, epithelial cell adhesion proteins and cytoskeletal elements are found to be downregulated. Some of the common contributors to this degradation process are proteases from dust mites and peptidases from pollens. Once the protective element of the ocular surface is compromised, allergens penetrate and cause an allergic reaction. The degree of severity depends on a number of factors including the allergen load, the degree of allergen dilution within the tear film, and the expression of epithelial cell molecules. Allergen proteins cross-link with IgE to initiate an allergic cascade resulting in mast cell degranulation and in turn the release of allergen molecules including principally histamine. Ocular itching has been shown to result from histamine's stimulation of the H_4 receptors. Histamine's actions on H_1 and H_2 receptors result in the redness of the conjunctiva. Chemosis and lid swelling also result from H_1 receptor activation [2,3]. Alcaftadine is a potent antagonist of the H_1 receptor ($K_i = 3.1$ nM) and the H_2 receptor ($K_i = 58$ nM) and, additionally, is an antagonist of the H_4 receptor ($K_i = 2900$ nM). Clinical pharmacological studies identified one active metabolite of significance, the corresponding carboxylic acid of the aldehyde group found in alcaftadine. The metabolite forms through non-CYP-mediated enzymatic processes [3]. In an allergic mouse model, alcaftadine was compared to olopatadine where alcaftadine showed differentiation under the experimental protocol and doses chosen. Alcaftadine was found to significantly inhibit eosinophil recruitment when compared to olopatadine and the vehicle control group. The effects of eosinophils have been ascribed to H_4 receptor stimulation. Alcaftadine was found to protect epithelial tight junction proteins, assessed by measuring zonula occludens (ZO-1) and E-cadherin expression levels. Alcaftadine ophthalmic topical solution was assessed in clinical studies where it was found to be safe and effective in preventing ocular itching and redness of the conjunctiva. In a dose escalation study, a 0.25% alcaftadine ophthalmic solution was found to be the most effective at relieving ocular itching and conjunctive redness. Alcaftadine (0.25%) ophthalmic solution was found to have a fast onset of action (3–15 min) and a long duration of action (16 h) making it suitable for use as a once-a-day therapy. In Phase III studies using the conjunctival allergen challenge (CAC) model, alcaftadine (0.25%) ophthalmic solution showed statistically significant lower scores for conjunctival redness versus placebo at 7, 15, and 20 min after an allergen challenge with results persisting for 16 h.

Alcaftadine (0.25%) ophthalmic solution was found to be effective at preventing ocular itching 3, 5, and 7 min after an allergen challenge, demonstrating a fast onset of action. From the Phase III studies, alcaftadine (0.25%) ophthalmic solution was found to prevent ocular itching, reduce conjunctival redness and almost all other allergic signs and symptoms at 15 min and 16 h postdose [4–6]. In July 2010, the FDA approved alcaftadine (0.25%) ophthalmic solution for use in patients with allergic conjunctivitis to prevent itching. The once-daily ophthalmic solution, containing 2.5 mgs of alcaftadine, is marketed by Vistakon, a subsidiary of Johnson and Johnson, under the brand name Lastacaft^{TM}.

2. ALOGLIPTIN (ANTIDIABETIC) [7–15]

Class	DPP-4 inhibitor
Country of origin	Japan
Originator	Syrrx Inc. (now Takeda San Diego)
First introduction	Japan
Introduced by	Takeda Pharmaceuticals, Furiex Pharmaceuticals
Trade names	Nesina®
CAS registry no.	850649-61-5 850649-62-6 (benzoate)
Molecular weight	339.4



Alogliptin is a dipeptidyl-peptidase IV (DPP-4) inhibitor that was approved in Japan in 2010 for treatment of type 2 diabetes, a disease in which insulin resistance and β-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 worldwide 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 [7,8]. As a diabetic patient's metabolic control deteriorates, there is a need to escalate therapeutic intervention by increasing diabetic drug doses and then prescribing combination therapy. The progression of diabetes is attributed to several factors. The process of being in a hyperglycemic state with increases in free fatty acids, cytokines, adipokines, and associated metabolites leads to the loss of β-cell function and β-cell mass in islets [9]. As islet function is lost, the severity of insulin resistance increases. The introduction of DPP-4 inhibitors has brought a novel class of insulinotropic agents for the treatment options available to type 2 diabetic patients. The therapeutic potential of glucagon-like peptide 1 (GLP-1), an incretin peptide, for the treatment of type 2 diabetes was realized in the 1990s. The insulinotropic effects of GLP-1 depend closely on glucose concentrations providing the possibility of glucose normalization without the risk of hypoglycemia. GLP-1 has other non-insulinotropic physiological actions that are advantageous. It suppresses glucagon secretion from α cells and slows gastric emptying, which contributes to satiety and to a slower passage and reabsorption of carbohydrates. GLP-1 also contributes to satiety *via* a central mechanism as a neurotransmitter with effects on the hypothalamus. GLP-1 stimulates β-cell formation from precursor cells and inhibits their apoptosis leading to an increase in β-cell mass and to an improvement in β-cell function. GLP-1 reduces inappropriate glucagon secretion from the pancreas. The observation that oral intake of glucose gives a greater insulin response than IV glucose administration is termed the incretin effect; in type 2 diabetes, the incretin effect is impaired. In patients with type 2 diabetes, infusion of GLP-1 has been found to increase insulin secretion and to normalize both fasting and post-prandial blood glucose. GLP-1 is a 30-amino acid peptide that 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. DPP-4 inhibitors are the first class of agents to utilize the pharmacology of GLP-1 and thus offer a novel way to increase endogenous incretin peptide concentrations. 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

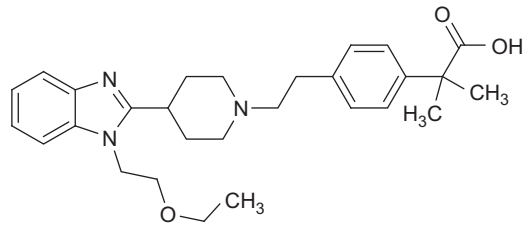
β-cell apoptosis and increase β-cell survival. In animal models, DPP-4 inhibitors increase the number of insulin positive β-cells in islets. Islet insulin content is found to be increased and glucose-stimulated insulin secretion in isolated islets is improved [8–10].

Alogliptin (SYR-322) has been described as a potent, highly selective DPP-4 inhibitor. The discovery of alogliptin arose out of a designed series of quinazolinone-based inhibitors of DPP-4. The lead quinazolinone was found to inhibit CYP3A4 and to have micromolar affinity for the hERG channel. Replacement of the quinazolinone ring with a pyrimidinedione addressed both of these issues with none of the unwanted off-target activities observed. This discovery resulted in alogliptin (SYR-322). Alogliptin inhibits DPP-4 with an $IC_{50} < 10$ nM and is highly selective $>10{,}000$-fold) against DPP-8 and -9 as well as over other endopeptidases. The synthesis of alogliptin described in the literature starts with chloropyrimidinedione. One of the nitrogen atoms is selectively benzylated followed by methylation of the remaining nitrogen. This is followed by chloro displacement using 3-aminopiperidine to give alogliptin [11]. In animal models, alogliptin rapidly inhibits DPP-4 activity (15 min postdose); plasma DPP-4 inhibition is sustained for 12 h in rats and dogs and for 24 h in monkeys. The animal pharmacokinetic profile was found to be supportive for once-daily dosing of alogliptin in man. The reported efficacy of alogliptin in multiple animal models of diabetes has been reported. In a 4-week ob/ob mouse model of type 2 diabetes, alogliptin dose dependently reduced plasma DPP-4 activity and increased GLP-1 levels. In addition, plasma insulin levels were increased, plasma glucose levels were decreased and HbA1c levels were reduced. Glucagon and triglyceride levels were also decreased [12,13]. In clinical studies, alogliptin has been found to be safe and well tolerated. In dose escalation studies, the pharmacokinetic parameters were linear over the 25–800 mg dose range. In man, alogliptin is rapidly absorbed and eliminated primarily intact with 40% hepatic and 60% renal elimination. There are two metabolites formed at very low levels. An active metabolite (M1) resulting from CYP 2D6 N-demethylation is formed as $<2\%$ of parent drug concentration. A second inactive metabolite resulting from the N-acetylation of M1 is $<6\%$ of total parent drug concentration. The half-life of alogliptin determined over six Phase III studies is 10.9–21.8 h. Alogliptin has been studied as monotherapy and in combination with pioglitazone and as an add-on with metformin, glyburide, pioglitazone, and insulin. As monotherapy, alogliptin significantly improved HbA1c levels from baseline as both the 12.5 and 25 mg doses, which are now the marketed doses [14,15]. Alogliptin benzoate, Nesina®, a highly selective DPP-4 inhibitor for the treatment of type 2 diabetes, received regulatory approval from the Japanese Ministry of Health, Labor and Welfare in April 2010. Nesina® is the

fourth marketed inhibitor of DPP-4. Nesina® is being codeveloped by Takeda Pharmaceutical Company and Furiex Pharmaceuticals, Inc.

3. BILASTINE (ANTIALLERGY) [16–23]

Class	Selective histamine H_1 receptor antagonist
Country of origin	Spain
Originator	FAES FARMA, S.A.
First introduction	European Union
Introduced by	FAES FARMA, S.A., Menarini, Pierre Fabre Medicament, Merck-Serano
Trade names	Bilaxten™
CAS registry no.	202189-78-4
Molecular weight	463.6



Bilastine, a potent and selective histamine H_1 receptor antagonist, was approved in Europe in 2010 for the treatment of allergic rhinoconjunctivitis (AR) and urticaria (hives or skin rash). The prevalence of AR is estimated to be >20% worldwide with some studies suggesting that 42% of the worldwide population is affected. In the United States, the allergies in America survey found that 14.2% of the population had been diagnosed with AR. The total worldwide market for antihistamines is >4.2 billion euros with one quarter of the market share in Europe. AR affects quality of life. Sufferers have symptoms of sneezing, nasal congestion, rhinorrhea, itching, headaches, and associated ocular conditions. In many AR patients, sleep and social functioning are affected. Thus, in addition to medical costs, there are indirect costs of AR such as decreased productivity and absenteeism from work or school. AR is a major risk factor for the development of asthma [16]. The inflammatory response in AR is triggered by an IgE-mediated reaction to allergens. One of the major mediators of this response is histamine. In response to stimuli, histamine is released from mast cells and basophilic granulocytes and interacts with

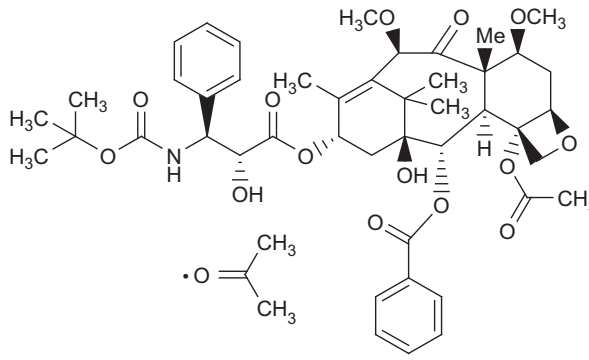
the H_1, H_2, and H_4 histamine receptors. The resulting biological processes that are triggered include stimulation of sensory nerve and cough receptors, increased vascular permeability, and smooth muscle contraction. The main pharmacological agents to intervene with these processes are histamine H_1 antagonists. Bilastine is a potent and selective histamine H_1 receptor antagonist with a $K_i = 44$ nM (guinea pig ileum) and no activity (>100 μM) for the H_2 and H_3 receptors. In *in vitro* experiments conducted in guinea pig and rat tissues, bilastine showed no activity against serotonin, bradykinin, leukotriene (LTD4), muscarinic (M3), and adrenoreceptors. When tested in a panel screen (MDS Pharma Services), no activity was observed for the 30 assays which included adenosine, adrenoreceptors, dopamine, muscarinic, opiate, serotonin, and steroidal receptors. The functional antagonist activity of bilastine was demonstrated by its ability to block histamine and interleukin IL-4 release from human mast cells and peripheral blood granulocytes [17,18]. In animal studies, orally administered bilastine was found to have a rapid onset of action and a long duration of action supporting once-daily dosing in man. Bilastine was effective in rat models used to assess its antihistamine activity as measured by the reduction in the increase of histamine-mediated capillary permeability. In guinea pigs, bilastine was shown to be effective at reducing the microvascular extravasation induced by histamine in the trachea. As well, the antiallergic effects of bilastine were demonstrated in several other animal models. Based on the preclinical data, bilastine was advanced into clinical trials [19,20]. The original synthesis of bilastine [21] involves alkylation of 2-piperidinyl-1H-benzimidazole with a phenethyltosylate, the *para* position of which is substituted with a dimethyloxazoline moiety serving as a masked carboxylic acid group. Alkylation of the benzimidazole nitrogen with 2-chloroethyl ethyl ether followed by unmasking of the oxazoline moiety with sulfuric acid provided bilastine. An alternate synthesis of bilastine has since been reported [22].

In healthy male volunteers, bilastine was found to be rapidly absorbed with a T_{max} of 1 h. Bilastine showed linear pharmacokinetics over the dose range of 10–100 mg given once daily. The half-life was found to be shorter on day 1 when compared to day 14 (4.7 *vs.* 9.6 h for the 20 mg dose). After a single dose, bilastine is excreted in the feces (67%) and in the urine (33%). In Phase III clinical studies, a once-daily oral dose of 20 mg of bilastine effectively relieved the symptoms of allergic rhinitis. In addition, bilastine was effective at improving quality of life as measured by reduction of sleep disturbances and parameters of general discomfort. Studies in healthy volunteers and patients have demonstrated that bilastine is safe, lacking the unwanted sedative and cardiotoxic effects associated with some antihistamine drugs. In two major clinical trials, bilastine was effective at relieving allergic rhinitis as assessed by measuring the severity of

nasal (obstruction, rhinorrhea, itching, sneezing) and nonnasal (ocular itching, tearing, ocular redness, itching of ears, and/or palate) symptoms. A total of 28 clinical trials were conducted with bilastine in 5000 patients [23]. In September 2010, the German health agency (BfARm) approved bilastine for treatment of AR and urticaria. Bilastine will be sold under the trade name Bilaxten™ in Spain as once-daily oral dosage of 20 mg.

4. CABAZITAXEL (ANTICANCER) [24–30]

Class	Tubulin inhibitor
Country of origin	France
Originator	Sanofi-Aventis
First introduction	United States
Introduced by	Sanofi-Aventis
Trade name	Jevtana®
CAS registry no.	183133-96-2
Molecular weight	835.9



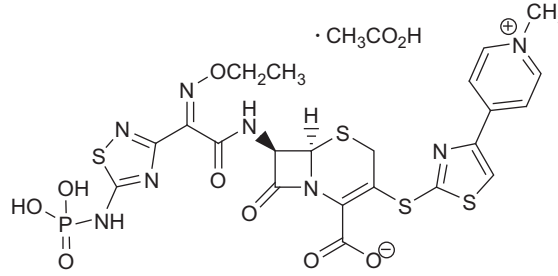
In June 2010, the U.S. FDA approved cabazitaxel (also referred to as XRP6258 and RPR 116258A) in combination with the steroid prednisone for the treatment of metastatic Castration-Resistant Prostate Cancer (mCRPC) for patients who were previously treated with a docetaxel-containing regimen for late-stage disease. The 2010 statistics from the U.S. National Cancer Institute are that ~220,000 men will be diagnosed with prostate cancer and ~32,000 men will die of the disease. Depending on the stage of the disease, prostate cancer symptoms may include urinary problems, impotence, blood in the urine or semen, and pain in the lower back, hip, or upper thighs. Chemotherapeutic standard of care for mCRPC usually involves treatment with the anticancer drug docetaxel in

combination with prednisone. Cabazitaxel is a semisynthetic analog of the natural product taxol®, which is isolated from the bark of the yew tree. Cabazitaxel is a microtubule inhibitor that binds to the taxol-binding site of tubulin. Similar to other tubulin inhibitors of the taxol class, cabazitaxel inhibits microtubule disassembly resulting in mitotic blockade and cell death. Docetaxel, also a semisynthetic taxol analog, was approved by the FDA for the treatment of mCRPC in 2004. However, docetaxel is a substrate for P-gp, which is thought to contribute to the constitutive and acquired resistance of cancer cells to taxanes. Cabazitaxel has poor affinity for P-gp and showed antitumor activity in preclinical *in vitro* studies and *in vivo* tumor models that overexpress this protein. Cabazitaxel is synthesized on a commercial scale from 10-deacetylbaccatin [24]. Preclinical *in vitro* studies suggested that the antitumor activity of cabazitaxel is comparable to docetaxel with IC_{50}s ranging from ~4 to 35 nM. Moreover, cabazitaxel is active in cancer cell lines that are resistant to docetaxel with resistance factor ratios ranging from 1.8 to 10 for cabazitaxel versus 4.8–59 for docetaxel. In preclinical human tumor xenograft models, cabazitaxel showed complete regression rates in colon, lung, pancreatic, head and neck, kidney, and prostate carcinoma cell lines, when dosed intravenously [25,26].

Cabazitaxel exhibited dose-proportional pharmacokinetics over a dose range of 10–25 mg/m^2 following a 1-h IV infusion every 3 weeks to patients ($n = 25$) with solid tumors in a Phase I clinical trial [27]. The C_{max} and AUC increased in a dose-proportional fashion with a mean terminal half-life of ~77 h. The clearance and volume of distribution were high with mean values of 53.5 L/h and 2034 L/m^2, respectively. Cabazitaxel is extensively metabolized (>95% in liver) predominantly by CYP3A4/5 and to a minor extent by CYP2C8. The safety and efficacy of cabazitaxel were established in an open-labeled, randomized, Phase III study comprising 755 men with hormone-refractory metastatic cancer who were previously treated with a regimen that contained docetaxel [28]. Of the 755 patients, 378 were treated with cabazitaxel at 25 mg/m^2 dosed intravenously every 3 weeks for a maximum of 10 cycles along with 10 mg of prednisone orally and 377 were treated with 12 mg/m^2 of mitoxantrone dosed intravenously every 3 weeks for a maximum of 10 cycles along with 10 mg of prednisone dosed orally. The Phase III study clearly demonstrated that cabazitaxel-treated patients showed improvement in the median overall survival of 15.1 months compared to 12.7 months for patients in the mitoxantrone group. Most common serious adverse events (>5%) associated with cabazitaxel treatment were neutropenia, febrile neutropenia, leukopenia, anemia, diarrhea, fatigue, hypersensitivity, and asthenia. The recommended dose of cabazitaxel is 25 mg/m^2 administered intravenously over 1-h every 3 weeks along with 10 mg of oral prednisone administered daily throughout cabazitaxel treatment [29,30].

5. CEFTAROLINE FOSAMIL (ANTIBACTERIAL) [31–38]

Class	Bacterial cell wall synthesis inhibitor
Country of origin	Japan
Originator	Takeda
First introduction	United States
Introduced by	Forest Laboratories Inc.
Trade name	Teflaro®
CAS registry no.	402741-13-3
Molecular weight	684.7



Ceftaroline fosamil, also referred to as TAK-599, is a cephalosporin antibacterial agent that was approved in the United States in October 2010 for the IV treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Ceftaroline fosamil is the water-soluble, *N*-phosphono prodrug of ceftaroline (T-91825), a broad-spectrum, bactericidal agent with potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains, multidrug resistant *S. pneumonia*, and common gram-negative organisms [31–33]. Infections due to drug-resistant gram-positive bacteria, particularly MRSA, are a continuing and growing concern worldwide. For example, in 2005 more than 100,000 people in the United States developed serious MRSA infection and nearly 19,000 people died during a hospital stay due to serious MRSA infections [34]. About 85% of all invasive MRSA infections in the United States were associated with healthcare, with two-thirds occurring outside of the hospital and one-third occurring during hospitalization. In the European Union, a study published in 2010 showed that more than 150,000 patients within the healthcare setting have MRSA infections, with the proportion of MRSA infections ranging from 1% to 50%, depending on the country [35]. New MRSA strains have also emerged as community and livestock-associated human pathogens. Like other β-lactam antibiotics, ceftaroline acts by inhibiting the essential transpeptidase activity

of penicillin-binding proteins (PBPs), which leads to inhibition of bacterial cell wall synthesis and, ultimately, bacterial cell death. MRSA resistance to β-lactams arises from an alteration in PBP to a new form, PBP2a, which retains function in cell wall synthesis, but has lower affinity for β-lactam antibiotics. Ceftaroline binds to PBP2a [36] as well as other PBPs with high affinity and, as a result, retains potent activity. Ceftaroline exhibits activity against most gram-positive pathogens, including β-lactam-susceptible and -resistant *S. aureus*, vancomycin-resistant *S. aureus*, and resistant and susceptible forms of *S. pneumoniae* but has weak activity against *Enterococcus* sp. The gram-negative antibacterial activity of ceftaroline is limited mainly to respiratory pathogens such as *Moraxella catarrhalis* and *Haemophilus influenzae*. Ceftaroline has demonstrated *in vivo* efficacy in a number of preclinical infection models [31–33], including murine pneumonia, murine soft tissue infection, rat and rabbit endocarditis, and rabbit osteomyelitis models. Ceftaroline fosamil is synthesized by coupling 4-(pyridin-4-yl)thiazol-2-amine with a protected 7-amino-3-methanesulfonyloxy cephalosporinic acid ester derivative. Quaternization of the pyridine nitrogen with methyl iodide followed by deprotection of the 7-amino and 4-carboxylic acid groups provides the amino cephalosporin intermediate [37,38]. Reaction of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(ethoxyimino)acetic acid with phosphorous pentachloride provides the requisite C-7 side-chain intermediate. Coupling of the two fragments, followed by acidic hydrolysis, affords ceftaroline fosamil, which is converted to its acetate salt. The aqueous solubility of ceftaroline fosamil is >100 mg/mL compared with 2.3 mg/mL for ceftaroline. Ceftaroline fosamil is available as 600 or 400 mg of sterile powder in single-use 20 mL vials. The powder is dissolved in 20 mL of sterile water and then further diluted with ≥ 250 mL of an appropriate vehicle prior to administration. The recommended dosage is 600 mg administered every 12 h by IV infusion over 1 h.

Ceftaroline fosamil is rapidly converted into bioactive ceftaroline by plasma phosphatases. After a single 600 mg dose of ceftaroline fosamil as a 1-h infusion in healthy volunteers, the ceftaroline pharmacokinetic parameters were $C_{max} = 19$ μg/mL; $T_{max} \sim 1$ h; AUC = 57 μg h/mL; half-life = 1.6 h. Pharmacokinetic parameters were similar for single and multiple dose IV administration of ceftaroline fosamil. The average binding of ceftaroline to human plasma proteins is ~20%. The steady-state volume of distribution was similar to extracellular fluid volume. As with other β-lactam antimicrobial agents, the time that unbound plasma concentrations of ceftaroline exceed the minimum inhibitory concentration (MIC) of the infecting organism correlates with efficacy in preclinical infection models with *S. aureus* and *S. pneumoniae*. Ceftaroline is not a substrate or an inhibitor of hepatic CYP450 enzymes. Hydrolysis of the β-lactam ring occurs to form the microbiologically inactive, ring-opened metabolite M-1 to an extent of ~30%. Ceftaroline and its metabolites were primarily eliminated

by the kidneys: there was ~90% recovery of radioactivity in urine and 6% in feces within 48 h of a 600 mg IV dose. Of the radioactivity recovered in urine, ~64% was excreted as ceftaroline and ~2% as M-1. The renal clearance of ceftaroline was 5.56 L/h, suggesting that ceftaroline is predominantly eliminated by glomerular filtration. Four Phase III trials were used to demonstrate the efficacy of ceftaroline fosamil in ABSSSI and CABP. In two ABSSSI trials, half of the ~1500 patients received ceftaroline fosamil (600 mg, 1-h IV infusion) and half received vancomycin plus aztreonam. These studies included patients with infections caused by both susceptible and resistant organisms. Clinical cure rates were similar and high (>90%) for both the ceftaroline and vancomycin plus aztreonam groups. For CABP, a total of ~1200 adults were enrolled in two randomized, double-blind, non-inferiority trials comparing ceftaroline fosamil (600 mg, 1-h IV infusion every 12 h) with ceftriaxone (1 g, 30-min IV infusion every 24 h). One trial included oral clarithromycin as adjunctive therapy. Patients with known or suspected MRSA were excluded from both trials. Treatment duration was 5–7 days. Clinical cure rates by pathogen were higher for ceftaroline fosamil than for ceftriaxone for gram-positive organisms and were similar for gram-negative organisms. Like most cephalosporins, ceftaroline fosamil was safe and well tolerated. The most common adverse events occurring in >2% of patients were diarrhea, nausea, and rash. No single adverse event occurred in >5% of patients. In the four pooled Phase III clinical trials, treatment discontinuation due to adverse events occurred in 2.7% of patients receiving ceftaroline fosamil and 3.7% of patients receiving comparator drugs. In a randomized, positive- and placebo-controlled crossover thorough QTc study, no significant effect on QTc interval was detected at peak plasma concentration or at any other time in healthy subjects given a 1500-mg single dose by IV infusion over 1 h. Ceftaroline was approved in the United States in October, 2010, and is marketed under the trade name Teflaro®.

6. CORIFOLLITROPIN ALFA (INFERTILITY) [39–43]

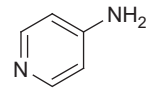
Class	Follicle-stimulating hormone receptor agonist
Country of origin	Netherlands
Originator	N.V. Organon
First introduction	European Union
Introduced by	Merck
Weight	47 kDa
Trade names	Elonva®
CAS registry no.	195962-23-3

Corifollitropin is a follicle-stimulating hormone (FSH) receptor agonist that was approved as an infertility treatment in the European Union in 2010. Infertility is a recognized worldwide public health issue by the World Health Organization (WHO). The prevalence in more- and less-developed countries is similar; however, the reasons contributing to infertility may differ. There is a steady rise in age-related infertility in more-developed countries, whereas in less well-developed countries, infections play a large contributing role to infertility. Worldwide on average, 9% of women of child bearing years are infertile. Infertility has social consequences as a large percentage of couples identify having children as one of their life-long goals. However, only 50% of infertile couples have been reported to seek fertility services [39]. Nearly all of the assisted reproductive techniques (ART) used to increase the chances for conception can be categorized as *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), and controlled ovarian stimulation (COS). Multifollicular development resulting from COS is essential to ART and is primarily governed by circulating levels of FSH [39,40]. FSH belongs to the gonadotropin family of glycoproteins that are excreted from the pituitary gland by gonadotrope cells. Other members include thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG). TSH and LH are produced in the pituitary gland, whereas hCG is produced in the placenta. The gonadotropins all have a dimeric structure in which the α-subunit is a shared, nearly identical, substructure, and the glycosylated β-subunit is varied and is responsible for receptor selectivity. Variants of FSH have been used in therapies to enhance conception since the 1950s. Since the 1990s, rFSH has been employed. The dosing regimen of FSH requires several daily injections over a 9-day period and has the drawbacks of low patient compliance and injection discomfort. Several approaches have been applied to increase the half-life of FSH *via* formulation or chemical modification [41–43]. A unique approach developed by Boime and his research group involved using the carboxy peptide terminus (CPT) of the β-chain of hCG to increase the half-life of FSH, while maintaining the β-chain of FSH to confer selectivity and potency for the FSH receptor. These hybrid glycopeptides were produced using recombinant DNA methods in Chinese Hamster Ovary (CHO) cells. One of the analogs produced from this effort was corifollitropin alfa. Corifollitropin has been compared to rFSH both *in vitro* and *in vivo*. Corifollitropin binds to the FSH receptor with equal potency compared to rFSH. In an FSH receptor transactivation assay, corifollitropin was 1.8-fold less active than rFSH but remained a potent activator with an $EC_{50} = 5$ pM. Corifollitropin alfa lacks activity for the LH and TSH receptors. In a rat PK model, corifollitropin alfa has two times the C_{max} and 1.6 times the half-life of rFSH. A similar result was reported in beagle dogs, with

the half-life of corifollitropin alfa being 47 h compared to 23 h for rFSH. In a rat model of fertility, the extended half-life of corifollitropin resulted in better efficacy in increasing ovarian weight when compared to rFHS when both were dosed in combination with hCG. In another rat efficacy model, the number of ova per rat was found to be increased to higher levels with corifollitropin alfa when compared to rFSH [41–43]. In humans, the mean half-life from Phase I and Phase II studies is 65 h, compared with 35 h for rFSH, and the AUC is dose proportional over the dose range of 60–240 μg. Peak levels of corifollitropin are reached between 25 and 45 h after injection. In human efficacy studies, a single dose of corifollitropin alfa is able to sustain follicular development for 1 week. The exposure of corifollitropin alfa was found to have some variability with regard to body weight. Based on this finding, in Phase III studies, subjects weighing more than 60 kg were given a 150-μg subcutaneous dose and subjects weighing less than 60 kg were given a 100-μg subcutaneous dose. In the largest double-blind fertility agent trial ever performed, the ENGAGE trial studied 1506 patients. The ENGAGE trial (Phase III) compared a single dose (150 μg) of corifollitropin alfa to rFSH (200 IU/day) over 7 days to induce multifollicular growth in subjects weighing more than 60 kg who were undergoing COS as part of IVF or ICSI. The primary endpoint of the study was pregnancy rate as assessed 10 weeks after placental implant. After the 7 days, subjects were then treated with daily rFSH up to the day that the subjects were given hCG. The maximal duration of drug stimulation was 19 days. Patients also received ganirelex (GnRH antagonist) starting on day 5. The rate of pregnancy and number of oocytes retrieved were comparable between the corifollitropin alfa and rFSH groups. The ENSURE trial (Phase III) compared corifollitropin alfa to rFSH in patients weighing less than 60 kg undergoing COS as part of IVF or ICSI. The primary endpoint of this study was the number of oocytes retrieved. In this study, patients were given a single dose of corifollitropin (100 μg) or daily injections of rFSH (150 IU/day) for 7 days to induce multifollicular growth. From day 8 onward, subjects received daily injections of rFSH dose adjusted up to 200 IU until the day that hCG was given to cause oocyte maturation. The maximal total duration of stimulation was 19 days. Patients received ganirelex on day 5. The number of oocytes and ongoing pregnancy rate were comparable between the corifollitropin alfa and rFSH groups [41–43]. In January 2010, the EC approved corifollitropin alfa injection for COS in combination with a GnRH antagonist for the development of multiple follicles in women participating in an assisted reproductive technology (ART) program. Merck and Co., Inc. market corifollitropin alfa injection under the brand name Elonva®. Elonva® is the first in a class of sustained follicle stimulants (SFS).

7. DALFAMPRIDINE (MULTIPLE SCLEROSIS) [44–50]

Class	Potassium channel blocker
Country of origin	United States
Originator	Rush University Medical Center
First introduction	United States
Introduced by	Acorda Therapeutics Inc.
Trade name	Ampyra®
CAS registry no.	504-24-5
Molecular weight	94.1



Dalfampridine (also referred to as 4-AP) is the first drug approved by the FDA to improve walking in patients with multiple sclerosis (MS). MS is an autoimmune disease that affects the brain and spinal cord. MS is caused by inflammation-mediated damage to the myelin sheath, the insulating layer that surrounds the core of a nerve fiber or axon and facilitates the transmission of nerve impulses. Repeated episodes of inflammation can occur along any area of the brain, optic nerve, and spinal cord. Among the many symptoms that negatively affect the quality of life in MS patients, fatigability of strength (defined as the decrease in strength that occurs with repetitive movements) is the most common impairment that is not addressed by currently available therapies. For example, in a survey of 1011 people conducted by the United States National MS society, 64% reported difficulty with walking; of this group, 78% reported that this impacted their ability to work [44]. Dalfampridine addresses this issue *via* a novel mechanism of action. In MS patients, the normal pattern of nerve conduction is slowed down because of damage to myelinated fibers, which is manifested clinically as weakness and fatigability of strength. Dalfampridine is a voltage-gated potassium channel blocker that readily penetrates the CNS and increases the conduction and duration of action potential across nerve fibers resulting in enhanced functionality as observed in the walking speed of MS patients [45]. 4-AP has been widely used in clinical practice based on trials with immediate-release formulations that showed improvement in motor and visual functions in some patients. However, fluctuations in peak drug levels leading to unintentional overdose [46] or inadequate serum levels (requiring frequent dosing) necessitated the development of an extended-release formulation to improve pharmacokinetic parameters and minimize side effects of 4-AP.

A 10 mg dose of extended-release dalfampridine administered to healthy volunteers or patients with MS gave peak concentrations of ~20 ng/mL over 3–4 h post-administration [47]. In contrast, administration of 10 mg dose of immediate-release dalfampridine led to a C_{max} of ~43 ng/mL with a T_{max} of ~1.3 h. Extended-release dalfampridine tablet has a relative bioavailability of 96% when compared to an aqueous oral solution (immediate-release formulation). Dalfampridine shows very little binding to human plasma proteins (1–3%) and has a volume of distribution of ~2.6 L/kg. After two Phase II trials showed some level of efficacy, extended-release dalfampridine was evaluated in two Phase III studies. In the first randomized, multicenter, double-blind, placebo-controlled Phase III trials, 301 patients were enrolled [48]. The second trial involved 240 patients [49]. Walking speed as measured by the Timed 25-foot Walk (T25FW) was the primary measure of efficacy in both trials. Results from both clinical studies showed that extended-release dalfampridine (10 mg, twice daily) significantly improved walking speed and strength in a majority of the MS patients compared to placebo (T25FW responder rate in Trial 1: 34.8% *vs.* 8.3% for placebo; Trial 2: 42.9% *vs.* 9.3% for placebo). From a safety perspective, seizure was the most important adverse event from various dalfampridine clinical trials. Therefore, dalfampridine is contraindicated in patients with a history of seizures. Since dalfampridine is primarily excreted by the kidney as unchanged drug, it is also contraindicated in patients with moderate to severe renal impairment. Assessing the overall benefit–risk profile from various clinical trials, the FDA approved dalfampridine (daily oral dose of 10 mg, b.i.d.) to improve walking in MS patients with existing gait impairment [50].

8. DENOSUMAB (OSTEOPOROSIS AND METASTATIC BONE DISEASE) [51–59]

Class	Recombinant monoclonal antibody
Country of origin	United States
Originator	Amgen
First introduction	United States
Type	Fully human IgG2, anti-RANKL
Introduced by	Amgen
Weight	~147 kDa
Trade names	Prolia®/Xgeva®
Expression system	Rodent CHO-cell line
CAS registry no.	615258-40-7

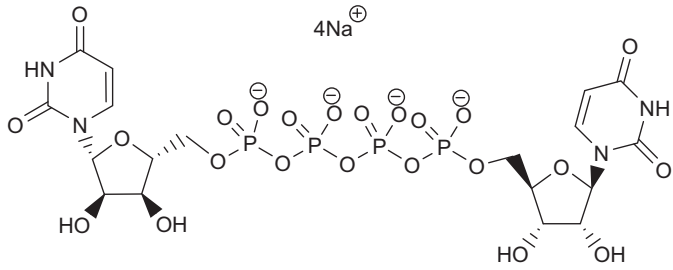
Denosumab, which was approved in the United States in 2010, is a fully human sequence IgG2 monoclonal antibody that inhibits bone resorption by blocking the activity of receptor activator of nuclear factor-κB ligand (RANKL). RANKL is a TNF family protein that is expressed in both secreted and cell surface forms by a variety of bone marrow cell types and mediates bone resorption through its receptor (RANK), which is found on osteoclasts and osteoclast precursors [51]. Denosumab was discovered using Xenomouse^{TM} transgenic mice comprising human immunoglobulin genes [52,53]. The antibody is approved for treatment of postmenopausal women with osteoporosis at high risk for fracture, and for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Denosumab competes directly with bisphosphonates such as alendronic acid in postmenopausal osteoporosis and with zoledronic acid in both of these indications. It has been shown to have comparable efficacy and safety to bisphosphonates with some tolerability and patient acceptability advantages. The drug is formulated as a solution for subcutaneous injection. The recommended dosage for treatment of postmenopausal women with osteoporosis is 60 mg administered every 6 months. At this dose, the observed mean C_{max} was 6.75 mcg/mL followed by serum concentration decline with a mean half-life of 25.4 days. The recommended dosage for patients with bone metastases is 120 mg administered every 4 weeks. With multiple subcutaneous doses, up to a 2.8-fold accumulation in serum denosumab concentrations was observed and steady state was achieved by 6 months. At steady state, the mean serum trough concentration was 20.5 mcg/mL, and the mean elimination half-life was 28 days. For both regimens, administration of vitamin D and calcium supplements is recommended to treat or prevent hypocalcemia. Denosumab was tested in three randomized Phase III trials in postmenopausal osteoporosis and three randomized Phase III trials in cancer patients with bone metastases. In all six of these trials, subjects were randomized 1:1 to either denosumab treatment or a control regimen. The largest of these trials, the pivotal FREEDOM trial [54], enrolled 7868 women who had low bone mineral density. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. Denosumab reduced the risk of new radiographic vertebral fracture (a cumulative incidence of 2.3% *vs.* 7.2% in the placebo group, $p < 0.001$), hip fracture (cumulative incidence of 0.7% *vs.* 1.2% in the placebo group, $p = 0.04$), and nonvertebral fracture (a cumulative incidence of 6.5% *vs.* 8.0% in the placebo group, $p = 0.01$). There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia. The two supportive, non-pivotal, Phase III trials in postmenopausal osteoporosis patients, the STAND [55] and DECIDE [56] trials, enrolled 504 and 1189 women, respectively, and directly compared denosumab to alendronic acid. The STAND trial examined the effect of transitioning from bisphosphonate

therapy to denosumab. Subjects received open-label alendronate 70 mg once weekly for 1 month and then were randomly assigned to either continued weekly alendronate therapy or subcutaneous denosumab 60 mg every 6 months and were followed for 12 months. In subjects treated with denosumab, total hip bone mineral density increased by 1.90% at month 12 compared with a 1.05% increase in subjects on alendronate ($p < 0.0001$). Bone mineral density at the lumbar spine, femoral neck, and one-third radius was also greater with denosumab at 12 months (all $p < 0.0125$). In the DECIDE trial, patients were treated with either denosumab or alendronate without necessarily transitioning from prior alendronate therapy (~12% had received prior bisphosphonate therapy). Subjects were randomized to receive subcutaneous denosumab injections (60 mg every 6 months) plus oral placebo weekly or oral alendronate weekly (70 mg) with subcutaneous placebo injections. Denosumab treatment increased total hip bone mineral density compared with alendronate at month 12 (3.5% *vs*. 2.6%; $p < 0.0001$). Greater increases in bone mineral density were also observed with denosumab treatment at all measured skeletal sites (12-month treatment difference: 0.6%, femoral neck; 1.0%, trochanter; 1.1%, lumbar spine; 0.6%, one-third radius; $p \leq 0.0002$ all sites). In both the STAND and DECIDE trials, adverse events and serious adverse events occurred with similar types and frequencies in the denosumab and alendronate treatment groups. Prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three randomized, double-blind trials comparing denosumab with zoledronic acid in 2046 breast cancer patients [57], 1776 solid tumor (excluding breast cancer and prostate cancer) and multiple myeloma patients [58], and 1901 prostate cancer patients [59]. In all three trials, patients were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously every 4 weeks (dose adjusted for reduced renal function). In each trial, the main outcome measure was demonstration of non-inferiority of time to first skeletal-related event as compared to zoledronic acid. The percentage of patients having skeletal-related events in the denosumab-treated groups for each of the three trials was 30.7%, 31.4%, and 35.9%, respectively. The percentages for the zoledronic acid-treated groups were 36.5%, 36.3%, and 40.6%. Median time to first skeletal-related event was not reached in the denosumab arm of the breast cancer trial. It was 26.4 months for the zoledronic acid arm. For the other two trials, the denosumab-treated group had median first event times of 20.5 and 20.7 months, compared to 16.3 and 17.1 months, respectively for zoledronic acid treatment. The p values for non-inferiority for denosumab over zoledronic acid were <0.001 for all three trials. The p values for superiority were 0.01, 0.06, and 0.008, respectively. Overall survival and progression-free survival were similar between arms in all three trials; however, mortality was higher with

denosumab in a subgroup analysis of 180 patients with multiple myeloma (hazard ratio of 2.26; 95% CI: 1.13, 4.50). For this reason, denosumab is not approved for prevention of skeletal-related events in patients with multiple myeloma. Adverse events and serious adverse events (including new malignancies and serious infections) occurred with similar types and frequencies in the denosumab and zoledronic acid treatment groups for all three trials. Cumulative incidence of osteonecrosis of the jaw across the three trials was 1.9% for the denosumab-treated patients and 1.3% for the zoledronic acid-treated patients. The incidence of adverse events associated with renal toxicity was higher with zoledronic acid, despite dose adjustments for patients with reduced renal function. Acute phase reactions were also more frequent in the zoledronic acid cohorts. Overall experience with denosumab shows that the drug is relatively nonimmunogenic. Cumulative data from 8115 postmenopausal osteoporosis patients and 2758 cancer patients treated with denosumab showed that less than 1% of the patients tested positive for antidrug antibodies and none of the 10,873 patients tested positive for neutralizing antibodies.

9. DIQUAFOSOL (OPHTHALMOLOGIC, DRY EYE) [60–67]

Class	$P2Y_2$ purinergic receptor agonist
Country of origin	United States
Originator	Inspire Pharmaceuticals
First introduction	Japan
Introduced by	Santen
Trade name	Diquas
CAS registry no.	211427-08-6 (tetrasodium salt) 59985-21-6 (acid)
Molecular weight	878.2 (tetrasodium salt)



Diquafosol (INS-365) was approved in Japan in 2010 as a 3% ophthalmic solution for treatment of dry eye disease [60]. Dry eye disease is a common condition that begins with symptoms of ocular discomfort such as burning, stinging, or a sandy/gritty sensation. The disease is characterized by a lack of tear volume and/or an improper tear composition and damage to the ocular surface. Dry eye is a highly prevalent condition, affecting 14–33% of the population worldwide [61]. Clinical diagnosis of dry eye is difficult because the condition presents a variety of symptoms. Treatment options include tear supplements (lubricants), anti-inflammatory drugs (*e.g.*, cyclosporine eye drops or steroid eye drops), and tear retention devices. Diquafosol is a unique agent for the treatment of dry eye in that it acts as a $P2Y_2$ purinergic receptor agonist with the ability to activate this receptor on the ocular surface and stimulate water, lipid, and mucin secretion [62]. These are the three main processes that are needed to produce an appropriate tear. Diquafosol is a full agonist at the $P2Y_2$ receptor ($EC_{50} = 0.10$ μM) and is nearly as potent as the native agonist uridine diphosphate (UDP; $EC_{50} = 0.03$ μM) [63,64]. It is also a full agonist at the $P2Y_4$ receptor ($EC_{50} = 0.4$ μM) and a weak agonist at the $P2Y_6$ receptor ($EC_{50} = 20$ μM). Diquafosol is prepared by treatment of uridine triphosphate (UTP) with DCC, followed by condensation with uridine monophosphate (UMP) to give diquafosol in ~30% yield [64,65]. Alternatively, the compound could be prepared by activation of UDP with CDI, followed by the addition of a second molecule of UDP. Diquafosol is administered topically, which limits exposure to the local site of action. In 25 dry eye patients monitored over 6 months of treatment, there were no detectable systemic concentrations of diquafosol or its metabolites. Diquafosol is metabolized by phosphodiesterases to UTP, UDP, UMP, and uridine. Diquafosol has been well tolerated in clinical trials, with side effects being local to the ocular surface. In one Phase III trial, burning and stinging were reported in 7% of diquafosol subjects compared with 2% on placebo. For approval of a new prescription drug for the treatment of dry eye disease, the FDA requires demonstration of efficacy for both a sign (an objective measure such as corneal staining) and a symptom (a subjective measure such as sensation of a foreign body in the eye) of the disease [66]. There have been five Phase III trials with 2% solutions of diquafosol conducted. Results have been mixed with some endpoints being met, but with failure to meet others. Three additional Phase III trials have been carried out in Japan using a 3% ophthalmic solution of diquafosol [67]. The 3% solution was reported to improve dry eye symptoms by promoting secretion of mucin and water, thereby bringing the tear film closer to a normal state. In addition,

no serious ocular or systemic adverse drug reactions were found during the clinical trials [60]. The 3% solution of diquafosol is the approved treatment for dry eye in Japan.

10. ECALLANTIDE (ANGIOEDEMA, HEREDITARY) [68–72]

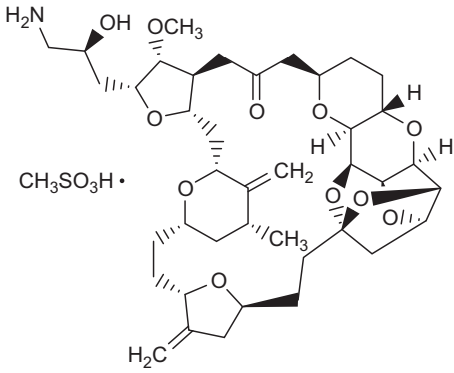
Class	Plasma kallikrein inhibitor
Country of origin	United States
Originator	Dyax Corp.
First introduction	United States
Introduced by	Dyax Corp.
Trade name	Kalbitor®
CAS registry No.	460738-38-9
Weight	7053.8
Type	Modified tissue factor pathway inhibitor, 60 amino acid recombinant protein
[Glu^{20},Ala^{21},Arg^{36},Ala^{38},His^{39},Pro^{40},Trp^{42}] tissue factor pathway inhibitor (human)-(20-79)-peptide	

Ecallantide, also known as DX-88, was approved in 2009 in the United States for treatment of hereditary angioedema (HAE), a condition characterized by episodic attacks of localized edema in cutaneous and mucosal tissues. The pain and swelling of face, genitalia, extremities, and abdomen affects quality of life with swelling of the pharynx and larynx being life threatening. Patients with HAE can have one to three episodes per month with each episode lasting between 2 and 5 days. HAE is a rare autosomal disease affecting between 1:10,000 and 1:50,000 people in the United States [68]. There is no difference in prevalence with regard to sex or ethnic group, but women have more severe clinical symptoms than men. HAE results from deficiencies or disorders of C1-esterase inhibitor protein (C1-1NH). Mutation of the gene that encodes C1-1NH causes the lack or altered activity of the serine protease, C1-1NH. C1-1NH regulates the kallikrein–kinin (contact activation) and complement cascade systems. C1-1NH inhibits the complement system by binding C1 and prevents the formation of the C1 complex. Overactivation of the kinin–kallikrein system leads to the overproduction of plasma kallikrein. Left unchecked, plasma kallikrein produces high levels of bradykinin and stimulates release of C5a, further activating the complement cascade system. Activation of the complement system causes the release of cytokines, TNF-α and interleukins [68,69]. Bradykinin is a potent

vasodilator, and the increased vascular permeability leads to the accumulation of fluids that is seen in HAE patients. There are three manifestations of the disease. Type I results from low serum levels of C1-1NH and represents 85% of the cases. In Type II HAE, C1-1NH levels are normal to elevated, but dysfunctional, affecting 15% of patients. A third type of HAE, primarily affecting women, has been characterized and is caused by mutations in the factor XII gene [69,70]. Ecallantide (DX-88) was designed to inhibit the action of plasma kallikrein. Ecallantide is a potent and selective inhibitor of plasma kallikrein with a $K_i = 25$ pM. The discovery program that identified ecallantide used phage display technology and a library of designed variants of the first Kunitz domain of TFPI. Ecallantide, a 60-amino acid peptide, with 3-disulfide bonds, differs from TFPI by 7-amino acids. Ecallantide has been developed as a subcutaneous administered formulation [70,71]. In Phase I studies with healthy volunteers, ecallantide was found to have a high volume of distribution (26.4 L $\pm$ 7.81) with a mean elimination half-life of 2.0 $\pm$ 0.5 h. The bioavailability was found to be 90%. Ecallantide, in Phase III EDEMA3 and EDEMA4 trials, was found to be effective in relieving HAE symptoms and the frequency and duration of HAE attacks. The drug was effective in moderate and severe HAE patients and was found to have a 24-h duration of action in the EDEMA trials. The most serious adverse events reported for ecallantide are hypersensitivity and anaphylaxis, with incidences of 3.9% (10 patients) and 2.7% (5 patients), respectively. In all cases, the condition resolved with treatment and without further complications. Ecallantide is given as three 10 mg subcutaneous doses and is a first-in-class drug targeting plasma kallikrein to treat HAE [71,72]. In December 2009, the U.S. FDA granted approval for Kalbitor® (ecallantide) for the treatment of acute attacks of HAEin patients 16 years of age and older.

11. ERIBULIN MESYLATE (ANTICANCER) [73–79]

Class	Tubulin inhibitor
Country of origin	United States
Originator	Eisai
First introduction	United States
Introduced by	Eisai
Trade name	Halaven™
CAS registry no.	253128-41-5 (free base) 441045-17-6
Molecular weight	729.9 (free base)



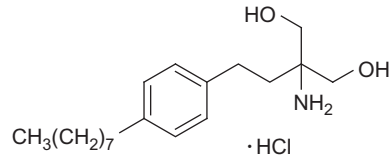
The U.S. FDA approved eribulin mesylate (also referred to as E7389) in November 2010 for the treatment of metastatic breast cancer (MBC) for patients who previously received at least two chemotherapeutic regimens for late-stage disease. Although the overall incidence of early stage breast cancer has been declining in recent years, one-third of the women in this group will develop MBC within 5 years of their initial diagnosis. Despite significant advances in the understanding of tumor biology, MBC is still incurable and accounted for over 40,000 deaths in the United States in 2009. A number of cytotoxic agents are currently available for the treatment of breast cancer, but their use in a metastatic setting is more limited. For example, taxane-based therapies are restricted by cumulative neurotoxicity and tumor progression on earlier taxane-based therapy. Therefore, development of novel cytotoxic agents is still desirable. Eribulin is a synthetic analog of the marine natural product halichondrin B, which is isolated from the sea sponge *Halichondria okadai*. Eribulin retains most of the structural elements that constitute the right hand side of halichondrin B; structure–activity relationship (SAR) studies suggested that the antitumor activity of halichondrin B resides in that part of the molecule [73]. Eribulin is a microtubule inhibitor that binds close to the *vinca*-binding site of tubulin. Unlike most tubulin inhibitors like taxanes, epothilones, and *vinca* alkaloids that inhibit microtubule dynamic instability by changing tubulin addition and loss parameters, eribulin's effects on dynamic instability are novel in that eribulin inhibits the growth phase of microtubules without affecting the shortening phase by binding to microtubule plus ends [74]. The net effect is blockage of cell cycle progression at the G2–M phase leading to apoptotic cell death after prolonged mitotic blockage. Eribulin has 19 stereocenters and protocols for its synthesis are outlined in the patent and open literature [75–77]. Among the key steps involved in the reported synthetic approaches to eribulin are catalytic asymmetric Ni–Cr-mediated coupling reactions and a Ni–Cr-mediated

macrocyclization. Eisai's process route for the commercial production of eribulin is purported to involve 62 steps. Preclinical *in vitro* studies demonstrated the cytotoxic ability of eribulin to inhibit breast, prostrate, colon, and melanoma cancer cell lines with IC_{50} values ranging from 0.09 to 9.5 nM. The cytotoxic activity of eribulin was maintained in taxol-resistant® cell lines including those with mutations in β-tubulin. Cytotoxicity was not observed up to a concentration of 1 μM in IMR-90 human fibroblasts as well as in *in vivo* studies (*e.g.*, body weight loss and water consumption). Eribulin demonstrated *in vivo* activity in various mouse xenograft models (MDA-MB-435, COLO 205, LOX, OVCAR-3) when given intravenously or intraperitoneally at doses ranging from 0.05 to 1 mg/kg. In addition to showing a wider therapeutic window (four- to fivefold) in these studies compared to paclitaxel (twofold), tumor regrowth was suppressed to a significant extent after treatment cessation with eribulin when compared to paclitaxel.

In a Phase I clinical trial, eribulin showed linear kinetics over a dose range of 0.25–4.0 mg/m^2 following IV administration to patients with solid tumors. The C_{max} (0.086–0.231 μg/mL) and AUC (0.171–0.563 μg h/mL) increased in a dose-proportional fashion with a mean elimination half-life of ~41 h. The mean clearance and volume of distribution were 2 L/h and 72 L/m^2, respectively. Eribulin is not extensively metabolized (metabolite concentrations $<0.6\%$ of parent) and is primarily eliminated in feces. Eribulin competitively inhibits CYP3A4-mediated testosterone and midazolam hydroxylation of human liver microsomal preparations with an apparent $K_i = 20$ μM. Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, and CYP2D6 in human liver microsomes up to a concentration of 5 μM. The human plasma protein binding of eribulin ranges from 49% to 65% at concentrations of 100–1000 ng/mL, respectively. The safety and efficacy of eribulin mesylate were established in an open-labeled, randomized, multicenter Phase III EMBRACE study, comprising 762 women with MBC who were previously treated with at least two different chemotherapy regimens for late-stage disease [78]. Of the 762 women, 508 were treated with eribulin mesylate and 254 were treated with an agent of their physician's choice. The EMBRACE study indicated that eribulin mesylate-treated patients showed improvement in the median overall survival of 13.12 compared to 10.65 months for patients who were treated with a single-agent therapy chosen by their physician. Most common serious adverse events ($\geq$25%) associated with eribulin treatment were neutropenia (although it did not translate into a high rate of febrile neutropenia), anemia, hair loss, weakness, peripheral neuropathy, nausea, and constipation. In addition, ECG monitoring is recommended in patients with CHF and bradyarrhythmias. The recommended dose of eribulin mesylate is 1.4 mg/m^2 administered intravenously over 2–5 min on days 1 and 8 of a 21-day cycle [79].

12. FINGOLIMOD HYDROCHLORIDE (MULTIPLE SCLEROSIS) [80–87]

Class	Sphingosine-1-phosphate (S1P) receptor agonist
Country of origin	United States
Originator	Yoshitomi Pharmaceutical Industries (now Mitsubishi Tanabe Pharma)
First introduction	Russia
Introduced by	Novartis
Trade name	Gilenya®
CAS registry no.	162359-56-0 162359-55-9 (free base)
Molecular weight	307.5 (free base) 343.9 (hydrochloride salt)



Approved by the U.S. FDA in September 2010, fingolimod (also referred to as FTY720) is the first approved oral therapy for the relapsing-remitting form of multiple sclerosis (RRMS). MS is a chronic autoimmune demyelinating disease of the CNS that affects over 2.5 million individuals worldwide. The relapsing–remitting form of MS, which occurs in approximately 85% of newly diagnosed patients, is characterized by recurrent acute exacerbations (relapses) of neurological dysfunction, followed by recovery. Six drugs are currently approved by the FDA for the treatment of patients with MS: an interferon beta-1b (IFNβ-1b) product, two IFNβ-1a formulations, glatiramer acetate (GA), mitoxantrone (an antineoplastic anthracenedione), and natalizumab, a recombinant monoclonal antibody. However, these drugs are not orally administered and have other limitations. For example, IFNβ-1a is administered subcutaneously and causes side effects that include influenza-like symptoms. Natalizumab has been associated with hypersensitivity reactions and progressive multifocal leukoencephalopathy (PML). Because of these limitations, there has been a significant effort in the industry and academia to identify novel treatments for the treatment of MS that are effective and orally bioavailable. Fingolimod was first described as an immunosuppressant based on SAR studies around the fungal metabolite myriocin or ISP-1 isolated from *Isaria sinclairii* [80]. Because of fingolimod's structural resemblance to sphingosine, a metabolite of sphingolipids that constitutes the cell membrane of all eukaryotic cells, it was hypothesized that

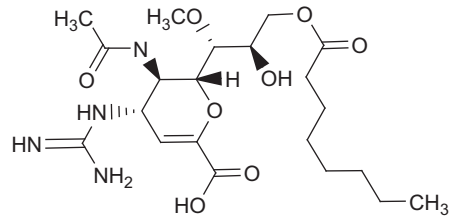
fingolimod may be affecting sphingolipid metabolism in cells. A series of elegant *in vitro* and *in vivo* studies [81,82] confirmed that fingolimod is converted to (*S*)-fingolimod phosphate primarily by sphingosine kinase-2 and that (*S*)-fingolimod phosphate mediates multiple biological processes by binding to novel GPCR's referred to as sphingosine-1-phosphate (S1P) receptors. S1P receptors are divided into five subtypes, $S1P_{1-5,}$ which have varying tissue and cellular distribution. $S1P_{1-3}$ receptors are ubiquitously expressed in the immune, cardiovascular, and central nervous systems, $S1P_4$ is restricted to the hematopoietic system, and $S1P_5$ is mostly localized in the white matter of CNS. $S1P_{1-3}$ receptors play important roles in endothelial barrier function, maintaining vascular tone, regulating heart rate and allowing for lymphocyte egress from secondary lymphoid organs. The functional role of $S1P_4$ is unknown, while the $S1P_5$ receptor is thought to be involved in natural killer cell trafficking and oligodendrocyte function. *In vitro* binding and functional studies revealed that (*S*)-fingolimod phosphate is a full agonist at $S1P_1$, $S1P_4$, and $S1P_5$ receptors ($EC_{50} = 0.3–0.6$ nM); a partial agonist at $S1P_3$ receptor ($EC_{50} \sim 3$ nM); and inactive at the $S1P_2$ receptor. Fingolimod itself is significantly less potent at the $S1P_1$ and $S1P_5$ receptors ($IC_{50} \sim 300$ and 2600 nM, respectively) and inactive at $S1P_{2-4}$ receptors ($IC_{50} > 5000$ nM). Binding of (*S*)-fingolimod phosphate to lymphocytic $S1P_1$ leads to internalization of the receptor and sequestration of naïve T cells and self-reactive central memory T cells in lymph nodes, thereby preventing their recirculation and entry into the CNS. Since naïve T cells and self-reactive central memory T cells are believed to be responsible for the inflammation and neural damage found in MS, their retention in lymph nodes is believed to be responsible for the beneficial effects seen with fingolimod in MS patients. Effector memory T cells are not affected during fingolimod treatment, and lymphocytes are not destroyed; therefore, immune functions such as activation and proliferation and effector functions of T and B cells remain unaffected during treatment. The synthesis of fingolimod has been described in a number of publications and patents [83a–c]. One approach to the synthesis of fingolimod employs a Friedel–Crafts acylation followed by reduction to install the C8-side chain and alkylation of an amino malonate unit followed by reduction to install the amino diol head piece [83a,b]. An alternate approach to the synthesis of the amino diol headpiece employs a Petasis reaction of an appropriately substituted arylvinylboronic acid, benzyl amine, and dihydroxyacetone in a key step [83c].

Fingolimod was shown to be efficacious in preclinical models of MS (rat experimental autoimmune encephalomyelitis) at doses ranging from 0.3 (prophylactic administration) to 12–28 mg/kg (therapeutic administration). Phase I multiple dose pharmacokinetic studies with fingolimod indicated that at a dose of 1.25 mg/day, the mean C_{max} observed was 5.0 ± 1.0 ng/mL and at a dose of 5 mg/day, the mean C_{max} was 18.2 ± 4.1 ng/mL. The median T_{max} was ~12 h for both doses. Fingolimod

has a half-life of ~9 days partly because of a large volume of distribution (>1000 L); pharmacokinetic steady state is achieved after ~2 months. Fingolimod is highly protein bound (>99.8%) and is predominantly metabolized by CYP4F2. A dose-dependent decrease in peripheral lymphocyte count is observed at both the 1.25 mg (77%) and 0.5 mg (73%) doses of fingolimod. The cell counts remained stable for the entire treatment period and returned to normal range within 6 weeks after stopping fingolimod treatment. After an initial 6-month placebo-controlled Phase II study that showed benefit in RRMS patients, fingolimod was evaluated in two Phase III studies. In the 2- year double-blind FREEDOMS study [84], involving 1272 patients with RRMS, fingolimod was compared with placebo, and in the 1 year, double-blind TRANSFORMS study [85] involving 1292 patients with RRMS, fingolimod was compared with IFN-β1a. Both studies used 0.5 mg and 1.25 mg once-daily doses of fingolimod. In the FREEDOMS trial, patients on fingolimod had an annualized relapse rate significantly lower than in patients who received placebo [0.18 (0.5 mg); 0.16 (1.25 mg) *vs.* 0.40 (placebo); $p < 0.001$]. Disability progression was significantly delayed, compared to placebo, with both doses of fingolimod. In the TRANSFORMS study, patients on fingolimod had an annualized relapse rate significantly lower than in patients who received IFN-β1a [0.16 (0.5 mg); 0.20 (1.25 mg) *vs.* 0.33 (IFN-β1a); $p < 0.001$]. From a safety perspective, bradycardia and atrioventricular block were observed on first dose of fingolimod treatment. Macular edema was seen in four patients in the 1.25 mg group (1%) and two patients in the 0.5 mg group (0.5%). Other serious adverse events include basal cell carcinoma and a 2–3% reduction in the mean FEV_1. The most common adverse events occurring in 10–20% of fingolimod-treated patients were fatigue, influenza, lower respiratory tract or lung infection, back pain, diarrhea, cough, and elevations in liver-enzyme levels. Assessing the overall benefit–risk profile, the FDA approved fingolimod for RRMS at 0.5 mg once daily [86,87].

13. LANINAMIVIR OCTANOATE (ANTIVIRAL) [88–97]

Class	Neuraminidase inhibitor
Country of origin	Japan
Originator	Sankyo Co., Ltd.
First introduction	Japan
Introduced by	Daiichi-Sankyo Co., Ltd.
Trade name	Inavir®
CAS registry no.	203120-17-6
Molecular weight	346.34



Laninamivir octanoate (CS-8958) [88,89], an ester prodrug form of the neuraminidase (NA) inhibitor laninamivir (R-125489), was approved in Japan in 2010 for treatment of influenza virus infections. Laninamivir octanoate is given by intranasal administration at a 20 mg or 40 mg dose. It has a long half-life in humans such that efficacy can be achieved after only a single dose. It is the second NA inhibitor approved in 2010, the first being peramivir (*vide infra*). Influenza is a serious and contagious respiratory illness that is caused by influenza A and B viruses. Influenza is a global health concern, with both seasonal epidemics and unpredictable pandemics resulting in significant morbidity and mortality, particularly for patients at high risk for influenza-associated complications. In addition to vaccines for immunoprophylaxis, antiviral drugs play an essential role in the treatment of influenza virus infections [90]. Two viral proteins have been targeted for therapeutic intervention: the M2 ion channel and NA. The M2 ion channel is blocked by drugs such as amantadine and rimantidine, which inhibit viral replication at the stage of viral entry and viral release. These agents have seen declining use due to widespread resistance and lack of activity against influenza B. Zanamivir (intranasal) and oseltamivir (oral) are the two approved drugs in the NA inhibitor class. These agents act by inhibiting the release of newly formed virus particles from infected cells by blocking the cleavage of the terminal sialic acid residues from glycoconjugates. The frequency of resistance to NA inhibitors is much lower than for M2 inhibitors; however, resistance has been documented, particularly to oseltamivir. For example, in a study of H1N1 strain of influenza A viruses from the 2009 pandemic, 0.7% of viruses were resistant to oseltamivir but remained sensitive to zanamivir and laninamivir [91]. More than 99% were resistant to amantadine. Laninamivir differs from zanamivir by the replacement of the 1′-hydroxyl group on the side chain at the 2-position of the 3,4-dihydro-2*H*-pyran core with a methoxy group. Laninamivir octanoate is prepared starting from a neuraminic acid precursor [88,92]. The route from 2,3-didehydroneuramic acid entails a multistep sequence to protect the acid and hydroxyl groups at the 4-, 2′-, and 3′-positions. Methylation of the remaining 1′-hydroxyl by treatment with dimethylsulfate and NaH is followed by conversion of the 4-hydroxyl to an amine.

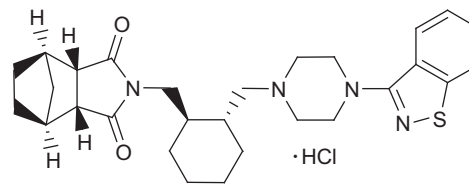
Cleavage of the 2′,3′-dihydroxy protecting group, conversion of the 4-NH_2 to the guanidine, and acylation of the 3′-OH group afford laninamivir octanoate. This three-step sequence can be reordered such that the guanidine is introduced first, followed by deprotection of the 2′,3′-diOH groups and acylation. An alternative sequence involves a Boc-protected guanidine intermediate, which is converted in a four-step sequence (deprotection of the acid and 2′,3′-hydroxyl groups, reprotection of the acid as its diphenylmethyl ether, acylation of the 3′-OH and deprotection of the guanidine group) to laninamivir octanoate [92]. Laninamivir can also be synthesized from the α-methyl glycoside of *N*-acetylneuramic acid methyl ester by an analogous route. Laninamivir is a less potent NA inhibitor than zanamivir or oseltamivir against many influenza A strains, but it has superior potency for inhibition of viral replication (two- to fivefold depending on the virus strain) [92,93]. It is a more potent inhibitor of NA from the highly pathogenic avian influenza A H5N1 strains. The prodrug laninamivir octanoate is inactive. Laninamivir octanoate shows efficacy in a variety of preclinical influenza models, including a model of prophylaxis where a single dose given intranasally 7 days before infection was effective in prolonging survival time in infected mice [93]. Zanamivir was not efficacious under these conditions. It is believed that long retention of the compound in the lungs may contribute to the long-lasting activity. Laninamivir octanoate was also active in *in vivo* infection models with the avian H5N1 influenza A virus [94].

In Phase 1 studies, healthy male volunteers received single intranasal doses from 5 to 120 or 20 or 40 mg doses twice daily for 3 days [95]. The T_{max} for laninamivir octanoate was 0.5–1 h, while the T_{max} for laninamivir parent drug was 4 h. The half-life for laninamivir octanoate was 1.8 and 70–80 h for the parent drug. AUC and C_{max} increased proportionally with dose. The cumulative excretion in urine over 144 h was 2.3–3.6% for the prodrug and 10.7–14.6% for laninamivir. Plasma protein binding is 67% for laninamivir octanoate and $<0.1\%$ for parent drug. There were no adverse events related to test drug in these studies. Laninamivir octanoate was evaluated in a double-blind, randomized, non-inferiority clinical trial in $\sim$1000 patients in comparison with oseltamivir [96]. Most patients were infected with influenza A virus, of which $\sim$65% were H1N1 and $\sim$35% were H3N2 strains. The H1N1 strains were oseltamivir resistant (H274Y mutation, mean $IC_{50} = 690$ nmol/L) and laninamivir-sensitive (mean $IC_{50} = 1.7$ nmol/L). The H3N2 strain was sensitive to both drugs. Laninamivir octanoate inhaled once at 20 or 40 mg was compared with 75 mg of oseltamivir given orally twice a day for 5 days. In H1N1 infected patients, there was little difference in the median times to illness alleviation for the 40-mg laninamivir octanoate group (73 h) compared with the oseltamivir group

(74 h). However, the proportion of patients shedding virus at day 3 in the 40-mg laninamivir octanoate group was significantly lower than in the oseltamivir group, which is consistent with the greater potency. Time to illness alleviation and reduction in viral shedding were similar for the two drugs in H3N2-infected patients. The 20-mg laninamivir octanoate dose group had a longer median time to illness alleviation (86 h). Both drugs were well tolerated with the most common adverse events being gastrointestinal events. In a similar trial in pediatric patients (median 9 years of age) infected with oseltamivir-resistant H1N1 influenza A, single inhalation doses of 20 or 40 mg laninamivir alleviated influenza illness more rapidly than oseltamivir given twice daily for 5 days at 2 mg/kg body weight [97]. Overall, laninamivir has proven to be effective, long-lasting, and well tolerated for the treatment of influenza infection.

14. LURASIDONE (ANTIPSYCHOTIC) [98–104]

Class	D_2, 5-HT_{2A}, and 5-HT_7 receptor antagonist; 5-HT_{1A} partial agonist
Country of origin	Japan
Originator	Dainippon Sumitomo Pharma
First introduction	United States
Introduced by	Dainippon Sumitomo Pharma
Trade name	Latuda®
CAS registry no.	367514-87-2 (free base) 367514-88-3 (HCl salt)
Molecular weight	492.3 (free base)



The atypical antipsychotic lurasidone (also known as SM-13496) was approved in the United States in 2010 as an oral agent for the treatment of patients with schizophrenia [98,99]. Schizophrenia is a debilitating mental disorder that affects 1% of the population worldwide. The disease is characterized by three symptom domains: positive (psychotic)

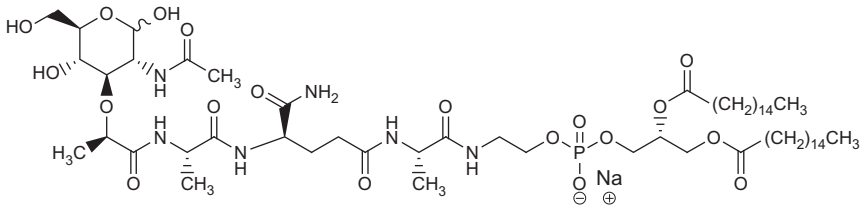
symptoms, such as delusions and hallucinations; negative symptoms, such as emotional flatness and a lack of motivation for daily activities; and cognitive symptoms, including difficulties with memory and concentration, and an inability to organize thoughts. Available drug treatments for schizophrenia are primarily aimed at decreasing dopaminergic transmission. First-generation antipsychotic agents such as haloperidol are dopamine D_2 receptor antagonists that are effective at treating positive symptoms but have little impact on negative and cognitive symptoms and are associated with significant side effects, particularly movement disorders (extrapyramidal side effects, EPS). Second-generation, or atypical, antipsychotics act at both D_2 and 5-HT_{2A} receptors and treat positive symptoms as well as some negative symptoms. While the atypical agents have less EPS, other issues such as weight gain, prolactin and glucose elevation, and sedation are observed with these agents, primarily as a result of off-target activities. The overall efficacy/side-effect profile of these agents is related to their complex, multitarget, pharmacological profile and leads to their differentiation in the clinical setting. Lurasidone has potent affinity for D_2 ($K_i = 1.7$ nM) and 5-HT_{2A} ($K_i = 2.0$ nM) receptors and acts as an antagonist at both receptors [100]. It is also a partial agonist at the 5-HT_{1A} receptor and, unlike other atypical agents, is a potent antagonist at the 5-HT_7 receptor; both of these activities are thought to confer beneficial cognitive properties. Lurasidone is further differentiated by its lack of affinity for muscarinic and histamine H1 receptors and its weak affinity for the 5-HT_{2C} receptor. Antagonism at H_1 and 5-HT_{2C} receptors has been implicated in weight gain associated with atypical agents, while muscarinic receptor antagonism is associated with cognitive deficits. Preclinical behavioral studies have shown lurasidone to be efficacious in models of psychosis, depression, and anxiety [100]. In cognition models, lurasidone has shown efficacy in a MK-801-induced impairment models of learning and memory, while other atypical antipsychotic agents were inactive [101,102]. At doses up to 1000 mg/kg, lurasidone did not induce catalepsy in rats or mice. It showed weak activity in additional rodent models for motoric side effects, indicating a lower potential for EPS [100]. The compound is synthesized by treatment of 1-(1,2-benzoisothiazol-3-yl)piperazine with the di-mesylate of (*R*,*R*)-cyclohexane-1,2-diyldimethanol under basic conditions to give an intermediate spiropiperazinium salt that undergoes reaction with bicyclo[2.2.1]heptane-2,3-dicarboximide to provide lurasidone [103].

In healthy volunteers and patients [98,103,104], lurasidone showed dose-proportional pharmacokinetics over a range of 20–160 mg, with 9–19% of drug being absorbed. Lurasidone reached peak levels 1–3 h after oral administration and had an elimination half-life of 18 h after a single dose, extending to 36 h at steady state. The clearance rate was

found to be 3.9 L/min. The compound is highly protein bound (~99%) in serum. Lurasidone is not a significant inhibitor of P450 isozymes. The metabolism of lurasidone is mainly mediated by CYP3A4, with elimination occurring primarily *via* the liver (~80%) and to a lesser extent *via* the kidney (~10%). Use of lurasidone in combination with CYP3A4 inhibitors (*e.g.*, ketoconazole) or inducers (*e.g.*, rifampin) is contraindicated as a result of observations in drug–drug interaction trials. The major metabolic pathways for lurasidone are N-dealkylation, oxidation of the [2.2.1]-bicycloheptane ring, and oxidation of the benzoisothiazole sulfur atom. In a food effect study, exposures of lurasidone were three times higher for C_{max} and two times higher for AUC in subjects given food compared to those who were fasted. Therefore, it is recommended that lurasidone be taken with a meal. Positive emission tomography (PET) studies with [^{11}C]-raclopride following single oral doses lurasidone showed ~40% D_2 receptor occupancy at a 10 mg dose, increasing to 75–85% at 60 mg and 70–80% at 80 mg. The efficacy of lurasidone for the treatment of schizophrenia was established in four 6-week, placebo-controlled studies in adult patients (mean age of 38.8 years, range 18–72) who met diagnostic criteria for schizophrenia. In a 6-week, placebo-controlled trial with 145 subjects, doses of 40 or 120 mg per day of lurasidone were superior to placebo on the Brief Psychiatric Rating Scale-derived (BPRSd) total score and the Clinical Global Impression severity scale (CGI-S). In a similar trial with 180 subjects, treatment with an 80-mg/day dose of lurasidone was superior to placebo using the same rating scales. In a 6-week, placebo- and active-controlled trial with 473 subjects with 40 or 120 mg/day of lurasidone, both lurasidone doses and the active control olanzapine were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score and the CGI-S. In a 6-week, placebo-controlled trial ($N = 489$) with 40, 80, or 120 mg/day of lurasidone, only the 80 mg/day dose was superior to placebo on the PANSS total score and the CGI-S. Based on these results, the recommended starting dose for lurasidone is 40 mg/day and the maximum recommended dose is 80 mg/day. The 120 mg/day dose did not provide additional benefit and was associated with an increase in some adverse events. Commonly observed adverse events (incidence $\geq 5\%$ and at least twice the rate for placebo) included somnolence, akathisia, nausea, parkinsonism, and agitation, all of which appeared dose-related. The overall discontinuation rate due to adverse events was 8% for lurasidone versus 4% for placebo. Lurasidone showed a neutral effect on weight and was not associated with significant QTc prolongation. Like all atypical antipsychotics, lurasidone carries a black box warning for increased mortality in elderly patients with dementia-related psychosis. Lurasidone is supplied as an HCl salt in 40 and 80 mg tablets for oral administration.

15. MIFAMURTIDE (ANTICANCER) [105–112]

Class	Activator of monocytes and macrophages
Country of origin	Switzerland
Originator	Novartis
First introduction	Austria
Introduced by	Takeda
Trade name	Junovan®
CAS registry no.	838853-48-8 (sodium salt) 83461-56-7 (anhydrous, free acid)
Molecular weight	1277.5 (sodium salt)



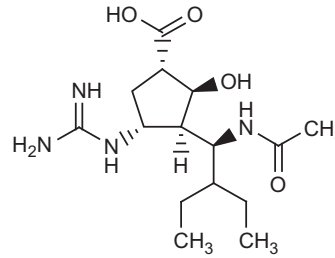
Mifamurtide (also referred to as MTP-PE) was approved by the EC in 2009 for the treatment of high-grade nonmetastatic osteosarcoma patients between the ages 2 and 30 in combination with postoperative multiagent chemotherapy. Osteosarcoma, which is a primary malignant bone tumor, is diagnosed in over 1000 new patients each year in North America and Europe. The standard of care for osteosarcoma is surgical removal of the tumor followed by chemotherapy. Doxorubicin, cisplatin, high-dose methotrexate with leucovorin rescue, and ifosfamide are the approved chemotherapeutic agents for osteosarcoma. These agents increase the event-free survival (EFS) of patients at 3–5 years by 60–70% in nonmetastatic conditions. Despite these advances, there is a need to improve the EFS of patients with nonmetastatic osteosarcoma. Mifamurtide is the first new drug approved for the treatment of osteosarcoma in over 20 years. The active component of mifamurtide is muramyl dipeptide (MDP), a component of bacterial cell walls, which is linked *via* an alanine moiety to phosphatidyl ethanolamine (PE) to form the tripeptide MTP-PE. Mifamurtide is combined with a liposome formulation consisting of synthetic phospholipids dioleoyl phosphatidyl serine and 1-palmitoyl-2-oleoyl phosphatidyl choline in a ratio of 3:7. This liposome formulation (L-MTP-PE) allows for the specific *in vivo* targeting of monocytes and macrophages in the liver, spleen,

and lungs by mifamurtide [105]. *In vitro* and *in vivo* studies have shown that activation of monocytes and macrophages by mifamurtide leads to the production of proinflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, NO, prostaglandin E2 and PGD_2, and adhesion molecules such as LFA-1 and ICAM-1 [106]. MTP-PE is a ligand for nucleotide-binding oligomerization domain (Nod)-2 receptor, and it has been postulated that the activation of monocytes and macrophages is mediated by Nod-2 following phagocytosis of L-MTP-PE and liberation of MDP [105,107]. *In vitro*, human monocytes treated with MTP-PE had tumoricidal activity on allogeneic and autologous tumor cells but were nontoxic toward normal cells. The liberation of proinflammatory cytokines following activation of monocytes and macrophages and the tumoricidal activity of MTP-PE are not clearly understood. Mifamurtide is synthesized by DCC coupling of (a) *N*-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine with 2-aminoethyl-2,3-dipalmitoylglyceryl-phosphoric acid [108] or (b) *N*-acetylmuramyl-L-alanyl-D-isoglutamine and alanyl-2-aminoethyl-2,3-dipalmitoylglyceryl-phosphoric acid [109]. In a Phase I pharmacokinetic study in 21 healthy subjects, mifamurtide dosed at 4 mg intravenously over 30 min showed a C_{max} of ~16 nM, an AUC of ~17 nM h, and a mean half-life of ~2 h. The safety and efficacy of mifamurtide were established in a randomized, Phase III study comprising 662 patients with nonmetastatic resectable osteosarcoma [110]. All patients received similar doses of cisplatin, doxorubicin, and methotrexate. Patients were then randomly assigned to receive or not to receive ifosfamide and/or mifamurtide. There was a clear trend in the mifamurtide group toward better EFS ($p = 0.039$) and overall survival ($p = 0.030$) compared to the ifosfamide group. These results demonstrated that the addition of mifamurtide to chemotherapy improved the 6-year overall survival from 70% to 78% ($p = 0.03$). Most common serious adverse events associated with mifamurtide treatment were fever, chills, and tachycardia. The recommended dose of mifamurtide is 2 mg/m^2 administered as adjuvant therapy intravenously over 1-h twice weekly for an initial 12 weeks followed by once weekly for an additional 24 weeks for a total of 48 infusions in 36 weeks [111,112].

16. PERAMIVIR (ANTIVIRAL) [113–120]

Class	Neuraminidase inhibitor
Country of origin	United States
Originator	BioCryst Pharmaceuticals Inc.
First introduction	Japan

Introduced by	BioCryst Pharmaceuticals Inc.
Trade name	Rapiacta, PeramiFlu
CAS registry no.	330600-85-6
Molecular weight	328.4



Peramivir is a neuraminidase (NA) inhibitor that was approved in Japan in 2010 for treatment of patients with influenza. It is the only NA inhibitor available for IV use and is the first of two NA inhibitors approved in 2010, the second being the inhaled drug laninamivir octanoate (*vide supra*). Peramivir is given as a 300-mg single dose for adult and pediatric uncomplicated seasonal influenza infection, and as single- and multiple 600 mg dose for patients at high risk for complications associated with influenza virus infection. From October 2009 to June 2010, peramivir was given Emergency Use Authorization (EUA) in the United States for treatment of certain hospitalized patients with suspected or confirmed cases of H1N1 influenza virus infection [113]; this is the first time an EUA has been granted for an unapproved drug [114]. Influenza is an infectious respiratory tract disease that annually affects approximately 10% of the world's population [115]. The virus that causes the disease is divided into three main types: A, B, and C. Influenza A viruses are responsible for seasonal flu, including the pandemics in 1918, 1957, 1968, and, most recently, in 2009 with the pandemic caused by the H1N1 strain of influenza A. While influenza is usually a self-limiting disease, there is a risk of complications and death, often in high-risk populations such as the very young or the elderly, but also in healthy individuals infected with highly pathogenic strains such as H5N1 (avian influenza A). In addition, influenza is highly communicable and causes a significant economic burden, for example, due to lost work time. Vaccines are highly effective in prophylaxis and controlling a flu epidemic; however, limitations in vaccine efficacy and delay in strain-specific production make antiviral drugs important prophylactic and treatment options [90,116]. Two classes of antiviral drugs have been approved for treatment of influenza: M2-ion channel inhibitors (amantadine, rimantidine) and NA inhibitors (zanamivir, oseltamivir). A major concern with antiviral agents is the development of resistance. Indeed, resistance to M2 inhibitors is widespread,

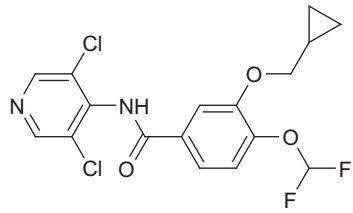
although some strains remain susceptible. Resistance to NA inhibitors has also emerged, although thus far with lower frequency. Zanamivir is approved for intranasal use, while oseltamivir is an oral agent. Peramivir is the only NA inhibitor approved for IV use, which gives it a unique place in influenza treatment for seriously ill patients. Peramivir was discovered using structure-based drug design and is synthesized in six steps from Boc-protected methyl (*1S,4R*)-4-amino-cyclopent-2-enecarboxylate, which is prepared from 2-azabicyclo[2.2.1]hept-5-en-3-one [117–119]. Cycloaddition of the cyclopentene olefin with a nitrile oxide provided an intermediate fused cyclopentane-dihydroisoxazole. Hydrogenolysis and acetylation set up a fully functionalized cyclopentane with all four stereocenters established. Deprotection of the amine and acid groups was followed by installation of the guanidine moiety to provide peramivir. Like zanamivir and oseltamivir, peramivir is a potent inhibitor of influenza virus A and B NA [strain A(H1N1) $IC_{50} = 0.34$ nM; strain A(H3N2) $IC_{50} = 0.60$ nM; strain B $IC_{50} = 1.36$ nM]. However, peramivir is less potent against oseltamivir-resistant viruses that have the H275Y NA mutation. These viruses remain sensitive to zanamivir. Peramivir is active against influenza A and B viruses and has a low enzymatic off-rate, suggesting that it could inhibit NA activity for a prolonged period and allow lower frequency of dosing. Peramivir has proven efficacious in preclinical animal models of influenza infection [90].

The recommended dose of peramivir in adults is 600 mg IV over 30 min once daily for 5–10 days. Based on several Phase I trials in adults [114], there is a linear relationship between the IV dose of peramivir and the C_{max}. The half-life was 7.7–20.8 h. The AUC following a single 600 mg IV dose of peramivir was 80 μg·h/mL. Peramivir is excreted unchanged by the kidneys after IV dosing, with renal clearance of unchanged parent drug accounting for ~90% of total clearance. Peramivir clearance was 7.58 L/h/70 kg in adults with influenza and was 6.19 L/h/70 kg in healthy adults. There was no accumulation following multiple dose administration. The most common adverse events related to peramivir include diarrhea, nausea, vomiting, and neutropenia [114]. Similar rates of gastrointestinal events were observed in patients treated with peramivir and placebo. In a Phase II clinical study, 200 or 400 mg of peramivir proved beneficial when given IV to patients hospitalized within 72 h of the onset of symptoms [90]. In a Phase III clinical trial [115], previously healthy adult subjects were recruited within 48 h of the onset of influenza symptoms and randomized to single IV infusion of 300 mg peramivir, 600 mg peramivir, or matching placebo. Peramivir significantly reduced the time to alleviation of symptoms at both the 300 and 600 mg doses compared with placebo. No serious adverse events were reported. In another Phase III trial [90], peramivir when given IV over multiple days at 300 or 600 mg per day alleviated symptoms in all patients. In a limited study under an emergency IND, severely ill patients in the United States with H1N1 viral pneumonia and with progressing disease despite

oseltamivir treatment were treated with IV peramivir for 1–14 days [120]. The drug was associated with recovery in most patients. Overall, peramivir has shown consistent efficacy in patients and has been safe and well tolerated. Peramivir was approved in Japan in January 2010 and is marketed under the trade name Rapiacta.

17. ROFLUMILAST (CHRONIC OBSTRUCTIVE PULMONARY DISORDER) [121–126]

Class	PDE4 inhibitor
Country of origin	Germany
Originator	BYK Gulden Lomberg Chemische Fabrik GmbH
First introduction	Germany
Introduced by	Nycomed (Altana)
Trade name	Daxas®
CAS registry no.	162401-32-3
Molecular weight	403.2



Roflumilast is a selective, orally active PDE4 inhibitor that was approved in Germany in July 2010 as an add-on to bronchodilator treatment for maintenance therapy of severe chronic obstructive pulmonary disorder (COPD) associated with chronic bronchitis in adult patients with a history of frequent exacerbations [121,122]. COPD is a chronic inflammatory disease that is characterized by an increase in neutrophils, macrophages, and $CD8^+$ T-lymphocytes in airways, lungs, and pulmonary vasculature. It is the sixth most common cause of death worldwide and is a major cause of morbidity. Disease manifestations include lung damage, progressive airway obstruction, chronic cough, and mucus hypersecretion. Acute exacerbations are accompanied by deterioration of lung function and worsening disability. PDEs are enzymes responsible for hydrolysis of cyclic nucleotide phosphates. PDE4 is expressed in several tissue types involved in diseases of the airway and is known to play a role in inflammation [123]. Inhibition of PDE4 blocks the hydrolysis of cAMP, leading to elevated levels of cAMP and

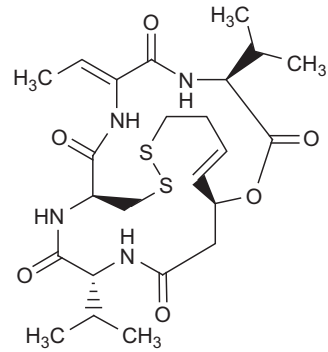
regulation of inflammatory cells. There are four known subtypes of the PDE4 family, PDEs A–D. Since PDE4D inhibition has been associated with nausea and vomiting, a challenge in the development of PDE4 inhibitors as therapeutic agents has been subtype selectivity. A classic example is rolipram, which showed promising antidepressant efficacy in early clinical trials, but development was discontinued due to drug-induced nausea. Roflumilast and its primary metabolite roflumilast *N*-oxide are potent and competitive inhibitors of PDE4 and are equipotent against PDE4A, B, and D but inactive against PDE4C and the other ten members of the PDE family (PDEs 1–3, 5–11). Despite its inhibition of PDE4D ($IC_{50} = 0.80$ nM, *N*-oxide $IC_{50} = 2.0$ nM), roflumilast shows the lowest incidence of nausea (3–5%) among the PDE4 inhibitors investigated in clinical trials. Anti-inflammatory effects of roflumilast have been demonstrated in preclinical cellular and animal models [122,124,125]. Roflumilast is synthesized in four steps from 3-(cyclopropylmethoxy)-4-hydroxybenzaldehyde [126]. The difluoromethyl ether is introduced by alkylation of the free phenolic group with chlorodifluoromethane and base. The aldehyde moiety is oxidized to the benzoic acid, which is then converted to an acid chloride and coupled with 3,5-dichloro-4-aminopyridine.

Roflumilast is rapidly absorbed and metabolized to its active metabolite, roflumilast *N*-oxide [121,122]. Metabolism is mediated by CYP3A4 and CYP1A2. Plasma protein binding is 98.9% for parent drug and 97% for the *N*-oxide. After a single 500 μg dose, the C_{max} for roflumilast was 5.3 μg/mL ($T_{max} = 1.3$ h) and for the *N*-oxide, 9.4 μg/mL ($T_{max} = 11$ h). AUCs were 35 and 350 μg·h/mL for the parent and *N*-oxide, respectively. Steady state concentrations were reached after 7 days of daily 500 μg doses of roflumilast, with the *N*-oxide C_{max} being twofold higher than with acute dosing. The absolute oral bioavailability was 80%, and terminal plasma half-lives were 18 h for the parent and 21 h for the *N*-oxide. There was no food effect on pharmacokinetics. Roflumilast and its metabolites are primarily excreted in the urine (70%). Roflumilast and its *N*-oxide metabolite are not inhibitors of CYP enzymes. Roflumilast is a weak inducer of CYP2B6, but not of other CYP isozymes. Roflumilast has been evaluated in several clinical trials involving over 9000 patients with COPD, including 6-month and 12-month Phase III trials [121]. Patients were allowed to continue with most other respiratory medications, including short-acting β2 agonists. Primary outcome measures were changes in FEV_1 and numbers of exacerbations. In the 6-month trials with patients with moderately severe disease, roflumilast-treated patients (250 or 500 μg daily oral dose) showed greater improvements in FEV_1 and quality of life than placebo-treated patients, but these changes did not reach clinical significance. Exacerbations were decreased with roflumilast treatment, but more patients discontinued treatment in the roflumilast arms than in the placebo group. In 12-month trials in patients with more

severe COPD, daily treatment with 500 μg roflumilast statistically increased FEV_1 but did not change the rate of exacerbations overall. However, a subset of patients with more severe airway obstruction did have a significant reduction in exacerbation frequency. In 12-month trials in patients with chronic bronchitis, a 500-μg daily oral dose roflumilast also gave a significant improvement in FEV_1 and a reduction in exacerbation rate. Roflumilast was well tolerated, with slightly more discontinuations than placebo. Diarrhea, nausea, and headache were the most common reasons for discontinuation. Weight loss was also observed, particularly in patients with GI effects and severe COPD. The incidence of insomnia, anxiety, and depression was two to three times higher in patients who received 500 μg of roflumilast than those receiving 250 μg or placebo. Another potential adverse event was cancer, in that of the cancers observed during the trial, 60% were in the roflumilast-treated group compared to 40% in placebo. The significance of this finding is still unclear. In addition to the German approval in July 2010, the U.S. FDA approved roflumilast in March 2011. Roflumilast is an oral drug taken daily to decrease the frequency of flare-ups (exacerbations) or worsening of symptoms from severe COPD.

18. ROMIDEPSIN (ANTICANCER) [127–133]

Class	Histone deacetylase inhibitor
Country of origin	Japan
Originator	Fujisawa (Astellas Pharma)
First introduction	United States
Introduced by	Celgene
Trade name	Istodax®
CAS registry no.	128517-07-7
Molecular weight	540.7



The U.S. FDA approved romidepsin (also referred to as FK228) in 2009 for the treatment of cutaneous T-cell lymphoma (CTCL) for patients who received at least one systemic therapy. The annual incidence of CTCL in the United States is 0.96 per 100,000 persons, and the overall prevalence is 16,000–20,000 cases. Early-stage CTCL is primarily managed by dermatologists using skin-directed therapies like phototherapy, topical agents, and local radiation. Besides romidepsin, there are three approved systemic therapies for advanced disease. Vorinostat and bexarotene are indicated for cutaneous manifestations of CTCL and not for cases with blood, lymph node, or visceral involvement. Denileukin diftitox is approved for CTCL patients expressing the CD25 epitope (30–50% of CTCL cases). However, the relapse rate for patients treated with most therapeutics for CTCL, regardless of the disease stage, is high, and newer therapeutic options for patients with relapsed or refractory CTCL are still needed. Romidepsin is a natural product that was first isolated from the fermentation broth of *C. violaceum*. Romidepsin is the second histone deacetylase (HDAC) inhibitor approved for CTCL, the other being vorinostat, which was approved by the FDA in 2006. Unlike vorinostat which is a pan-HDAC inhibitor, romidepsin shows modest selectivity for class I HDACs in *in vitro* assays. It has been shown that after romidepsin enters the cytoplasm, the disulfide bond is cleaved by glutathione to release the sulfhydryl group which chelates with the active site zinc of class I HDACs and inhibits the enzymatic activity at nanomolar concentrations [127]. Although romidepsin inhibits class I HDACs, it is 17–23 times less potent as the parent than the corresponding reduced form at each isozyme. For example, the IC_{50} of romidepsin at HDAC1 is 36 ± 16 nM while that of the reduced form is $IC_{50} = 1.6 \pm 0.9$ nM [127]. Romidepsin has also been shown to induce cell cycle arrest, differentiation, and apoptosis in tumor cells by mechanisms that cannot be completely explained by HDAC inhibition alone. The synthesis of romidepsin has been reported in the patent and open literature [128,129]. In the first reported total synthesis, Simon *et al.* [129a] employ the Carreira catalytic asymmetric aldol reaction to build the thiol containing β-hydroxy acid followed by a modified Mitsunobu macrolactonization and iodine-mediated intramolecular oxidative coupling to form the disulfide ring. The synthesis by Williams *et al.* [129b] utilizes Noyori's asymmetric transfer hydrogenation of a propargylic ketone as a key step in the synthesis of the β-hydroxy acid. Katoh *et al.* [129c] employ a Julia-Kocienski olefination of a 1,3-propanediol-derived sulfone as the critical step to access the β-hydroxy acid.

In vitro studies show that romidepsin induces apoptosis in a variety of tumor cells such as primary CLL cells, MM cell lines, primary myeloma cells, and small cell lung cancer cells. Preclinical *in vivo* studies demonstrated that romidepsin improved the survival rates of mice bearing murine ascitic tumors (P388 and L1210 leukemia's and B16 melanoma) and inhibited the growth of human solid tumors (Lu-65 and LC-6 lung carcinomas and SC-6

stomach adenocarcinoma) implanted in normal or nude mice. The pharmacokinetic parameters of romidepsin were evaluated at a dose of 17.8 mg/m^2 in a Phase I trial in cancer patients [130]. Following a 4-h IV infusion, romidepsin had a C_{max} of ~1.02 μM and an AUC of ~4.2 μM h, which increased in a dose-proportional fashion, and it showed a mean elimination half-life of ~41 h. The mean clearance was 10.5 L/h/m^2 and the terminal half-life was ~8.1 h. Romidepsin is extensively metabolized *in vitro* by CYP3A4 with minor contributions by CYP3A5, CYP1A1, CYP2B6, and CYP2C19. The human plasma protein binding of romidepsin ranges from 92% to 94% at concentrations of 50–1000 ng/mL, respectively, primarily because of binding to α1-acid-glycoprotein. Romidepsin approval for CTCL was based on two multicenter, single-arm clinical studies in patients with CTCL [131,132]. The first study had 96 patients with CTCL after failure of at least one systemic therapy. The second study comprising 71 patients was also in patients with CTCL who received at least two prior skin-directed therapies or one prior systemic therapy. Patients in these studies were given romidepsin at a starting dose of 14 mg/m^2 infused over 4 h on days 1, 8, and 15 every 28 days. The overall objective disease response (ODR) and complete response (CR) rates in both studies were similar (~34% and 6%, respectively). The median response duration was ~15 months in study I and ~11 months in study II. The median times for CR for studies I and II were 6 and 4 months, respectively. Most common serious adverse events associated with romidepsin treatment were neutropenia, lymphopenia, thrombocytopenia, anemia, fatigue, and nausea. The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over 4 h on days 1 and 8 and 15 of a 28-day cycle [133].

19. SIPULEUCEL-T (ANTICANCER) [134–138]

Class	Therapeutic cancer vaccine for hormone-refractory prostrate cancer
Country of origin	United States
Originator	Dendreon
First introduction	United States
Introduced by	Dendreon
Trade name	Provenge®
CAS registry no.	917381-47-6

Sipuleucel-T is the first FDA-approved therapeutic cancer vaccine. It is approved for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant (hormone-refractory) prostate cancer.

Sipuleucel-T is described as a therapy rather than a precisely defined therapeutic agent because it is an autologous vaccine that is generated from each individual patient's own blood cells. Patient peripheral blood mononuclear cells (PBMCs) are isolated by leukophoresis and then cultured together with a recombinant fusion protein, comprising human prostatic acid phosphatase (a protein found in prostate and prostate cancer cells) fused at its COOH terminus to full length human GM-CSF *via* a gly-ser linker (PA2024, PAP-GM-CSF). The recombinant PA2024 molecule is largely removed by washing, or is catabolized by PBMC during culture, and it is not a significant component of the dosed vaccine. Preparations are produced fresh for each treatment by a manufacturing process that takes 3–4 days and includes *in vitro* culture for 36–44 h at 37 °C followed by washing, resuspension, and packaging. The resulting vaccine is delivered in an infusion bag comprising a 250-mL cell suspension in Ringer's lactate solution. The actual cellular composition of the infusion bag is incompletely defined. The release assay is a count of the number of activated antigen presenting cells, defined as positive for expression of the cell surface marker CD54 [134]. Each dose is required to contain at least 50 million CD54 positive cells. However, other lymphocytic cells (such as T cells, B cells, and NK cells) that could contribute to the activity of sipuleucel-T are found in the infusion bag, and the actual number and activation state of these cell types is not controlled and will vary for each individual manufactured dose. T cells may be a particularly important component of the activity, and T cell activation has been reported to be specifically induced by PA2024 during sipuleucel-T manufacture [135]. The therapeutic course for sipuleucel-T comprises three infusions, given at approximately 2-week intervals. Patients are premedicated approximately 30 min prior to each dose with oral acetaminophen and an antihistamine such as diphenhydramine to minimize infusion reactions. The safety and efficacy of this treatment schedule were examined in three randomized (2:1) Phase III trials enrolling 737 asymptomatic, or minimally symptomatic, patients with metastatic, castration-resistant prostate cancer. In each of these trials, the control group received placebo infusions comprising the patient's own leukophoresed PBMCs that had been cultured in the absence of recombinant PA2024. The placebo infusion bag was released with the same requirements, >50 million CD54 positive cells, as sipuleucel-T. Two of the Phase III trials were completed: the pivotal trial enrolling 512 patients [136] and a smaller trial enrolling 127 patients [137]. A third trial was not completed; however, 98 patients were enrolled and followed for time to progression and survival [138]. The predefined endpoint for the smaller non-pivotal trials was time to progression, and statistical significance was not reached; however, in the 127-patient trial, sipuleucel-T was observed to have a beneficial effect on overall survival, with a median survival difference of 4.5 months ($p = 0.01$, log-rank; HR, 1.70; 95% CI, 1.13–2.56). The data from

the uncompleted trial were not inconsistent with a positive survival benefit for vaccine therapy [137]. The primary endpoint for the pivotal trial was overall survival, and sipuleucel-T was again found to have a beneficial effect, with a median survival difference of 4.1 months (25.8 months in the sipuleucel-T group *vs.* 21.7 months in the placebo group). There was an observed relative reduction of 22% in the risk of death as compared with the placebo group (HR, 0.78; 95% CI, 0.61–0.98; $p = 0.03$). The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group. The Kaplan–Meier estimated survival probability did not show a difference beyond 48 months; however, the number of patients still at risk at these time points is too small to draw conclusions. Consistent with the earlier trials, in the pivotal trial, the difference in time to progression for the sipuleucel-T and the placebo groups was not significant. Because of the difference in the mechanism of action compared to cytotoxic therapy, time to progression may not be an appropriate endpoint for a therapeutic cancer vaccine where activity is not expected until the host immune system becomes engaged. In rapidly progressing cancers, such as metastatic castration-resistant prostate cancer, this engagement may be too slow to see an effect on progression. Acute infusion reactions (reported within 1 day of infusion) are a frequent occurrence for sipuleucel-T therapy. The most common adverse events observed in the pivotal study for the sipuleucel-T group within 1 day after infusion were chills (in 51.2%), fever (22.5%), fatigue (16.0%), nausea (14.2%), and headache (10.7%). Grade 3 or higher adverse events within 1 day after infusion were reported in 6.8% of the sipuleucel-T group. These included chills (in four patients), fatigue (three patients), and back pain, hypertension, hypokalemia, and muscular weakness (in two patients each). Overall, only 3 of 338 patients (0.9%) in the sipuleucel-T group were unable to receive all three infusions because of acute infusion-related adverse events. In the pivotal trial, there was no statistically significant difference in cerebrovascular events, including hemorrhagic and ischemic strokes, between the sipuleucel-T group (2.4%) and placebo group (1.8%) ($p = 1.00$). Overall experience in controlled studies found cerebrovascular events observed in 3.5% of sipuleucel-T treated patients compared with 2.6% of patients in the control groups.

20. TESAMORELIN ACETATE (HIV LIPODYSTROPHY) [139–142]

Class	Growth hormone-releasing factor
Country of origin	Canada
Originator	Theratechnologies

First introduction	United States
Introduced by	Theratechnologies
Trade name	Egrifta™
CAS registry no.	804475-66-9
Molecular weight	5135.9 Da

44-Amino acid polypeptide-*trans*-3-hexenoyl-YADAIFTNSYRKV LGQLSARKLLQDIMSRQQGESNQERGARARL-NH_2

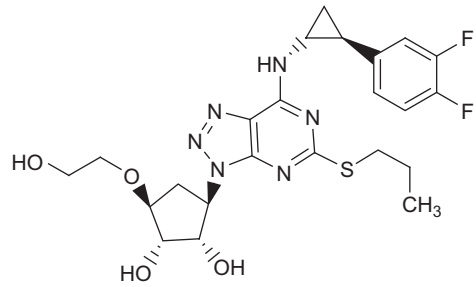
Tesamorelin acetate is an analog of growth hormone-releasing hormone (GHRH) that was approved in the United States in 2010 for treatment of lipodystrophy in HIV patients. With the advent of potent antiretroviral treatment (ART) in the 1990s as a treatment regime for HIV infection, some patients were observed to have either a loss or an accumulation of fat, termed lipodystrophy. Individuals with lipodystrophy can develop excess fat notably in the abdominal visceral adipose tissue (VAT), liver, trunk, and breasts. Up to 30% of patients undergoing ART experience increases in abdominal fat. Patients with HIV-associated lipodystrophy have an increased need for health services when compared to ART patients without lipodystrophy. The market size for the treatment of HIV-associated lipodystrophy in the United States is currently projected to be $800 million to $1.2 billion [139]. Lipodystrophy has both medical and social implications. Increased VAT has been associated with dyslipodemia, thereby increasing the risk of the progression of metabolic diseases. Excess VAT is associated with increased coronary artery calcification, increasing the risk of cardiovascular events. The pathogenesis of lipodystrophy is not clearly understood, but several biological processes have been implicated. Impaired fatty acid metabolism in the adipocyte, deficiencies in adiponectin, increases in leptin, and alteration in growth hormone secretion have all been studied. Decreased growth hormone (GH) levels are found in HIV patients with increased VAT. The impairment of the GH secretion through suppression of GH by elevated fatty acids and decreases in ghrelin levels may contribute to lipodystrophy. The observation of lower GH levels in patients with lipodystrophy and the observation that GH treatment to prevent HIV-related wasting results in improved lipodystrophy have led to efforts to target the GH axis to treat lipodystrophy [140,141].

Tesomorelin is an analog of GHRH. GHRH stimulates the synthesis and release of GH. In the pituitary, GH is secreted in a pulsatile manner. GH control is regulated by somatostatin and the negative feedback regulator, IGF-1. Direct administration of GH to patients with lipodystrophy decreases VAT but has associated side effects such as fluid retention and joint swelling. Because of the side effects associated with direct GH administration, GHRH represents a attractive mechanism for increasing GH levels. Tesomorelin is an analog of GHRH in which the N-terminal

amino acid, Tyr, is amidated with a *trans*-3-hexenoyl group. Capping of the N-terminus protects GHRH from cleavage by DPP-4. Tesomorelin demonstrates enhanced stability compared with GHRH in animal models. After subcutaneous administration, GH levels were increased out to 8 h when tested in rats, dogs, and pigs. In healthy male volunteers, tesamorelin administered subcutaneously showed a linear increase in pharmacokinetic parameters when dosed at 0.5, 1, or 2 mg per day. In Phase II studies comparing 1 and 2 mg doses of tesamorelin, the 2 mg dose showed better efficacy at reducing trunk and visceral fat. IGF-1 levels were found to be significantly increased relative to placebo. In two Phase III clinical trials, tesamorelin was shown to significantly reduce VAT and to improve body image. Significant reductions in trunk fat were observed in the tesamorelin-treated group. Lean body mass increased and waist circumference decreased. Tesamorelin was found to affect metabolic biomarkers by reducing triglycerides and total cholesterol levels [141,142]. In November 2010, tesamorelin, a GRF analog, was approved by the U.S. FDA for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Tesamorelin is marketed under the trade name Egrifta™ by Theratechnologies and EMD Serono. Egrifta™ is available as a subcutaneously administered 2 mg dose. Egrifta™ is the first FDA-approved treatment specifically approved for lipodystrophy.

21. TICAGRELOR (ANTITHROMBOTIC) [143–150]

Class	$P2Y_{12}$ antagonist
Country of origin	United Kingdom
Originator	Astra-Zeneca
First introduction	European Union
Introduced by	Astra-Zeneca
Trade names	Brilique™ and Possia® in the European Union
CAS registry no.	274693-27-5
Molecular weight	522.57



In December 2010, the $P2Y_{12}$ receptor antagonist ticagrelor (also known as AZD6140) was approved in Europe for the treatment of acute coronary syndrome (ACS), a condition that covers several clinical symptoms with the potential to cause acute myocardial ischemia (MI). The symptoms range from unstable angina, to non-Q wave infarctions and Q-wave myocardial infarctions, which can lead to life-threatening events. ACS is the leading cause of death in the United States and represents 50% of the deaths related to cardiovascular disease. In Europe, ACS affects an estimated 1.4 million people every year [143]. Despite the availability of current treatment options for ACS, data suggest that up to 15% of patients die within 1 year of their cardiovascular event. The economic impact of ACS is substantial and estimated to be $150 billion per year. The rupture of an atherosclerotic plaque in coronary arteries triggers events that lead to the formation of a platelet-rich thrombus plug or clot. This results in an ischemic event, myocardial infarction, or stroke and often is fatal. When a plaque ruptures, a cascade of biochemical events, termed platelet activation, is set in place. At initiation, several agonists of platelet activation are released; among these are thrombin and adenosine diphosphate (ADP). ADP binds to two purinergic receptors, the $P2Y_1$ and $P2Y_{12}$ receptors. The action of ADP binding to the $P2Y_{12}$ receptor results in activation of the GP IIb/IIIa (integrin) receptor. GP IIb/IIIa initiates and prolongs platelet aggregation, which in turn results in the cross-linking of platelets through fibrin and finally thrombus formation. Inhibition of ADP stimulation of the $P2Y_{12}$ receptor has been found to be an effective strategy for managing the atherothrombotic events associated with ACS and potentially resulting from percutaneous coronary intervention (PCI, stent implantation) [144,145].

The first $P2Y_{12}$ inhibitor drugs to reach the market were of the thienopyridine class represented by clopidogrel and prasugrel. Both are converted by CYP-mediated processes to an active metabolite that binds covalently and irreversibly to the $P2Y_{12}$ receptor. A second class of $P2Y_{12}$ receptor inhibitors has been developed that are reversible and bind directly to the receptor. Drug design efforts began with the structure of the endogenous antagonist adenosine triphosphate (ATP). ATP contains several functionalities which would in themselves make the discovery of an orally active drug difficult. These are the acidic and unstable triphosphate functionality, the ribose core and the purine-sugar bond. Astra-Zeneca researchers postulated that many of these structural features could be modified and replaced, resulting in the discovery of orally bioavailable antagonists of the $P2Y_{12}$ receptors. The phosphate moiety was addressed by replacing the phosphate with dicarboxylic acids, then monocarboxylic acids and ultimately with nonacidic, neutral groups, such as the hydroxyl-ethyl ether group found in ticagrelor. The purine group was replaced with a triazolopyrimidine, a known bioisostere, and through substitution on the amino group, molecules with potent binding

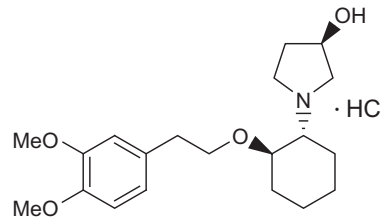
were identified. In addition, the ribose sugar was replaced by a cyclopentane to prevent the possibility of enzymatic cleavage. The optimal molecule discovered from this medicinal chemistry effort is AZD6140, ticagrelor. The synthesis of ticagrelor is convergent. The cyclopentyl core is built up from mono-protected cyclopentene diol. After elaboration to add the adjacent diols and the ethyl alcohol *via* ether bond formation, one of the ring alcohols is converted to an amine group. This amine is then used to build up the triazolopyrimidine ring. Addition of the fully functionalized phenyl-cyclopropyl amine to chloro ethylthio-triazolopyrimidine completes the synthesis of ticagrelor. Ticagrelor binds reversibly to the $P2Y_{12}$ receptor and has been found to be a noncompetitive (with ADP) allosteric antagonist with rapid on-/off-rate kinetics [146].

The metabolism, distribution, and elimination profiles of ticagrelor have been published. In a study in six healthy male subjects, radiolabeled ticagrelor was found to reach T_{max} in 1.5 h. The major active metabolite formed, AR-C124910XX, results from O-deethylation of ticagrelor. AR-C124910XX circulates at 29% peak and 40% total exposure relative to ticagrelor. Very little parent drug and AR-C124910XX were found in the urine with the primary direct elimination pathway being in the feces. Secondary *O*-glucuronide metabolites and ticagrelor metabolites where the cyclopropyl-phenyl group is cleaved represent the metabolites excreted in the urine. A total of 10 metabolites of ticagrelor were reported [147]. Ticagrelor has been studied in several Phase II and Phase III studies. The DISPERSE II trial, a Phase III trial, compared ticagrelor to clopidogrel in non-ST-segment elevation myocardial infarction in 990 patients with atherosclerotic disease where efficacy and bleeding events were evaluated. In this study, ticagrelor lowered the incidence of MI and showed a low bleeding risk and effective inhibition of platelet aggregation. Ticagrelor was studied in patients with stable coronary artery disease in the ONSET/OFFSET (Phase III) trial. The purposes of this trial were to show how rapidly platelets were inhibited after dose administration and what the duration was for restoration of platelet function after drug discontinuation. The results of the study showed that ticagrelor had a faster and greater inhibition of platelet activation when compared with clopidogrel. After termination of drug administration, platelet function was restored within 5 days in the ticagrelor-treated groups compared to 7 days in the clopidogrel-treated group. The RESPOND trial (Phase III) was designed to look at the effectiveness of ticagrelor in patients who are nonresponders to clopidogrel. The outcome was that ticagrelor was effective in both patients that respond to clopidogrel and those that are nonresponsive to clopidogrel. The PLATO trial (Phase III) was a large $>18{,}000$ patient trial. Patients hospitalized for ST-elevation ACS with scheduled primary PCI or for non-ST-elevation ACS were evaluated for reduction in the event rate of MI, vascular-related death, stroke- and drug-related

bleeding risk. Ticagrelor was found to reduce all primary outcome events, including MI, stroke, and death from vascular complication, ischemia, and stent thrombosis [147–150]. In December 2010, the EC granted marketing approval for Brilique™ (ticagrelor) for the prevention of atherothrombotic events in patients with ACS.

22. VERNAKALANT (ANTIARRHYTHMIC) [151–154]

Class	Atrial potassium channel blocker
Country of origin	Canada
Originator	Cardiome Pharma Corp.
First introduction	European Union
Introduced by	Merck and Cardiome Pharma Corp.
Trade name	Brinavess™
CAS registry no.	794466-70-9
	748810-28-8 (HCl)
Molecular weight	349.46

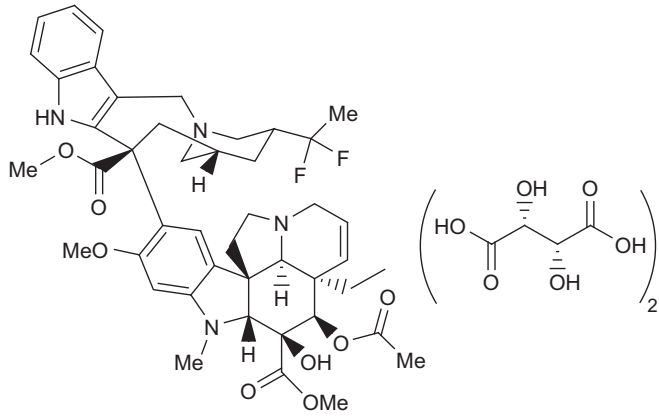


Vernakalant is a potassium channel blocker that was approved in Europe in 2010 for treatment of atrial fibrillation (AF), a condition of cardiac arrhythmia in which the atria of the heart beat irregularly due to changes in cardiac ion channel function and distribution. Patients with AF can have events that last from minutes to weeks to years depending on the severity of the condition and other complicating factors. AF affects quality of life by causing shortness of breath, chest pains, palpitations, and general weakness. AF is associated with congestive heart failure (CHF) and increases the risk of stroke through the increased chance of blood clot formation. The risk of AF rises with age. There are an estimated 2.2 million patients with AF in the United States and 4.5 million in the European Union. The annual U.S. sales for antiarrhythmics are $1.6 billion [151]. The worldwide market for treating AF is growing as the population ages and as the incidence of diabetes and hypertension increases. For the patient with AF, therapeutic intervention involves heart rate management

(β-blockers or calcium-channel blockers), reducing the risk of stroke (warfarin or aspirin) and restoring sinus rhythm (SR) to normal (Class Ia, Ic, or III antiarrhythmic agent) [152]. The pathogenesis of AF involves a multitude of events which result in irregular impulses disrupting a normal heartbeat. These irregular impulses originate from the atria which are out of coordination with the ventricles of the heart. The changes in the atria are both electrical and structural. Currently, marketed antiarrhythmic agents vary in their safety and efficacy profile [152,153]. Antiarrhythmic agents target sodium and potassium ion channels of the heart. Side effects result from the lack of selectivity of agents for ion channels in atrial and ventricular tissues. This results in ventricular proarrhythmias and an increased risk of Torsades de Pointes (TdP). Class I antiarrhythmic drugs primarily affect the inward sodium current (I_{Na}), whereas Class III antiarrhythmic drugs target the rapidly activating I_{kr} and ultra rapidly activating (I_{kur}) delayed rectifier potassium currents. Both I_{Na} and I_{kr} are found in atrial and ventricular tissues, whereas I_{kur} is found only in the atria. Drugs with greater atrial selectivity have been sought by targeting I_{kur} (the Kv1.5 channel). Vernakalant has activity for cardiac Na+ and K+ channels and also for the atrial-selective Kv1.5 channel. Vernakalant (RSD1235) was characterized in animal models to assess efficacy, atrial selectivity, and reduction in side effects. In canine models of AF, vernakalant given intravenously at 1, 2, 4, and 8 mg/kg reduced in a dose-dependent manner the time of conversion of AF to normal SR with no increase in QT (hERG) intervals. Primates given IV vernakalant at 2.5, 5, and 10 mg/kg had dose-dependent increases in the atrial refractory period with fewer increases in the ventricular refractory period [151–153]. The absorption, metabolism, and distribution of vernakalant have been characterized by both oral and IV administration. IV administration of vernakalant showed linear pharmacokinetics over the dose range of 0.1–5 mg. The elimination half-life was found to be 2 h. Vernakalant is rapidly metabolized by CYP2D6 to the 4-*O*-demethyl metabolite (RDS-1385), which can form an inactive *O*-glucuronide. Vernakalant is cleared by both the liver and kidney. Vernakalant has been studied and characterized in several Phase III trials (ACT I, ACT II, and ACT III) where the drug was dosed as a 10-min IV infusion of 3 mg/kg followed by a second 10-min infusion at a dose of 2 mg/kg 15 min later if AF had not been terminated. In short duration AF patients (3 h to 7 days), 51.7% of the patients converted to normal SR versus 4% for the placebo-treated group. In patients with long duration AF (8–45 days), the effectiveness of vernakalant was lower with 7.9% achieving normal SR versus none in the placebo group converting to SR [152–154]. In September 2010, IV vernakalant (Brinavess™; Cardiome/Merck) was granted marketing authorization by the EC for rapid conversion of recent onset AF to SR in adults, for nonsurgery patients with AF of 7 days or less and for postcardiac surgery patients with AF of 3 days or less.

23. VINFLUNINE DITARTRATE (ANTICANCER) [155–162]

Class	Tubulin inhibitor
Country of origin	France
Originator	Pierre Fabre
First introduction	United Kingdom
Introduced by	Pierre Fabre
Trade name	Javlor®
CAS registry no.	162652-95-1
	194468-36-5 [tartrate (1:2)]
Molecular weight	816.9



Vinflunine (also referred to as PM391) is a semisynthetic analog of the natural *vinca* alkaloids vinblastine and vincristine that was approved by the European Medicines Agency (EMEA) in 2009 for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. Bladder cancer is a significant health problem in the European Union with 104,400 new cases (82,800 men and 21,600 women) identified in 2006. Cisplatin-based combination chemotherapy or single-agent-based chemotherapy in patients unable to receive cisplatin is the standard first-line treatment for metastatic bladder cancer. However, responses to cisplatin-based regimens are not durable and most patients usually experience disease progression or recurrence. Single-agent therapies such as gemcitabine, paclitaxel, docetaxel, ifosfamide, and ixabepilone have produced low to moderate response rates (0–20%) in patients with platinum-pretreated advanced bladder cancer. Combination therapies have produced higher response rates (30–60%) although this is accompanied

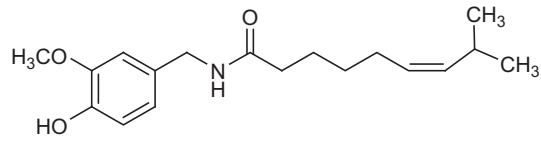
with increasing toxicities. Therefore, there is need for newer chemotherapeutics with increased response rates and manageable toxicities. Vinflunine binds to the *vinca*-binding site on tubulin and inhibits microtubule dynamics and treadmilling and induces cell cycle arrest at the G2/M phase. This leads to the accumulation of cells during the mitotic phase and eventually cell death by apoptosis [155]. Compared to other *vinca* alkaloids, vinflunine exhibits the greatest tubulin-binding affinity leading to higher antitumor activity (*e.g.*, compared to vinorelbine) and reduced neurotoxicity. Vinflunine is synthesized from anhydrovinblastine in a superacid media (HF-SbF_5) and in the presence of a chlorinated solvent like $CHCl_3$ or CCl_4 [156,157]. The net result is a novel gem-difluorination at the allylic position and simultaneous reduction of the double bond, followed by ring contraction to yield vinflunine.

The significantly superior anticancer activity of vinflunine compared to its close analog vinorelbine was demonstrated upon intraperitoneal dosing in a range of murine and human tumor xenografts [158]. Preclinical *in vitro* studies demonstrated the cytotoxic ability of vinflunine to inhibit colon, prostrate, bladder, breast, and ovary cell lines with IC_{50} values ranging from 60 to 300 nM [159]. Like other *vinca* alkaloids, vinflunine is a substrate for P-gp-mediated drug resistance mechanisms, although the induction of drug resistance is significantly lower than that of vinorelbine or vincristine. In a Phase I clinical trial, vinflunine showed linear pharmacokinetics over a dose range of 30–400 mg/m^2 following IV administration on day 1 of a 3-week cycle to patients with solid tumors [160]. A dose-proportional increase in exposure was noted and no accumulation was seen between cycles. The terminal half-life of vinflunine is $\sim$40 h. The mean clearance and volume of distribution were $\sim$44 L/h and $\sim$2422 L/m^2, respectively. The human plasma protein binding ranges from 40% to 78%. Vinflunine is predominantly metabolized by CYP3A4; 4-*O*-deacetylvinflunine (DVFL) is the major circulating and active metabolite. The safety and efficacy of vinflunine were established in a randomized Phase III study comparing vinflunine + best supportive care (BSC) versus BSC alone in patients with advanced transitional cell carcinoma of the urothelial tract (TCCU) and who were previously treated with a first-line platinum-containing regimen [161]. Of the 370 patients, 253 were treated with vinflunine + BSC and 117 were treated with BSC. The study indicated that vinflunine treated patients showed improvement in the median overall survival of 6.9 months compared to 4.3 months for patients who were treated with BSC ($p = 0.040$). Other parameters such as overall response rate, disease control, and progression-free survival were all statistically significant favoring the vinflunine + BSC group ($p = 0.006$, 0.002, and 0.001, respectively). The most common serious adverse events associated with the vinflunine + BSC group treatment were neutropenia (50%), febrile neutropenia (6%) anemia,

fatigue, and constipation. The recommended dose of vinflunine ditartrate is 320 mg/m^2 administered intravenously over 20 min once every 3 weeks [162].

24. ZUCAPSAICIN (ANALGESIC) [163–170]

Class	Transient receptor potential vanilloid type I channel activator
Country of origin	Germany
Originator	E Merck AG
First introduction	Canada
Introduced by	Winston
Trade name	Civanex®
CAS registry no.	25775-90-0
Molecular weight	305.4



Zucapsaicin is a topical analgesic that was approved in Canada in July 2010 for use in conjunction with oral COX-2 inhibitors or NSAIDs to relieve severe pain in adults with osteoarthritis of the knee [163]. Zucapsaicin is the *cis*-isomer of the natural product capsaicin. Capsaicin is available without a prescription in creams, lotions, and patches for the treatment of neuropathic and musculoskeletal pain. Zucapsaicin is available as a 0.075% by weight cream. The advantages of zucapsaicin compared with capsaicin are reported to be a lesser degree of local irritation (stinging, burning, erythema) in patients and a greater degree of efficacy in preclinical animal models of pain [163,164]. The analgesic action of zucapsaicin and capsaicin is mediated through the transient receptor potential vanilloid type 1 (TRPV1) channel [165–168]. TRPV1 is a ligand-gated ion channel that is expressed in the spinal cord and brain and is localized on neurons in sensory ganglia, with peripheral projections to the skin, muscles, joints, and gut and central terminals to the spinal dorsal horn. Activation of TRPV1 triggers an influx of calcium and sodium ions, which initiates a cascade of events associated with pain transmission, including membrane depolarization, neuronal firing, and release of pain transmitters. Topical application of an agonist such as zucapsaicin initially activates TRPV1. The constant activation of the channel results in

high intracellular levels of calcium, ultimately leading to desensitization to a variety of noxious stimuli through functional and morphological alterations to the peripheral ends of nerve fibers. The antinociceptive effects of zucapsaicin have been demonstrated with oral treatment in pain models in rats, including the formalin test, the thermal paw withdrawal test, and in the Chung model of neuropathic pain [169]. Zucapsaicin has been synthesized by coupling of vanillin amine with (*Z*)-8-methylnon-6-enoyl chloride [170]. In preclinical species, there was minimal absorption of zucapsaicin into systemic circulation following topical administration. The only evidence of a systemic effect was a decrease in mean body weight in male rats treated with 3.0% zucapsaicin cream. At the clinically relevant concentration of 0.075%, zucapsaicin cream produced slight erythema in minipigs and slight to moderate erythema in rats. In clinical studies, zucapsaicin serum concentration levels were below the level of quantitation for subjects receiving 0.075% cream applied three times daily to the knees for seven days. Zucapsaicin cream (0.075%) produced local reactions of burning and stinging that were tolerable and reversible. No serious adverse events were reported.

Evidence of efficacy for zucapsaicin was based on a single 12-week Phase III randomized, double-blinded, controlled study in subjects with osteoarthritis of the knee who were taking oral COX-2 inhibitors (42% of patients) or NSAIDs (58% of patients) [163]. Patients received applications of zucapsaicin as either a 0.075% by weight cream (the active arm) or a 0.01% by weight cream (the control arm) three times a day. Primary endpoints were knee pain assessment, physical function, and subject global evaluation. Patients with mild-to-moderate pain showed similar efficacy with both strengths of zucapsaicin cream. However, in patients experiencing severe pain, 0.075% zucapsaicin was significantly more efficacious in reducing pain than 0.01% zucapsaicin cream. Thus, patients who exhibited the best response to zucapsaicin were those in the worst condition as determined by baseline scores. Application site burning sensations were the most frequently reported adverse events and were predominantly mild to moderate. The number of withdrawals in the 0.075% zucapsaicin group was 7%, while fewer patient withdrawals occurred in the 0.01% zucapsaicin group (2%). On the basis of the safety and efficacy data, zucapsaicin was approved in Canada in 2010.

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